CENTERS FOR MEDICARE AND MEDICAID SERVICES

Medicare Evidence Development & Coverage

Advisory Committee

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Centers for Medicare and Medicaid Services

7500 Security Boulevard

Baltimore, Maryland

Panelists

Chairperson
Rita Redberg, MD, MS

Vice-Chair
Art Sedrakyan, MD, PhD

Voting Members
Ralph Brindis, MD, MPH, MACC
Raymond E. Faught, Jr., MD
Mark D. Grant, MD, MPH
Peter Heseltine, MD
Curtis Mock, MD, MBA
Jeffrey B. Rich, MD
J. Sanford Schwartz, MD
Robert L. Steinbrook, MD

CMS Liaison
Jyme Schafer, MD

Industry Representative
Shamiram R. Feinglass, MD, MPH

Guest Panel Members
G. Kevin Donovan, MD, MA
Robert Kormos, MD
Ileana L. Pina, MD, MPH, FAHA, FACC

Invited Guest Speakers
Keith Aaronson, MD
James Kirklin, MD
David C. Naftel, PhD
Lynne Warner Stevenson, MD

Executive Secretary
Maria Ellis

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PANEL PROCEEDINGS

(The meeting was called to order at 8:10 a.m., Wednesday, November 14, 2012.)

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 use of ventricular assist devices, VADs, as a clinical strategy for the management of heart failure.

The following announcement addresses conflict of interest issues associated with this meeting and is 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 introduction. We ask in the interest of fairness that all persons making statements or presentations disclose if you or any member of your immediate family owns stock or has another

form of financial interest in any company, including Internet or e-commerce organizations that certifies, accredits health care entities, or develops, manufactures, distributes and/or markets ventricular assist devices, artificial hearts or similar devices or is involved in oversight of their use. 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 of this room.

We ask that all presenters please adhere to their time limits, 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.

For the record, the voting members present for today's meeting are Dr. Art Sedrakyan, Dr. Ralph Brindis, Dr. Mark Grant, Dr. Peter Heseltine, Dr. Curtis Mock, Dr. Jeffrey Rich, Dr. J. Sanford Schwartz and Dr. Robert Steinbrook. 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 results will be available on our website following the meeting. I ask that all panel members please speak directly into the mics, and you may have to move the mics since we have to share.

This meeting is being webcast via CMS in addition to the transcriptionist. By your appearance you are giving consent to the use and distribution of your name, likeness and

voice during the meeting. You are also giving consent to the use and distribution of any personal identifiable information that you or others may disclose about you during today's meeting. Please do not disclose personal health information.

If you require a taxicab, there are

telephone numbers to local cab companies at the desk outside of the auditorium. Please remember to discard your trash in the trash cans located outside of this room.

And lastly, all CMS guests attending today's MEDCAC meeting are only permitted in the following areas of CMS single site, the main lobby, the auditorium, the lower level lobby and the cafeteria. Any person 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. Jyme Schafer.

DR. SCHAFER: Thank you, Ms. Ellis. I am Jyme Schafer, the director of the Division of Medical and Surgical Services, Coverage

Analysis Group, Center for Clinical Standards and Quality here at CMS. I have no conflicts of interest.

A Medicare Evidence Development and Coverage Advisory Committee meeting is called when CMS would like independent expert advice for a decision based on the reasonable application of scientific evidence. We do not

currently have an open national coverage determination on ventricular assist devices. However, we do anticipate opening an NCD.

Unlike many previous MEDCACs, we do not have a formal technical assessment. We do have something a bit unusual to have, we have accumulated data from a registry associated with this NCD and we will be examining that data in relation to policy today. In addition, we have something else associated with this NCD which is also a bit unusual. We have a requirement that the Joint Commission have a disease-specific certification for the facilities, so we will be looking at this also today, this is within the NCD.

Thank you very much, and I would like

to thank already Dr. Redberg, our chair, our vice chair Dr. Sedrakyan, our distinguished panel, and of course our distinguished presenters, and now I will turn this over to Dr. Redberg.

DR. REDBERG: Thanks very much. I am Rita Redberg, I am a cardiologist and professor of medicine at the University of California San Francisco, and will chair this committee.

I have no conflicts of interest.

I just also want to add my thanks to all of the panel members for taking the time, and we are all looking forward to hearing from our guest panelists and our attendees as well. At this time I'm going to turn it over to Dr. Sedrakyan, and ask the panel to introduce themselves.

DR. SEDRAKYAN: Thank you very much, Rita. I'm Art Sedrakyan, I'm an associate professor of public health and cardiac surgery at Weill Cornell Medical School, and am also the director of the patient-centered comparative outcomes research program at Cornell. I have no conflicts of interest to

disclose.

DR. BRINDIS: I'm Ralph Brindis, I'm a clinical professor of medicine at UCSF, and am past president of the American College of Cardiology, and I have no conflicts.

DR. GRANT: I'm Mark Grant, I'm the director of technology assessment at the Technology Evaluation Center, Blue Cross Blue Shield Association, and I have no conflicts of interest.

DR. HESELTINE: I'm Peter Heseltine. I'm a professor of clinical medicine at the University of California Irvine, and also chief medical officer at Prometheus Laboratories in San Diego. I have no conflicts of interest.

DR. MOCK: I'm Curtis Mock, I'm certified in family medicine and geriatrics. I'm a senior medical director with UnitedHealthCare.

DR. REDBERG: I'm sorry, do you have any conflicts?

DR. MOCK: I have no conflicts.

DR. RICH: Jeff Rich, I'm a practicing cardiac surgeon at Sentara Healthcare in

Norfolk, Virginia. I'm also the current president of the Society of Thoracic Surgeons. I have no conflicts.

DR. SCHWARTZ: Sandy Schwartz. I'm a professor of medicine and health management economics at the Medical School and Wharton School of the University of Pennsylvania, and I don't have any conflicts related to this topic.

DR. STEINBROOK: Robert Steinbrook, professor adjunct of internal medicine at the Yale School of Medicine. No conflicts of

interest to declare.

DR. FEINGLASS: Shamiram Feinglass. I am vice president for global medical and regulatory affairs for Zimmer. I work for industry but I have no conflicts in the field that we're considering today.

DR. DONOVAN: I'm Kevin Donovan, I'm the director of the Center for Clinical Bioethics at Georgetown, and I have no conflicts of interest.

DR. KORMOS: I'm Robert Kormos, I'm a professor or cardiothoracic surgery at the University of Pittsburgh and run the artificial

heart program, I have no conflicts of interest.

DR. PINA: I'm Ileana Pina. I'm a heart transplant cardiologist and associate chief of cardiology at Albert Einstein Montefiore in the Bronx, and I'm a consultant to the FDA in devices.

DR. REDBERG: Thank you very much.

I'm now pleased to introduce Dr. Kimberly Smith from CMS to go over the voting questions.

DR. SMITH: Thank you, good morning. My name is Kim Smith, I'm a lieutenant

commander in the commissioned corps of the Public Health Service and a medical officer in the Coverage and Analysis Group here at CMS. I will actually be covering two topics today, first our current national coverage policy, followed by the voting questions.

Medicare does currently have a national coverage determination which we often refer to as an NCD on this topic. For those of you who would like to look into this in more detail, that can be found in the document entitled Artificial Hearts and Related Devices

in Section 20.9 of the NCD manual. This policy encompasses ventricular assist devices for three different indications, for postcardiotomy or patients following open heart surgery, for bridge-to-transplant, and for destination therapy. We'll cover these last two indications in a little bit more detail here. It also covers artificial hearts both for bridge-to-transplant and for destination therapy.

Within the policy we do have the following definition: A ventricular assist device (VAD) or left ventricular assist device

(LVAD) is surgically attached to one or both intact ventricles and is used to assist a damaged or weakened native heart in pumping blood.

For bridge-to-transplant we must actually meet three criteria per our current coverage policy. The device that's implanted must be FDA-approved for bridge-to-transplant, the patient must be listed for heart transplant, and if the device is going to be implanted at a center other than the heart

transplant listing center, the implanting center must receive written permission from the transplant center to implant the device. Those are the three criteria for us to cover the device under the bridge-to-transplant requirement.

We also cover these devices as destination therapy. Similar to bridge-to-transplant, destination therapy requires that the device be FDA-approved for that indication, but there are also additional facility criteria as well as patient selection criteria for coverage as destination therapy.

Facility criteria include having at

least one team member with experience implanting at least ten VADs or artificial hearts over the previous 36 months; membership in the Interagency Registry for Mechanically Assisted Circulatory Support or INTERMACS, you'll hear much more about that registry as the morning progresses; they must be certified by the Joint Commission under their disease-specific certification program for ventricular assist devices; and the facility must have staff and

procedures in place for appropriate informed consent of patients.

As I said, there are additional patient selection criteria for destination therapy. The patient must have New York Heart Association Class IV chronic heart failure, they must not be a candidate for transplant, and they must meet additional specific clinical criteria. These include failure to respond to optimal medical management for at least 45 of the last 60 days, or they must be balloon pump dependent for the past seven days, or IV inotrope dependent for 14 days. In addition, they must have a left ventricular ejection fraction of less than 25 percent and functional

limitation with a peak oxygen consumption of less than or equal to 14 milliliters per kilogram per minute unless they're balloon pump dependent, inotrope dependent, or unable to perform the test.

So, onto the voting questions for today. This is the scale that will be used for all of the voting questions put before the panel. The scale ranges from one to five with

one being low confidence and five being high confidence.

Voting question number one: How confident are you that there's adequate evidence that specific patient criteria can be used to prospectively identify clinically meaningful changes in health outcomes, either improved, equivalent or worsened, that are likely to be experienced by patients who receive a VAD in addition to optimal medical therapy compared with optimal medical therapy alone?

There are a couple definitions in that question that we have loosely defined for the purposes of this meeting. Health outcomes of interest to CMS specifically are clinically

meaningful changes in mortality, adverse events, patient function and quality of life.

We have defined optimal medical therapy as treatment of contributing comorbidities, the standard lifestyle modifications that you would expect for this population, including dietary intervention, optimization of medical management,

pharmacotherapy, and appropriate use of other devices that are common in this population, including implantable cardiac resynchronization devices, cardioverters-defibrillators or pacemakers.

For this first question on patient selection criteria we have some discussion questions for the panel as well.

A, if there is at least intermediate confidence, mean on the scale of greater than or equal to 2.5 for question one, what prospective patient criteria predicts, one, clinically meaningful improvement in health outcomes; two, equivalent health outcomes; and/or three, clinically meaningful worsening of health outcomes.

B, do these criteria vary if the

intended use of the VAD at the time of implant is, one, bridge-to-transplantation, or two, destination therapy?

The second voting question is: How confident are you that there is adequate evidence that one or more facility and/or operator characteristics predict meaningful

improvements in health outcomes for patients who receive a VAD in addition to optimal medical therapy compared with optimal medical therapy alone?

This question also has discussion questions. A, if there is at least intermediate confidence, mean score greater than or equal to 2.5 in question two, what facility and/or operator characteristics predict clinically meaningful improvements in health outcomes?

B, please discuss the role, if any, of facility VAD-specific certification to assure attainment and maintenance of any characteristics identified in question 2.A.

And C, please discuss the role, if any, of the heart team concept in the management of patients who receive a VAD. The

heart team concept we have defined as a cohesive multidisciplinary team of medical professionals which embodies collaboration and dedication across medical specialties to offer optimal patient-centered care.

Voting question number three: How

confident are you that these conclusions are generalizable to the Medicare beneficiary population?

And the discussion question for voting question three is, which conclusions are likely or unlikely to be generalizable to the Medicare beneficiary population?

And then lastly, voting question number four: How confident are you that clinically significant evidentiary gaps remain regarding the use of VAD? And for discussion, if there is at least intermediate confidence, mean score of greater than or equal to 2.5 in question four, please discuss any significant gaps identified and how CMS might support their closure.

And with what, I'll turn it back over to Dr. Redberg.

DR. REDBERG: Thank you very much, and

I just wanted to introduce Dr. Faught before we start.

DR. FAUGHT: Yes, thanks. My name is Edward Faught, I'm a professor of neurology at Emory University.

DR. REDBERG: Please state if you have any conflicts.

DR. FAUGHT: No conflicts of interest.

DR. REDBERG: Thank you very much. We're pleased now to start the presentations with Dr. Lynne Warner Stevenson, who is professor of medicine at Harvard Medical School, and director of the heart failure program at Brigham and Women's Hospital. Dr. Stevenson.

DR. STEVENSON: Thank you very much. I'm very pleased to have a chance to review and reflect on the progress that we've made and the questions that remain in mechanical circulatory assist devices. I have no financial conflicts, I have no financial relationships with any industry, and I'm pleased to announce that we have tested the system this morning and found that CMS is completely impervious to the introduction of outside information on memory

sticks. So I will ask your indulgence, because the version of the slides that we're talking about this morning is not the final, but I hope I will be able to communicate the appropriate

information for you.

What I would like to review is several things to give you a background in heart failure for our panel and for our audience, who bring many different specialties to bear. I apologize if this is a confusing classification system for different stages of heart failure, which I'll try to walk you through. We'll talk about the general ingredients for medical therapy, the increasing complexity of medical therapy as heart failure progresses, what is reversible with mechanical support, and summarize the options for Stage D or refractory heart failure, and I have no relationships.

So first of all, the population with heart failure, there are about six million patients in the United States with heart failure. This is divided about evenly into patients with a low ejection fraction, a big weak heart, and patients with a preserved ejection fraction and a stiff heart. The only

patients that we're going to be discussing today are the half of the heart failure patients with a low ejection fraction, the big

weak heart as shown in the top. And just for reference, the average age is 74 years old.

So if we look at the common causes of this, previous heart attacks are the most common cause. Dilated cardiomyopathy comes close, and that can be due to viral infection; genetic causes; toxins such as chemotherapy and alcohol, idiopathic, meaning we really don't know, which is a large proportion of this; and also structural heart disease, valve disease and general heart disease.

So let's get into this classification issue. We begin with the New York Heart Class, which basically describes symptoms, going from Class I to IV, and we used that classification when all we had to treat were medicines for symptoms, and so we focused on symptoms, Class I meaning being able to do almost anything, Class II being limited with less than maximal exertion, Class III as being limited with less than ordinary exertion but able to do routine daily activities, Class IV meaning

being limited at rest or limited with minimal exertion such as activities of daily living.

Now that's what we use, and patients can go back and forth, so that you can be IV one day, III the next day, depending on medical therapy.

Then the next classification system of the ACC/AHA stages arose when we had therapy now to actually decrease disease progression even before there were symptoms, so then this different stage came up, and in these stages you only go in one direction. So once you ever have symptoms, you can't go back to an asymptomatic stage. And most important for today, once you develop Stage D, those are Class IV symptoms that are refractory to optimal medical therapy, and in general we assume once you're there, you don't go back. Now you can have Class IV symptoms and be in Stage C and still be able to go back and forth, but once you can no longer be treated and have a better symptom class, then you are Stage D or refractory Class IV symptoms.

Now, then when we developed therapy further, when we had a new therapy for these Class IV Stage D patients, now we have to

divide yet again and come up with another

classification to describe different levels of these refractory patients, and that's where the INTERMACS profiles come up that you'll hear about today. These integrate the severity and tempo of disease so that we can better understand different levels of the Stage D or Class IV patient.

Now the cornerstones of medical therapy for Stage C, symptomatic heart failure, include medications which have a remarkably broad extent of safety and efficacy. These are ACE inhibitors and ARBs, beta blockers, diuretics as needed to control fluid retention, and almost virtually everybody would be on these with symptomatic heart failure.

Now for selected patients there are rhythm devices, implantable defibrillators which can prevent sudden death, and cardiac resynchronization therapy, which is special pacing which improves synchronization of the heart, also called BiV and CRT. There are other medical therapies which are adjunctive in selected patients, aldosterone antagonists and hydralazine nitrates.

Now this becomes very complicated when we actually look at patients who move to the more severe forms of disease. As we move from mild to moderate to severe and into Stage D, you can see that we have these therapies here, but as patients become sicker, in fact many of them don't tolerate some of the cornerstones of medical therapy, so it becomes quite a complex combination of adding and subtracting therapies, so it is not possible to say this is optimal for any given patient who has severe symptoms or is in Stage D.

I was going to show you some pictures of heart failure, the classic Netter pictures, but I will just explain to you what it is like to have heart failure. Patients can be very short of breath, that's usually the most common crippling symptom that can prevent them from breathing at night. This can cause often crippling disability doing any minor activity like trying to get dressed in the morning, often severe fatigue.

Patients can develop symptoms of what we call right-sided heart failure, which is where they have a lot of peripheral edema that

can be very uncomfortable, abdominal congestion which can not only cause discomfort but limit the ability to eat and to be nourished. This is truly one of the most agonizing clinical pictures that we see, very difficult for patients to have a quality of life that is acceptable.

Now one of the things that we look at when a patient progresses into Stage D is what parts of this would be reversible if you could adequately support the hemodynamics and the left heart failure, in fact, one can reverse pretty easily with the kind of mechanical support that Dr. Smith talked with you about, and the secondary pulmonary hypertension, the high pressures in the pulmonary system can usually be improved with the support.

The right heart failure is difficult to predict because there is a component that can be reversed when you support the left side, but the degree to which the right heart has begun to fail can sometimes be unpredictable as to how much better we can make this with left ventricular support, and you'll hear a great deal about this as we go into the results of

VADs.

And particularly when we look at kidney dysfunction, liver dysfunction and malnutrition, we hope those things get better with left ventricular support, but they don't always. Other things are the deconditioning and frailty that develops, it's difficult to predict the degree to which that will improve in someone on left ventricular support, to the point where they might then become eligible for a therapy like transplantation.

One of the most difficult challenges we face outside the medical issues is the exhaustion of the personal and family relationships and coping mechanisms, as well as financial resources, that can certainly limit the potential for future rehabilitation.

So how much of this is reversible? With transplant, with mechanical support, will it be reversible early enough for good outcomes and complete enough for meaningful rehabilitation? Even the best answer that we can come up with, we have to be honest about this, is only an experienced guess. We anticipate the known, the known unknown and the

unknown unknown, and recognize that we never are going to know for sure what will happen with any individual patient.

And just to emphasize again, the left ventricle is only half of the problem. There's a lot of discussion, and you'll hear about that, because the devices support only the left heart, and we have to worry about the right half.

Our options for Stage D therapies, continued vigilance to relieve symptoms of fluid retention with the combination therapies, intravenous inotropic therapy, transplantation, mechanical circulatory support, and a focus on symptom palliation for quality of life through the end of life, which is in fact what is appropriate for most patients. There's poor survival with continuous home inotropic therapy, as shown here in multiple series reviewed, it's less than a 25 percent one-year survival. So this is not a therapy that we consider to be a viable therapy, it is a therapy that we use really just for palliation.

For transplantation, I think most of

the people know here that the results are

excellent. We basically have a ten-year survival now that is better than 50 percent, but of course the applicability is very limited by the number of donor hearts. It's been said that transplant is the answer to heart failure the way that the lottery is the answer to poverty.

This is partly why we've turned to the mechanical support, and I'm just going to briefly mention the INTERMACS profiles here, you'll hear a great deal about this. As I said, these have evolved to help us characterize in a more granular fashion those patients who had previously been characterized as Class IV. There's INTERMACS Level 1, which is crash and burn; INTERMACS Level 2, which is the patients who are sliding fast on inotropic and perhaps other therapy as well; INTERMACS Level 3, stable but inotrope-dependent, either at hospital or at home. And then we move into Class IV symptoms at home on oral therapy, or patients who have Class IV symptoms but are comfortable at rest, and we consider them

housebound.

Just to review, as Kim Smith

elucidated, the patients all meet current CMS indications for VADs, 1, 2 and 3, and 4 and 5 will also meet it if they've have the symptoms for 45 of 60 days and if they have an exercise peak VO2 that's less than 14.

So in terms of the therapies that we are left with after these, hospice is something that we are increasingly using, this is a study from the Medicare database from Pennsylvania and New Jersey, showing that there is a gradual increase in the use of hospice at endstage heart failure, we're actually a long way behind the use of this for cancer patients as shown here, but considerable progress has been made for this.

Because of this interplay between the therapies that we offer patients, it's very important that there be a palliative care program integrated into every place that offers ventricular assist devices. This is data from several years ago from Diane Meier, demonstrating that the vanguard VAD centers in

fact already had an integrated palliative care program as shown by those stars in red across the country.

So just to conclude, I hope I've given you a bit of heart failure background in order to better understand the things that we will be talking about this morning. I apologize again for the confusing classification symptoms for different stages of heart failure, the general ingredients for medical therapy, how that becomes increasingly complex as heart failure progresses, such that it's not possible to say specifically what optimal medical therapy is for any one patient, raised the questions of what is reversible with support, and listed the options for Stage D refractory heart failure.

DR. REDBERG: Thank you, Dr. Stevenson, that was a very clear presentation of what is clearly a complex field in classification. I will say, we can take only after all the speakers present any very brief clarifying questions, but there is time later in the day for an hour of discussion and questions for the speakers.

Next is Dr. Robert Kormos, who is professor of surgery at the University of Pittsburgh Medical Center, and he is the director of the artificial heart program and

codirector of heart transplantation.

Dr. Kormos.

DR. KORMOS: Thank you and good morning. I have been asked by CMS to provide a brief summary of what the field of mechanical circulatory support really is, and I first want to acknowledge that we don't like to duplicate efforts, it's always important that we take advantage of our partners in crime, and so a lot of what I'm going to show you is courtesy of Dr. Frank Pagani, who did a wonderful job in organizing some of this information. The first --

DR. REDBERG: Dr. Kormos, if you don't have any conflicts, would you state that?

DR. KORMOS: Yes, I'm sorry. I do not have a conflict of interest. The first thing I would like to do is help you understand the terminology and the classification of mechanical circulatory support, and we can look

at four boxes here. In the upper left it describes the ventricle that's supported, and this is either the left, the right, or both, and in some cases the total artificial heart where appropriate. Next in the top right panel

you see the anatomical position of the device, which can exist completely outside the body through percutaneous connections or it could be completely inside the body except for some of the electronic components and batteries. We also have devices that are paracorporeal which involve both portions of the pump sitting outside the body and connections inside that require full surgery, and then of course the orthotopic total heart.

We also could look at the intended use and some of this will come out in further discussions this morning, but you can look at the duration of support which can be very short, days or weeks where the patient remains in the hospital, or long-term durable support which is really meant to allow the patient to go home and live with the technology. We can also look at the indications which will be

discussed further, but currently bridge-to-transplant, bridge-to-recovery and destination therapy form the cornerstones of the therapy.

We could also look at pumping mechanism, which is either pulsatile or

continuous flow, and in the pulsatile systems these are electronically or pneumatically driven. On the continuous flow pumps, these are either broken down into axial flow devices which are a rotor that is supported by bearings, or could have magnetic suspension, or a centrifugal design where it's a little more complicated, and there's either a passive or active magnetic levitation system.

Another way to quickly look at this is to look at the continuous flow devices over on the left-hand side, the pulsatile devices on the right, and in the white box in the center you see the short-term devices which we're not going to discuss today, but the longer-term devices required surgical implantation at this period of time.

This is an example of a paracorporeal

device, the Thoratec percutaneous paracorporeal device. This is a device where you can see the connections are to the left ventricle on the first panel, the LVAD, biventricular support as a surrogate for the total artificial heart on the middle panel. And this is a CT scan, again showing you the connections of the LV inflow to

the aorta for the left-sided pump, and the RA or right atrial inflow into the pulmonary artery for the right-sided device.

Now when we move to the field of long-term or durable device, which is what you're going to hear a lot about when we discuss INTERMACS data and we look at other of the more current devices used for bridge-to-transplant or destination, we're really looking at devices that have a durability for somewhere between two, three to five years.

These are intracorporeal, they require operative placement. There may be some minimally invasive techniques that are applicable, but for the most part they require full cardiopulmonary bypass. These devices are

designed both for bridge-to-transplantation and destination therapy and they essentially allow hands free or untethered mobility for up to 12 hours a day because of battery support. This distinguishes the paracorporeal systems which require a controller that you take with the patient that provides an air system or electrical. It also should require minimum

frequent battery changes to allow good quality of life. And most importantly, this allows for home discharge.

This is an example of an axial flow device which has been approved for both bridge-to-transplant and destination therapy, the HeartMate II device. And to understand once again this device, which as Lynne has pointed out, supports the left side of the heart. It acts as a parallel pump, draining blood from the left ventricle and returning it to the ascending aorta in the chest.

The advantages of a pump like this is there are no valves, there is no flexing diaphragm as in a pulsatile system, and it allows you, therefore, to get more complex with

the types of power supply, and this again is a CT scan of that type of device in place.

The continuous flow pumps with axial design include the Thoratec HeartMate II, the Jarvik 2000 FlowMaker, and MicroMed are awaiting FDA approval.

In the centrifugal design we have the HeartWare device shown at the top, and the EvaHeart, which is also under clinical

investigation. The advantage of this device is it's completely within the chest and this has, no pun intended, revolutionized the field because of the shortened operative time and it allows the benefit of not having to do extensive dissection for the pocket, and again, the CT scan.

So in conclusion, I think current mechanical circulatory support system options with durable devices first and foremost require traditional open heart surgery techniques, thus opening up the plethora of adverse events and complications that are associated with open heart surgery. Considerations have to be made for other acquired abnormalities of the heart,

such as patent foramen ovale, tricuspid valve abnormalities and aortic valve insufficiency. And typical perioperative adverse events, which are complex and need to be separated from adverse events of the device itself, include those of bleeding, arrhythmia, right heart failure and infection, which are indeed commonplace in the field. Thank you.

DR. REDBERG: Thank you very much, Dr. Kormos. Next we'll have Dr. Keith Aaronson,

professor of medicine at the University of Michigan Health Systems and medical director of the Heart Failure Program.

DR. AARONSON: Good morning, everyone, and thank you for inviting me to speak to you today. I'm a cardiologist at the University of Michigan. As said, I'm speaking on behalf of CMS. I don't own stock or have any formal financial interest in any company. I have received speaking fees and research grant support from HeartWare, and I don't currently serve on, nor have I previously served on any other advisory committees or panels that considered this topic.

So I will review, start off with a review of devices with one or more pivotal U.S. trials, then review planned studies of full support devices briefly, and then even more briefly, planned studies of partial support devices. I will be talking about survival, adverse outcomes, quality of life and exercise capacity. This presentation will be largely limited to U.S. pivotal trials and their continuous access programs. I will be speaking about published data only except I believe once

when noted, and generally will be avoiding INTERMACS data, as that will be a subject of a longer presentation to follow, but there will be a little bit.

So, these are VADs with FDA-approved indication or published pivotal trials. I mention for historical purposes only the HeartMate XVE, a pulsatile device that was approved both for bridge-to-transplant and destination therapy, Dr. Kormos showed a picture of it a little while ago. This is really for historical purposes at this point because it's no longer produced or sold.

The HeartMate II, also shown, is approved both for BTT and destination therapy, and most of the data that I will show this morning are from that device. There's the HVAD, Dr. Kormos showed that near the end of the presentation, it's another continuous flow device. The FDA recommended its approval in April, it is not yet approved by the FDA, there's a destination therapy trial in progress comparing the HVAD to the HeartMate II, the details are there, and follow-up continues.

These are results for the HeartMate II study, I'm sorry, for the HeartMate II device for bridge-to-transplant looking at survival. There are four studies which I will largely refer to by the names of the first author. The Miller study looked at the pivotal trial population, the primary cohort of that study showed a 68 percent survival. The Pagani paper included that similar cohort as well, as well as about the first half of their continued access program, so about twice the number of patients and nominally higher survival, 74

percent. The Starling paper is the post-approval study as directed by FDA; these data were collected through INTERMACS and showed an 85 percent one-year survival. And then finally, the John paper included data on a large commercial group, commercial implants, and that's the most recent implant group from 2008 to 2010, and again, it showed an 85 percent one-year survival for the commercial group.

If we contrast clinical characteristics in the first paper, the pivotal trial by Miller, and the commercial experience

published by John, you see that age is a little bit higher in the commercial experience group, but the sex breakdown, the New York Heart Association severity in these studies are similar.

Looking at baseline hemodynamics and laboratory values, the hemodynamics are fairly similar between the two groups, perhaps a little more favorable in the commercial group, blood pressure is a little more higher, again, positive prognostically in the commercial

group. The BUN is a little bit lower but AST is higher, bilirubin is higher and serum sodium is a little higher. So things suggesting a somewhat better and somewhat worse prognosis, no clear pattern emerges.

Looking at concomitant medications or interventions, there's some limited data for the commercial group, but the one thing that does stand out is the percentage of patients on balloon pumps is substantially lower in the commercial group.

If one looks at this device, HeartMate II, with respect to destination therapy, the Slaughter paper examined results of the pivotal

trial's primary cohort, 134 patients with one-to-two-year survival of 68 and 58 percent. Subsequently Park published a paper where the results for that group were compared to the roughly first half of their continued access protocol of patients, and in that second group of patients one-to-two-year survival were nominally higher at 73 and 63 percent, although that difference was not statistically significant.

They term these two groups the early trial and the mid trial, so it's the primary cohort versus the first half of the CAP in the second and third columns. Again, comparing the groups, there's no significant difference in age, sex, etiology, the New York Heart Association class. And running through these baseline hemodynamics and laboratory values, again, no differences between the two groups, nor were there differences in concomitant medications or interventions.

With the HeartWare ventricular assist device, the HVAD, as I mentioned, this has been studied, published data for bridge-to-transplant, and that studied the

primary cohort, collected fairly recently in, between 2008 to 2010. There was 86 percent one-year survival. We are presenting data here that are not published from the manufacturer, showing that combining that primary cohort data with the continued access program data, out of 332 patients, one-year survival is 84 percent.

This shows you that there has been improving survival in the LVAD trials over

time. As you look from the bottom to the top on the right, the things that you will note is that the bridge-to-transplant studies appear at the top of the slide overall, so better survival in general for the bridge-to-transplant population, and also better survival with time as a temporal trend.

If one looks at studies in which data are available, that would be the HeartMate II bridge-to-transplant post-approval studies collected through INTERMACS, the HeartMate II DT commercial study, again collected through INTERMACS, and the HVAD bridge-to-transplant pivotal population in which INTERMACS profiles were collected. You see that there's a trend towards less INTERMACS profile 1 patients,

those are the so-called crash and burn patients, the sickest of the group. There is a shift to more patients relative in Class II, and then as you move to HVAD -- profile 2 -- and as you move to the HVAD bridge-to-transplant trial, a further shift toward more profile 3 patients. Looking at profiles 4 through 7, it's slightly under 20

percent in all these trials, enrolled patients who were in profiles 4 through 7.

With regard to the effect of patient-specific characteristics on survival, these next two slides show the effect of gender, and this is showing for the bridge-to-transplant indication, HeartMate II survival was similar for men and for women, and this is from an abstract that was just submitted showing that bridge-to-transplant survival was similar for men and women with the HVAD as well.

Now turning to patient and center characteristics influencing survival, we present the HeartMate II risk score. This was presented -- this is soon to be published -- that was presented at the heart-lung transplant

meeting earlier this year. The goals of this study were to derive and validate a risk model for predicting short- and long-term survival following implantation of the HeartMate II. The data were the clinical trial data from bridge-to-transplant and destination therapy studies with this device, a total of 1,122

patients. Patients were prospectively divided randomly into a derivation and a validation cohort for the model, and multivariant analyses were performed to identify risk factors following LVAD implantation, so these were all pre-implant risk factors. And you see that as INR is higher, as creatinine is higher and as age is greater, the risk for death after implant goes up. Conversely, the better the albumin, the higher the albumin, the lower the risk. Within the period of time in this trial, if you were implanted later in the study you had a lower risk of death, and if your LVAD center volume was 15 or greater during the trials, you had about half the risk of dying, patients had half the risk of dying.

Looking at the derivation and validation cohorts, you see that the risk

groups were statistically significantly different in both cohorts, and that the low risk group was associated with a relatively favorable outcome. If we look at patients over 65, a group that would be relevant to this panel, we see that survival for the low risk

cohort at 12 months was 92 percent versus 81 percent in the medium risk group, and certainly it was lower, around 60 percent in the high risk group.

Now I want to speak about quality of life and functional capacity. This is from the HeartMate II destination therapy program, again comparing the early trials, the primary cohorts in the pivotal trial, the term mid trial here is the first half of the continued access program, and what's shown is the proportion of patients who are New York Heart Association Class I or II, that was zero at the start of the study and as you see, around 80 percent both for the early and mid trial cohorts at six, 12, 18 and 24 months. The number of patients who were available for evaluation is present at the bottom of the slide and obviously there's a survivor effect here in

that we're only judging the Heart Association classes in those who in fact survived.

This shows the overall summary score from the Kansas City Cardiomyopathy Questionnaire. This is a 21-item questionnaire

which received a score of zero to five in each of those 21 items, and the scores can range between zero and 105. Higher scores mean a better heart failure-related quality of life, and you see a dramatic and sustained improvement in the overall summary score for heart failure-related quality of life over the course of the study.

This displays six-minute walk distance for comparative valuation. Patients who do not, were not present for follow-up visits are not included. A value of zero was imputed for patients who could not perform for medical reasons. The number of patients evaluated is present at the bottom of the slide, and again, one sees a very large improvement in six-minute walk distance. To put this in context, the improvement in six-minute walk distance that's seen here with CRT therapy is about 35 to 40 meters.

Now moving to the HVAD and its BTT and CAP evaluation, this has not yet been published, the EQ-5D, the EuroQol is a health utility measure, and the visual analog scale is

one of these thermometers from zero to a hundred, and you see that there's a 26-odd-point improvement in the EQ-5D scores, 62 percent actual improvement, this is an enormous improvement in health utility, and similarly, an improvement in the KCCQ of around 30 points. Improvements in the KCCQ with medical therapies that have been shown to be effective in heart failure are generally on the order of five to ten points.

This shows improvements in six-minute walk distance with the HVAD and the same experience, and an improvement here of a little shy of 200 meters.

I now move on to adverse events. Here we display some of the major adverse events that occur with VAD therapy, the columns are the HeartMate II pivotal primary plus the CAP, or the Pagani paper, the HVAD pivotal primary plus CAP, which is yet unpublished, the HeartMate II destination therapy pivotal

primary data, and the pivotal CAP data.

You see that the number of patients at risk and the patients' years of follow-up

displayed in the second row. Pump replacement ranges from about .04 to .10 per patient year. Ischemic stroke in .05 to .09 per patient year, hemorrhagic stroke from .03 to .09. Hemolysis is reported in .02 to .06. LVAD-related infections remain a substantial problem. I will note that the rate appears to be higher in the primary DT cohort for the HeartMate II as compared to the bridge-to-transplant studies, but did come down substantially in the CAP studies with more experience. Sepsis as well remains an issue with rates from .23 to .38 per patient year, bleeding requiring surgery from .14 to .45, and right heart failure from .13 to .29. It certainly appears to be encouraging that the right heart failure appears to be lower in the later data.

I would note that the destination therapy studies have a lower rate and that's probably a function of patient selection. When we're doing destination therapy we don't have an out as we do with the bridge-to-transplant,

where we can use temporary right-sided support and then transplant that patient.

This compares the early to later experience with the HeartMate II destination therapy and you see that there are either statistically significant or positive trends toward less bleeding requiring transfusion, modestly less ischemic stroke with statistically significantly less hemorrhagic stroke, with driveline infection, sepsis, and non-device-related infections and less right heart failure.

I want to mention a couple of other major complications. RV failure post LVAD is a major source of morbidity and mortality after ventricular assist device implantation. The preimplant diagnosis is challenging. There's a lack of consensus regarding diagnostic criteria. RV failure after LVAD support can be acute, more common, more chronic, lead to a high mortality and substantial morbidity with a prolonged length of stay. There are a host of predictive tools but there's a great deal of room for improvement in those tools.

I will mention one here, the RV

failure risk score, you see the four elements

of that in the upper left, vasopressor requirement, elevation in liver enzymes, bilirubin, elevation in creatinine using, from the logistic regression models, there are points derived from the model for each of those characteristics. Once you combine them to a risk score on the bottom left you can see at the rightmost column there the likelihood ratio for right ventricular failure. So for the high risk group with a score of 5.5 or greater the likely ratio compared to the whole cohort is 7.6, for the low risk group it's .49, so there's a 15-fold difference in risk for those two cohorts.

Since right ventricular failure is such a major possible morbidity or mortality, not surprisingly when we graph Kaplan-Meier survival for those three cohorts we see substantial differences in survival. We note that most or all the mortality here, or nearly all, was occurring in about the first three weeks.

Bleeding following left ventricular assist device implantation is a problem. The

incidence of nonsurgical bleeding post-LVAD occurs in about a third to half of patients, with the most common manifestation GI bleeding. About half of bleeds occur within two to four months of LVAD implant, and the bleeding does appear to be greater with continuous flow devices than pulsatile devices, and I would add that I wish we had updated that slide to see if that would be true of every continuous flow device.

The cause for increased bleeding includes the fact that these patients all require anticoagulation and antiplatelet therapy. There certainly are patients that are managed without each of those, and we generally suffer the consequences of doing that.

There is also an acquired bleeding diathesis because of this issue of von Willebrand factor multimers, this factor is created as a monomer and it's not biologically active, it combines to form multimers, but the sheer force of blood flowing through these devices at high RPMs, those von Willebrand multimers are both down.

There's also increased development of

AV malformations. We believe that's a function of the reduction in pulsatility that one sees with continuous flow devices, similar to what's been observed to a greater extent than what's been observed with aortic stenosis.

This is a study from Columbia showing that bleeding does increase with age, with increased age.

This is, this was presented by Stuart Russell from the HeartMate II clinical experience. You see a host of univariable predictors of GI bleeding on the right, and you see four multivariable predictors, increased age, lower albumin, female sex and ischemic etiology, all are associated with an increased risk of bleeding in the multivariable analyses.

I mentioned earlier that infection is a significant morbidity, as is, as are stroke and pump thrombosis, and pump thrombus and stroke are more likely to occur if there is an infection. So during a 14-day window around an infection, patients were four times more likely to have a hemorraghic stroke, eight times more likely to have an ischemic stroke, and nine times more likely to experience a pump thrombus

event.

Aortic insufficiency can occur during LVAD support. I don't know if this cartoon is going to work if I click, no. But in any case, one can set up a vicious cycle where blood is returned from, taken from the left ventricle and returned to the ascending aorta and then it is generated back into the ventricle as a result of aortic insufficiency. And in this analysis from Columbia, the freedom from AI was lower in continuous flow pumps than in a pulsatile flow pump. There's my little cartoon.

There are a number of planned studies of full support VAD. The Jarvik 2000 is a continuous axial flow device. Pivotal study is in progress for bridge-to-transplant, actually the primary sample cohort was completed in May. A pivotal study is planned comparing, a randomized controlled trial comparing to the HeartMate II.

The HeartMate III, a continuous flow centrifugal pump, you see there the dates of studies planned in the U.S. and Europe for both BTT and DT indications.

The MVAD is a very small axial flow pump. Studies are planned with it in the pericardial position as well as a study of the same, essentially the same device on a long stalk in which it's placed across, through the apex across the aortic valve.

And then the DuraHeart II, a continuous centrifugal flow pump, has both BTT and DT pivotal studies planned.

There are also planned studies of partial support VADs. The Circulite, a Synergy pump, Circulite is a small axial flow pump providing partial support. There's a feasibility study planned for all three, bridge-to-transplant, destination therapy, and something we haven't talked about, bridge-to-decision patients.

As well as a study of another partial support device, the C-Pulse device, which is a device that provides counterpulsation by pulsing the aorta externally, and again, pivotal studies planned.

There are also ongoing or planned destination therapy studies for less advanced

heart failure, ROADMAP and REVIVE-IT. ROADMAP

is an observational study enrolling patients with New York Heart Association Class IIIB or Class IV who are not requiring inotrope, and REVIVE-IT will be a randomized clinical trial versus optimal medical management in selected New York Heart Association Class III patients, selected largely on the basis of the Seattle Heart Failure Model score and exercise capacity.

A little bit about ROADMAP, which is a prospective multicenter industry-sponsored nonrandomized controlled observational study to look at the effectiveness of the HeartMate II device versus optimal medical therapy. I mentioned the New York Heart Association class, not dependent on inotropic support, you have to meet FDA-approved indications. 40 centers, 12 referring community sites, the target enrollment of 200. As of October 16th, 57 patients were enrolled at 25 sites.

REVIVE-IT was awarded to the University of Michigan and University of Pittsburgh in response to an RFA from the

NHLBI. It's a pilot open-label randomized clinical trial testing the strategy of early

LVAD versus optimal medical management in patients not transplant eligible, ambulatory systolic heart failure Class III and up on medications, no inotropes. Seattle Heart Failure Model based estimates of survival, enrolling patients with an estimated one-year mortality expected to be 17 percent or higher. One-to-one randomization to eachf strategy, so patients in the medical management arm could receive an LVAD if they meet standard contemporary destination therapy criteria. It will be an intention to treat analysis. The screen failures will be entered into a registry. We estimate this will include as many as 2,500 patients and it will be evaluating prognostic information including biomarkers in this larger and more heterogeneous group, which I think will be of interest perhaps to this panel at a future date.

The primary outcome for REVIVE-IT will be evaluated at two years and include the

composite outcome of survival and freedom from disabling stroke defined as a Modified Rankin Scale score of three or greater, and an

improvement of six-minute walk distance by 75 meters or greater from prerandomization baseline.

So in summary, durable implanted left ventricular assist devices have very high survival to transplant when used in the BTT indications. Survival when used for destination therapy is improving, likely as a result of better patient selection and management. Major adverse events include stroke, bleeding, infection, right heart failure, pump thrombus and aortic insufficiency, and in some of these we clearly have a long way to go. There are very large improvements in quality of life and functional capacity despite these adverse events, and there are studies planned in patients with less advanced heart failure with existing full flow devices as well as with partial flow devices. Thank you very much.

DR. REDBERG: Thank you, Dr. Aaronson,

that was excellent.

Next we'll hear from Dr. James Kirklin, professor of surgery at the University of Alabama at Birmingham, and director of the

division of cardiothoracic surgery, and Dr. David Naftel, professor of surgery and professor of biostatistics at the University of Alabama at Birmingham.

DR. NAFTEL: Thank you for this opportunity for me to present the introduction to the INTERMACS registry. I'm speaking on behalf of a large team of researchers and I'll give the introduction, and then Dr. Kirklin will give the full results.

Under disclosures, it's important to note that INTERMACS was originally funded by NIH. We're now in a second funding period where the funding is a cost sharing approach with NIH, hospitals that participate and industry. Beyond that the specific disclosures, I will speak for Dr. Kirklin, he has none, and then I'm a statistical consultant to several of the companies.

So, this registry is a partnership of

the entire community of VAD, of MCSD professionals in the country, so we have CMS, NHLBI, FDA, and then we have a number of hospitals, we're up to 144, I believe, we have industry involved, and then a large community

of clinicians. The original contract started in 2005 and went for five years. Now we're in a second contract and we certainly have a long-term business plan to continue INTERMACS into the foreseeable future. As of a couple days ago we had 144 hospitals and over 8,000 patients in this registry.

The goals of the registry have remained consistent throughout the whole time period and I believe they fit in very closely to the questions that have been posed to the panel. First of all, we're here to facilitate the refinement of patient selection to maximize outcomes with current and new devices. We attempt to identify predictors of good outcomes as well as risk factors for adverse events. We continue to work on developing consensus for best practice guidelines. We hope to and we've worked with companies to guide clinical

application and evolution of next generation devices, and then to specifically use registry information to guide improvement in technology.

The startup was relatively fast, it has picked up speed. The red line is the approved patients over the entire time period,

the blue line contains the cumulative hospitals across time. And the little dips that you see, that's in response to protocol revisions as we monitor the entire IRB process. INTERMACS has turned into a very large and we think a very good registry; however, we judge our registry by the same criteria that you would judge a clinical trial. We do everything we can to be like a clinical trial, knowing that we'll never meet those standards, but it's a good standard to set, I think, for any registry.

Just a few of the limitations and constraints. We have none of the device trial data, some of which you have just seen. We require informed consent of the patient and that acts as a filter. We have no formal adjudications of adverse events. We are living, as you know, in a very dynamic

landscape. The devices are changing, patient selection are changing. We do have the issue of hospital resources where the hospitals have to pay to be part of this registry and of course they have to find the resources to enter the data, and that is a challenge and a challenge that we try to meet daily. And then

we have to obviously work within HIPAA constraints and information security.

If you look on the other side of the slide, just a few of the advantages, we have, all of the DT hospitals are part of INTERMACS and that is required by CMS. Even though we don't have adjudication, we do have clinical review of the major adverse events by a team of 12 clinicians that look for internal consistency within the database. As near as we can tell by working with industry and getting their implant counts across the country, we have, it looks like 85 percent of the nation's device implants. And even though it's a dynamic landscape, an advantage of INTERMACS is that it's an opportunity for real world analysis to see what's really going on.

The database is audited, we have four full-time nurse monitors and that's about to move to six. We have quality assurance reports to the hospitals to give them a chance to see how they compare to INTERMACS and also, it's a way for them to see their data and react if the data are not correct and need some help. A huge advantage is that we do work with NIH and

FDA and CMS, so we have this coalition of federal partners that helps strengthen the database. And probably the biggest advantage of the entire registry is that we do have the involvement of the entire MCSD community.

So now, Dr. Kirklin will take over.

DR. KIRKLIN: Thank you very much. As David said, I have no conflicts.

So what we're going to do now is to present some analyses that are in the recent era of INTERMACS that I think will be most relevant to your deliberations today, and at the end I'm going to summarize some of the points which I think will highlight our analyses.

So the first slide here, you see is an

indication of the kinds of devices that have been implanted by year in INTERMACS, and what I want to emphasize is in the current era among adult patients, the vast majority of patients receive continuous flow devices, as you can see in red, and that is current since the introduction of the first continuous flow approved device in 2008. Similarly for destination therapy, we are talking really

solely in the current era about continuous flow pumps.

If we look at the evolution of destination therapy, another important fact to realize is that in the current era, as you can see in the boxes, destination therapy now accounts for over 40 percent of pumps implanted in the United States.

Survival. So these are actuarial, stratified actuarial depictions stratified by left ventricular assist device primarily, total artificial heart, and biventricular devices over the entire duration of INTERMACS, and one can see immediately that there's a decline in survival compared to isolated VADs when you

look at artificial hearts or biventricular support.

Continuous flow technology has been well demonstrated to be superior to other types of technology at least as collected in INTERMACS, and the survival curve for continuous flow pumps is indicated in the blue line, and so the risk factor analyses that we're going to present to you today are going to be solely on continuous flow technology.

So, this is the overall survival curve for continuous flow technology since June of 2006, and note that the one-year actuarial survival for all pumps, realizing that bridge-to-transplant therapy are censored at transplant, is 80 percent at 12 months and 70 percent at two years.

So now we're going to talk about some risk factor analyses, multivariable analyses and hazard function domain, and these are the general categories of variables that were entered into the analyses. This is the results of that risk factor analyses. And so of importance, you can see that there are, we've

organized the variables into what I think may be meaningful categories as you think about the role of this device therapy. Note that there is an early phase of risk which practically speaking is about the first two months after implantation, and that merges with a constant phase of risk factors which are present, of course, throughout the patient's experience as long as they have been followed.

So in this presentation we're going to go through various aspects and then supplement

the risk factor analysis by showing you two things. One is some stratified actuarials, which of course will be risk unadjusted but intended to show relationships between variables, and the second will be solutions to the multivariable analyses, so-called nomograms, which will depict those solutions that allow us to get a better picture of relationships between some of these risk factors.

So let's first look at age, and of course this has particular relevance because I know that you are interested in the Medicare

population. So this is a stratified actuarial looking at continuous flow technology, and you can see that there is some decrement in survival for patients over 65 years of age that is most prominent early, and then after the early phase at least for overall patient population, there's not any appreciable difference in survival after that.

Now it's of some interest as to whether there is an important further risk after, say age 70, so if you look at those patients who are stratified, again stratified

actuarial, there's no apparent difference at least among those patients who were selected for device therapy in the United States among those patients between 65 and 70 and those over 70 years, realizing of importance, those were the patients who the clinicians actually selected for device therapy.

So this is a solution of the multivariable equation looking at age along the horizontal axis and the probability of death for one, two and three years, and you can see that the patients over 65 years of age do have

a small increment in likely mortality but it is relatively small.

So now let's look at what information we have for you on INTERMACS level. As you know, and as Lynne Warner Stevenson indicated, levels are a refinement of New York Heart Association Class IV, and specifically, level 1 indicates those patients who are critically ill in shock, level 2 indicates those patients who have rapid cardiovascular deterioration, unstable, and we can see that the impact of those risk factors in this early phase. And of importance, the impact of this knowledge is

such that in the experience over the last year and a half even, there has been a gradual reduction in the proportion of patients who are implanted in cardiogenic shock, so that now it sits at about 16 percent of patients are implanted in cardiogenic shock.

If we look at the actuarial difference in survival, the effect of level 1, shock, is most pronounced early. It's not terribly dramatic, although it's quite important compared to the upper black curve, which are

the stable levels 4 through 7. After the early phase, though, you can see why it is not identified as a risk factor in the constant phase because the survival curves are quite parallel after the first several months.

If we look at the interaction between age along the horizontal axis and these levels on probability of death by one year, one can see that for elderly patients that they are particularly susceptible to multiorgan system dysfunction that has occurred in patients who are in shock, and they appear to be particularly vulnerable to death if they are implanted in the more critical levels of 1 and

2, compared to younger patients.

Destination therapy. There is a clear, small but real difference in survival with destination therapy compared to bridge-to-transplant therapy, although it is very important to remember that in actuarial depictions BTT patients are censored at transplant, so there is the opportunity of patients to develop complications which could be life-threatening or life-limiting, though

they can be saved with a heart transplant in the BTT group. Here is a depiction looking at the relatively small differences, however, at least based on the multivariable between these two populations in relationship to age at implant.

So let's look at a little information about renal dysfunction, which we know is a very important predictor of bad outcomes, both in heart failure and in device therapy. This is, again, risk unadjusted stratified by severity of renal dysfunction. If you have moderate categories of dysfunction, here defined by creatinine as greater than two or BUN greater than 60, you can see that there's a

small decrement in survival, but a very major decrement in survival in the green line if patients are on dialysis around the time of implant.

Right ventricular dysfunction. So we have categorized these variables in relationship to their probable association with right ventricular dysfunction, as you can see, and again, we've tried to give you some sense

of mild, moderate and severe categories, severe being the need for a biventricular assist support, moderate as you can see, by RAP greater than 18, bilirubin over two, presence of ascites. So again, moderate has some decrement, but a major decrement to survival if you require a right ventricular assist device.

And then surgical complexities, whether the patients have had previous cardiac surgery or if they have concomitant cardiac surgery, these are known to be risk factors but their impact, interestingly, is relatively small. This is, again, a solution for the multivariable, and you can see that throughout the age display along the horizontal axis, that there is a small consistent increase of risk

but it's not major.

So now let's look in a little more detail at the peer group of patients who received destination therapy. This is an analysis which was analyzed and presented at the American Association of Thoracic Surgeons that we'll share with you to give you some insight about the group of patients receiving

planned permanent therapy with devices. This is the stratified actuarial depiction and the hazard function below, indicating the higher early risk, and I want to emphasize the one-year survival in this entire group.

Now I want to make sure that I'm clear. Destination therapy in these first few slides will include both pulsatile and continuous flow pumps over the duration of the INTERMACS project. So 75 percent one-year survival, 62 percent two-year survival. If we look at continuous flow pumps, we can see immediately their superiority, and particularly bad is biventricular support with pulsatile technology.

So if we look at continuous flow pumps, we can see that in this overall

experience for destination therapy the one-year survival was about 76 percent. Age at implantation, again a risk factor, but relatively small, so you can see that the curves are bunched quite tightly together for those patients under 60, 60 to 70, and greater than 70 years, so inferences about the Medicare

population.

INTERMACS levels for destination therapy mirror those for the overall group. Note the decreased survival in level 1. And as we project to the future, we've circled here the more or less average two-year survival after transplantation based on ISHLT information, and you can see it's about 80 percent at two years. So if we use that as a comparison for strategy of destination therapy seeking risk factors that might identify groups who are particularly favorable with permanent device therapy, so that we could potentially begin to have a conversation about triaging patients. This is a risk factor analysis which shows the same general risk factors as were present for the entire group, age, history of certain medical problems, renal dysfunction,

INTERMACS levels, pulsatile therapy and so on.

So for example, if we look at the impact of previous cardiac surgery, this is a group now of patients solving the multivariable analyses in which we're looking at lower risk, that is, not on dialysis, don't have cancer,

they receive a continuous flow pump, no bi-VADs, and relatively normal renal function. And we can see that for patients who have previous cardiac surgery, you do not really approach that two-year mortality of 20 percent or less until you're less than about age 40, but without previous cardiac surgery that occurs if you're less than about age 65.

So of some importance is to scrutinize this database and these risk factors to see what proportion of patients might be potentially competitive in a conversation about triaging from heart transplantation. So if we look at the low risk group with the risk factors essentially being no, without previous cardiac surgery, that there are about, under 20 percent, so almost 20 percent of those patients who are stable, that is not in levels 1 and 2, will achieve an 80 percent two-year survival

and would therefore potentially be part of a conversation about the overall management between transplantation and mechanical support.

So let's turn to some adverse events. These apply now only to continuous flow

technology. So freedom from stroke in this database is about 89 percent at one year. Freedom from pump thrombosis, about 95 percent at one year. Now, we wanted to put this slide in to emphasize the very important difference in the requirement of device exchange or device failure contributing to death, relatively low with continuous flow pumps, dramatically different from the previous era of pulsatile technology.

Let's look at the right ventricular failure, that is the need for right ventricular assist device. We note that there is an important interaction, as would be expected, between how sick the patient is. So those patients who are in shock, they have only about a 91 percent freedom from needing a device, and of course it gets much better, that freedom, when you have less ill patients.

If we look at moderate or severe, that

is signs of right ventricular failure but not requiring biventricular support, then you can see that the same basic relationship holds, that is, those patients who are deteriorating

or in shock have the worst freedom from right ventricular dysfunction. And if we look at risk factors, we again see that those signs of right ventricular dysfunction before the implant are important, there is a clear interaction between renal dysfunction, and then the lower two, the sicker the patients, the greater the probability of right ventricular problems.

Pump-related infection. Well, there is endocarditis, infection on the inside of the pump or the inside of the heart, pocket infections and driveline, and clearly the only one that's important is driveline infections in the blue line, and you can see that there's a very important, probably 30 percent actuarial probability of having driveline infections by the first year.

Now one thing that's going to be very apparent as we move forward in the kinds of analyses that we will be doing is some notion

of an adverse event burden, if you will. Now we are very early in our attempts to depict what a burden of all adverse events might be to

a patient, but this is just the first pass looking at freedom from occurrence of infection, bleeding, device malfunction, stroke or death, and we can see that we have, you know, important ongoing issues. If we look at all of them, any of them, at the end of the first year there is about a 30 percent freedom from any of these. Now remember, at least in this depiction infection could be any infection, it's not necessarily just device-related infection or bleeding, so these aren't all equivalent, of course. This is the first attempt to show you both the magnitude of the cumulative effect perhaps of any adverse event, and to begin to look at who might be more vulnerable.

It's interesting that if we look at age, there's, the freedom from any event is not much different whether you're under 50 or over 65. It's not terribly different according to your INTERMACS level. Obviously INTERMACS level 1 has a greater chance of dying, but

other than that you don't accumulate or have less freedom from these adverse events than

other levels.

There is a major difference with bi-VAD therapy, that seems to be particularly prone to developing adverse events. But here in a very detailed depiction of the levels, we can see they're all bunched together and there's not really much difference in terms of freedom from specifically pump-related infection.

So let's look at a little bit of information that we have about quality of life. This is looking at the dimension of self-care, the dark blue indicates freedom from extreme problems, and at least in terms of extreme problems we can see there's a very significant improvement in the freedom from extreme problems which is sustained out to about a year. The same is true with usual activities; if you were severely constrained from being able to carry out usual activities there's a prompt improvement, which again is sustained out to the first 12 months.

If we look at the visual analog, and

that's the so-called thermometer that patients

roughly gauge their quality of life, and the visual analog scale is promptly improved after implant at the first three months, and is sustained out to the end of the first year.

Now some comments about knowledge gaps. One of the important questions you're asked to reflect about is medical treatment. Well, there is a dearth of medical treatment knowledge about many of these categories of level 4 -- sorry -- of New York Heart Association Class IV. Clearly medical therapy is known to be, in the current era at least, very suboptimal for INTERMACS levels 1 through 3. Lynne Warner Stevenson is heading up a very important effort sponsored by the NHLBI to develop a closely followed medical cohort of patients in INTERMACS levels 4 through 7 called MedaMACS. That is being initiated, so we look forward to good evidence about how these patients do in the same types of detailed analyses which are available through INTERMACS but currently that's not available.

Functional capacity data is sparse in

INTERMACS, and I draw your attention under the six-minute walk and the VO2 max about the percent column. Those are the percentage of patients who would be potentially available for that data who actually have that data entered into INTERMACS and you can see that it's low. So this is an important knowledge gap that remains to be filled in.

So in summary, these are -- there's a lot of information that I've presented this morning and of course it's all available to you, but in summary a few things that we believe we can infer from these analyses:

One, INTERMACS has the best available data to examine risk factors for survival as the primary marker of health outcomes. In the current era, discussions of outcomes and risk factors for device therapy in adults can largely be restricted to continuous flow devices. Destination therapy currently accounts for the primary strategy in more than 40 percent of approval of durable device implants. The Medicare population, aged 65 and older, have slightly reduced survival during the first six months post-implant but

thereafter the risk of death appears equivalent to younger age groups. Patients over 70 years that are selected for VAD therapy appear to enjoy survival similar, at least as far as those patients selected, to patients aged 65 to 70. Patients over 65 years of age are at particular risk for death if implanted in INTERMACS levels 1 and 2. Actuarial survival with destination therapy is slightly worse than bridge-to-transplant therapy, but remember, those patients are censored at transplant. And moderate right ventricular dysfunction or renal dysfunction at moderate levels have a modest negative impact on survival, but dialysis or RVAD requirement profoundly worsened survival.

INTERMACS level 1, patients are at greater risk of early mortality but thereafter their survival is reasonably similar to other levels. Among destination therapy patients the inferences regarding risk factors and outcomes for the overall population are generally applicable to the Medicare population. Among destination therapy patients in levels greater than 3, nearly 20 percent have an expected survival of 80 percent or more

at two years, which could be relevant to a conversation about rational triage of some patients from transplant lists.

Quality of life indicators suggest sustained improvement to at least one year post-implant. And finally, measures of overall burden of adverse events will shape the comparison of this therapy with others in the future. Thank you.

DR. REDBERG: Thank you, Dr. Kirklin, for a very helpful discussion of the INTERMACS registry. We will now return to Dr. Lynne Warner Stevenson for our last presentation before a few brief clarifying questions and then break.

DR. STEVENSON: Thank you very much. Well, I hope that I will speak for those other heart failure cardiologists in the room as well. I'm going to try to walk with you through how a heart failure cardiologist approaches decisions regarding individual patients. I'm intrigued by what I'm seeing on the monitor up here.

Let me just tell you that we try to do several things, and although I will discuss

them sequentially, in fact we do them at the same time when we evaluate a patient for ventricular assist devices. We're first of all evaluating whether we can optimize their medical therapy, and then we're trying to evaluate whether the patient is healthy enough to have a VAD and are they sick enough to have a VAD. Even while we're doing this, we're trying to begin providing the patient himself with information that will enable us to proceed with shared decision-making once we come up with whether or not he's eligible for a VAD.

The concept of triage, I think developed in World War I, is really crucial here to distinguish the patients in fact who may benefit from a very high level intervention from those patients who are so sick that they won't benefit from anything, and those patients who are healthy enough that they don't need anything done at the moment and are doing well on their chronic therapy without another intervention.

So let me just remind you when we talk about Class IV heart failure, which is defined

as disabling symptoms at rest or with minimal

exertion such as activities of daily living, this is a depiction from a standard textbook which just shows how imprecise the Class IV definition is. You can see that the mortality here extends all the way from 50 percent at a year down to immediate mortality. You can see why the INTERMACS profiles provide us with more granularity, and I want to recognize both Dr. Mariell Jessup and Ileana Pina for having contributed to the initial definition and establishment of these profiles.

So when we're looking now, let's talk about first the profile 1. In this patient we're assuming that he's extremely unlikely to survive without a VAD. Similarly to profile 2, we know from the REMATCH and INTREPID trials they are truly unlikely to survive without a VAD, maybe one-year survival at most 10 to 20 percent. So when survival without a VAD is close to zero percent, we really don't care a lot about what it is. What we want to know is the absolute survival with the VAD, that's all we need to know.

And I have approximated these numbers here, they may not be exactly what you saw from

Dr. Aaronson and Dr. Kirklin, but just for the point of argument. So it's pretty clear that if a patient is eligible, you would want to go for a VAD for these two.

So now let's talk about moving to profile 3. As I told you before, multiple series have shown very poor survival on continuous home IV inotropic therapy, less than 25 percent at one year, so once again, it's pretty clear that if this patient is eligible for a VAD, we would want to do that, the outcomes with VAD being even better in the profile 3 patients.

But now let's move on to the other, and you can see here from the INTERMACS registry, we only have 13 percent of those patients who are in profile 4, so now we're getting down to significantly smaller numbers. So let's look at what we know about with their likely survival at a year without a VAD.

This is a number of trials of oral therapies of what's called Class IV heart

failure, and once again you can see that the one-year survival is varying here from 50 percent to 85 percent depending on how people

define Class IV heart failure, making it very clear that we need to know more about the specifics of this population.

In the REMATCH destination study we have a small number of patients who in fact were not on inotropic therapy, they were on oral therapy only, so we do have that to try to fill in this box a little bit, and that was 40 percent at one year. I wouldn't be too reassured by that number because in fact that's only 15 patients, even though it makes a nice graph, so we really don't know much about the medical survival there, and now the difference becomes very important because we're no longer looking at such a small survival without VAD. But again, we're pretty reassured from what we've seen that there's very good survival in this population even though we don't have very large numbers yet, around 80 percent and 75 percent. So still it looks like a pretty significant survival advantage that as

cardiologists we are pretty comfortable that a VAD offers a lot in terms of survival.

I want to make a couple of comments about peak oxygen consumption, because this is

what is used to try to now define patients who are less sick than this. It's objective and reproducible, it describes both the functional capacity and prognosis, and integrates many cardiac and noncardiac factors. For REMATCH as a historical point, actually the real cutoff through most of the trial was a peak VO2 of 12, it was late in the trial that it increased to 14, and only a couple of patients actually got in with a peak VO2 between 12 and 14.

It is highly dependent on heart rate increase during exercise which is blocked by beta blockers. However, beta blockers also improved survival, so we have a bit of a paradox here to think about when you're looking at your patients using the peak VO2 now to try and see if they're eligible for VAD.

This is data from Butler on the left showing that if you have a peak oxygen between 10 and 14 and are on beta blockers that you

have an 81 percent one-year survival on medical therapy. On the right the O'Neill study shows that if your peak VO2 is less than 14 but you're on a beta blocker, you have a survival over 80 percent at three years. So this does

suggest that in our patients who are able to tolerate beta blockers, that using the peak VO2 cutoff of 14 may in fact give us some patients whose survival would still be pretty good on medical therapy but again, important to remember that most of the patients we are considering for VAD are not usually tolerating very high doses of beta blockers if at all.

So when we look at our first knowledge gap here from the standpoint of a cardiologist looking at a patient, in our housebound and walking wounded patients, they really stand at the edge of our current indications. If an ambulatory patient is comfortable resting at home on oral therapy and meets the VAD criteria with a peak VO2, what's the difference in anticipated survival with a VAD versus no VAD? And as soon as we move into an area where survival on medical therapy is more likely than

death, then we start being more concerned about early postoperative risk that could potentially shorten their survival for some patients, and we want to know more about does this patient lose if we wait until he or she gets sick, perhaps moves into a profile 3 or 4, and if we

do lose something, how much do we lose. So this patient now, the housebound and walking wounded, the profile 5 really stands right at the edge of our current indications in terms of what we should do as a cardiologist.

As Dr. Kirklin mentioned, MedaMACS has been developed to try to give us some information on the parallel outcomes in this group. It's a pilot study of ambulatory patients on oral medical therapy at U.S. transplant and VAD centers who have multiple high risk features for events. There was a screening pilot which was done led by Garrett Stewart, and now as you heard, there will be an initiation of an NHLBI and Thoratec-sponsored study of 300 ambulatory patients to try and fill in these boxes for the patients who are not in profiles 1, 2 and 3. They're designed

to be parallel with the INTERMACS data.

This just gives you some idea of when initial screening studies on this looking at patients who are on oral therapy now, you can see in the red line that those patients who are profile 4 had a very high event rate at six months of death, VAD or transplant. Once we

move into the profile 5, 6 or 7 the rate of events is much lower but it's still significant. I think this just highlights how important it's going to be to do the full study and get this information.

What about outcomes beyond survival? The patient clearly would like to live but really only if the quality of life is good and they're not severely limited. I'm going to show you the same table with the INTERMACS profiles but now basically with less information. So what we see now is not survival but looking at quality of life. If we look at profiles 1 and 2, obviously the quality of life really we can't even measure because the patients aren't alive. We have small numbers in those groups indicating on the scale

of zero to 100 on the EuroQol, pretty good outcomes for the profile 1 and 2 who survive in terms of, in that first column, 85 on a scale of a hundred; slightly less for the profile 2, 76 on a scale of a hundred; and 76 for the profile 3, all pretty reasonable.

You can see if we look at another question from this, which is the percent of

patients who have problems with their usual activities when they have the VAD, very very small numbers for level 1, so I wouldn't even really want to look at those. But if we look at level 2 and 3, 40 percent of patients describe problems with their usual activities with a VAD, and this was 55 percent in a small study done by Kathy Grady looking at the profile 4 patients.

This becomes something that we need to know about as we're looking at patients who are in these less sick profiles. The only data we have at the moment to compare it with is looking in this MedaMACS screening pilot in which the quality of life when they were enrolled was on the EuroQol about 51, which is

clearly not as good as the 70 which could be achieved with a VAD. But I think this just highlights how we need to know this information in order to have a better feeling for what quality of life might be in these ambulatory patients that go on to VAD.

So, our second knowledge gap in the housebound and the walking wounded, they stand at the edge of current indications not only for

survival but both for quality of life benefits, so what is the difference in the quality of life with and without a VAD? We have very little information on this. So the patient stands, again, at the edge of current indications in terms of whether a VAD is expected to improve their overall quality of life and ability to do the desired activities.

So we've talked about is the patient sick enough. I want to mention is the patient healthy enough but not in much detail, I think that's been very well reviewed by both Dr. Aaronson and Dr. Kirklin. There are many many things which we need to consider in terms of other organ functions in the

non-cardiovascular considerations, and then right ventricular function being the most important thing with the cardiac considerations.

And just to emphasize, many of these risk factors that predict bad outcomes with VAD also predict bad outcomes on medical therapy, so it becomes quite a complex balance of trying to sort this out.

I just want to put this up here to

remind you how complicated this is. This is a lot of factors that have to be taken into account. How do you suppose we're going to put these together as we move forward and I'm one doctor making a decision for one patient? Well, first of all, I want to remind you that we have this relatively difficult classification at the moment in which when we looked at before 2001 we didn't have very many destination patients, but we already had a significant number of patients who were the bridge-to-decision, the so-called uncertain. We saw some relative contraindications, weren't sure if they'd get better on a VAD, and let

them qualify for transplant or not. As we look now in 2011 and 2012, we're clearly having more of the destination therapy as shown in the blue, but we continue to have about a third of patients in whom we don't know at the time we put the VAD in if the relative contraindications are going to sort themselves out enough so that this patient will be a candidate for transplant.

So when we look back, we've been doing transplants now for over 30 years. Where have

we come to with VAD? Well, this is evolving much the same way. For transplant we have only a few absolute contraindications, we have lots of relative contraindications. It's not only having a certain other problem, it's the degree of severity of the other organ system dysfunction, do we have RV dysfunction that we talked about, but often it's the combined impact. For instance, the patient had a mild stroke, we're not sure about the support at home, they have borderline RV function and chronic renal impairment, and it's very difficult to put all these together and sort

out the chances for reversibility with LVAD support. And for VAD we have the additional complexity regarding the option of heart transplant as either a best option, or could we do a transplant as a bailout in case things aren't going well with the VAD.

I do not anticipate that we are ever going to come up with one risk score that is going to define whether the single patient standing in front of me is going to be eligible for a VAD or not with these multiple relative contraindications, and I would ask the panel to

think about whether it's more realistic to establish the criteria of center experience for patients to be evaluated, or to dictate precise combinations of contraindications which has certainly not been comfortable for cardiac transplantation.

So we talked about making a decision about the patient, but ultimately we need to make a decision not for the patient but with the patient, and this process of shared decision-making is something that we're gradually learning more and more about. So

what do we have to tell the patient to help them make a decision? There are multiple dimensions which are important to them besides just survival.

We've talked about quality of life and physical function, but there are also other costs and burdens which are very important to an individual patient, so it is not easy to predict exactly what's going to be most relevant to them in making a decision when we talk about these patients who have ambulatory heart failure.

In the MedaMACS screening pilot,

patients with advanced heart failure were asked what would be most important to you in understanding about whether or not you wanted to have a ventricular assist device, and you can see on the left that the vast majority of patients said that survival and quality of life would be equally important, very few patients feeling that one would be dominant.

We looked in that same group about, we gave them a very simple set of information about VADs and then asked their level of

enthusiasm, and you can see that 37 of patients in profile 4 indicated they definitely would be interested in a VAD, and then as the patients became less sick, the interest declined.

There has been, from the Institute of Medicine, a high priority on the issue of individualized medicine and patient-centered care. Harlan Krumholz has put forth a standard informed consent that we should be more and more looking for when we talk about doing advanced procedures with any disease, but I have looked at this particularly in relation to heart failure and adapted it. When talking to a patient and trying to help them make a

decision, in addition to the background and general benefits and risks, we should be able to translate the information that we have to tell them of a hundred patients like you, this many lived two years longer with a VAD, of a hundred patients like you, this many rated their daily activities near normal, this many had strokes that limited their ability to speak, walk or care for themselves. And perhaps to summarize that, of a hundred

patients like you, this many indicated after a year that they were satisfied with the outcome of their therapy and would recommend it to someone else. In INTERMACS Version 2.0 we in fact will have questions of patients who have had VADs that will indicate how they feel specifically about their satisfaction with their therapy and if they would recommend it.

I can't emphasize enough that when we think particularly about the complex technology of VADs, the Medicare population, that coping by patient caregivers has consistently been found to require more than we would have anticipated. Often patients when faced with this decision may reluctantly elect to go with

the VAD because they don't know what else is available, so we think it's really important that patients understand the other options available to them. They may fear isolation and suffering if they do not choose to have a VAD, and this is why most heart teams involved with VADs have recognized the vital role of the palliative care team working closely with the VAD members.

So, this role is important not only to help the patient make decisions consistent with their lifestyle preferences and goals, but to provide the patient with support to say no as a decision, understanding the alternative care to be offered to alleviate the symptoms and improve quality of life. Even if the answer is yes, though, they need to review with patients the possibility of undesired outcomes, with discussion to include family regarding the what if discussions, what if things don't go as you think, and recognize that many patients who receive VAD to enhance the quality and length of life, even when that successfully occurs, they will still have an LVAD in at the time of death and that will need to be planned for.

So to summarize, the knowledge gaps regarding the function and quality of life and patient satisfaction, this has traditionally not been a central focus of our funded data collection. The most useful data for the ambulatory population will be a comparison of before to after and what would happen if you had stayed on medical therapy for a year

compared to having a VAD. There's a bias of missing data in patients who are more ill, both before and after VAD. There is a new impetus in INTERMACS 2.0 to better inform the quality of life, and there is in print a new policy standard for collecting quality of life data but I anticipate that either a carrot or a stick will be required, perhaps from our federal partners, to encourage centers to obtain this data in the midst of a very very busy work schedule.

So to summarize making decisions one patient at a time, evaluations in parallel, making a decision about the patient and then share the decision with the patient, and a summary of the knowledge gaps. What is the anticipated survival for ambulatory patients

now at home on optimal oral therapy with a VAD and without a VAD. What are the quality of life and satisfaction with therapy for all eligible patient profiles with a VAD and without a VAD. And how can we redefine the intent of VAD therapy to emerge from the shadows that are currently cast by this

bridge-to-decision.

Thank you very much.

DR. REDBERG: Thanks very much, Lynne, for taking us through as a cardiologist and also introducing the point of view of the patient and the importance of incorporating that.

We are now finished with the presentations, and I said we could have one or two just very brief clarifying questions, and I have one very brief one for Dr. Aaronson, who on slide 23, at least in my deck, you said one of the predictors of better outcomes for centers were having LVADs greater than 15. Was that per year?

DR. AARONSON: No, that wasn't per year, that was during the trial experience. So in the trials if they put 15 or more at the

center, patients in those centers had better outcomes than patients from centers that put in less than 15 during the trial.

DR. REDBERG: Thank you. Were there any other brief clarifying questions? Yes, Robert.

DR. STEINBROOK: Yes, a question for Dr. Kirklin, and I may have just misunderstood this, but in the next to last of your summary slides there was something about 20 percent of the patients having an 80 percent survival at a year or two, and I missed something.

DR. KIRKLIN: So among destination patients receiving continuous flow pumps, if you look at the entire experience of INTERMACS, excluding those patients who are rapidly deteriorating, that is levels 1 and 2, just short of 20 percent of the overall experience would have risk factors which predict and actually achieved an 80 percent survival at two years.

DR. STEINBROOK: So that's excluding the sickest in the first two levels?

DR. KIRKLIN: Yes, and the reason for that is, the purpose of that analysis to

examine the possibility of a conversation, if you will, about triaging patients off a transplant list. Well, if they're rapidly deteriorating and dying, they're not part of that conversation.

DR. STEINBROOK: Thank you.

DR. HESELTINE: If I could follow up to that, doesn't that actually mean that when you have that initial conversation, you need to say you've got about a one in ten, a one in 60 percent chance of survival at two years, rather than this somewhat convoluted 20 percent emanating from 80 percent.

DR. REDBERG: Let's just save the questions for later and we'll have brief clarifying questions now, but we will come back to that after the break. Yes, Dr. Brindis.

DR. BRINDIS: This is for David Naftel. I would like you to describe a little bit about the lack of adjudication in the INTERMACS registry for adverse outcomes and your auditing process, and then maybe your definition of, in particular stroke, and how that is followed up.

DR. NAFTEL: Yes, thank you. So, the

typical premarket study with FDA has 150 patients in each group and those studies are adjudicated, as you know, by a clinical research committee and under strict standards.

We're up to 8,000 patients and adjudication was sort of this document. We just decided at the beginning that it was not practical, we don't have the source documents.

However, we do have onsite audits, we hit every center, we're scheduled once every five years, we'll go more often than that, and we do go more often when there's for cause audits. So the nurses totally understand the events and they look to do the best they can to get the events in properly.

Perhaps more importantly, we do have this 12-member team of clinicians that review the data within INTERMACS and they look for, whether or not adjudicating, they look for internal consistency. For example, if they see there are two bleeding events in the same day they look at the details, the source of the bleeding, and they'll say well, that's the same event so let's get rid of one of them. They look at ongoing infections, they look at

neurological dysfunction. So it's an attempt at adjudication, it's nowhere near, but it is an attempt to have consistency.

DR. BRINDIS: And the question of stroke, which would be particularly important as you make decisions or recommendations for lower risk patients, how do you assess that long term, what strategies, ranking or scores?

DR. NAFTEL: Right. So again, we don't have adjudication, at the moment we don't have the Modified Rankin Scale although we plan to put that in our next version, so we will have that. But we simply don't have the level that maybe you would look for in a clinical trial for the follow-up to stroke.

Again, we have our nurses looking and making sure that we at least are capturing it the best we can.

DR. REDBERG: Thank you, Dr. Naftel, and one more question.

DR. KORMOS: And David, while you're there, so 15 percent of the data is missing, presumed partly or largely because there's no consent; is that correct?

DR. NAFTEL: Right, of the patients is

what you're talking about. So the patients that are missing, there are two reasons. One,

the hospital is not part of INTERMACS, and that's now a very few hospitals that are not DT hospitals, so we're missing a few hospitals. The informed consent is the main reason that we are missing data.

DR. KORMOS: So consent is not required for SRTR data; is that correct?

DR. NAFTEL: That's true.

DR. KORMOS: So, would there be some process to modify the consenting requirement that would be beneficial here?

DR. NAFTEL: Well, yes. And so we do not have a DSMB, we have an OSMB, observational study monitoring board, and they have given us the mission of pursuing with all vigor the waiver of consent approach, so we are doing that. Actually NIH is leading that charge and we're trying to do that. And of course what we're not saying out loud, but let's do say it out loud, is we're concerned about the patients who are too sick, so we don't get informed consent and perhaps they come in on a Saturday, have a VAD, die on Sunday, and we never know

about those. So we're very concerned about

missing those. We do have a screening form where we collect every single patient in the screening sense, and we do ask a few basic pieces of information, what was the device, where was it placed, and we ask, did the patient die within 48 hours. All of the IRBs in the country except two have agreed to that information, so we do have an estimate of that early mortality, and it is a little bit higher in those that don't have informed consent, so we're going after it.

DR. REDBERG: Thank you very much, and we will return to any other questions after the break. I want to thank all of the speakers, I think it was very helpful. There is clearly a lot of information, there are a lot of classifications that are changing, there are a lot of devices and a lot of new devices, and a lot of changes in indications, so it was very helpful to have all the speakers. I want to thank you all also for staying on time, which was great, so we're now at 10:20 and we will take a 15-minute break and come back, I'm sorry, a five-minute break, and come back at

10:25, and then we'll have scheduled public comments.

(Recess.)

DR. REDBERG: Thank you. I want to welcome everyone back after the break, which was a little bit longer than we previously said. I will personally say there was a line for the ladies room. Okay. We will start with Dr. Darrel Scott, the senior vice president of regulatory and legal affairs from DNV. Dr. Scott, and you have five minutes. Thank you.

MR. SCOTT: Thank you, and in spite of the compliment, I'm not a physician but I appreciate the compliment, thank you very much. My name is Darrel Scott, I'm senior vice president for DNV Healthcare, and DNV Healthcare accredits and certifies healthcare entities. My financial interest with DNV is as a salaried employee.

On November 28, 2011, the DNV submitted a formal request for reconsideration of the NCD for artificial hearts and related devices. DNV requested that the facility criteria for this NCD be amended to include the DNV mechanical circulatory support

certification program as an acceptable credential as one of the criteria for facilities qualifying under this NCD. This request remains under review by the Coverage and Analysis Group of CMS.

DNV believes that its formal request for reconsideration of this NCD regarding facility criteria has a direct impact on Question 2.B to be addressed by the committee, and for those members of the audience that may not have that question before them, it reads: Please discuss the role, if any, of facility VAD specific certification to assure attainment and maintenance of any characteristics identified in Question 2.A.

DNV believes that the approval of a second VAD facility certification program will broaden the base of objective criteria regarding facility evaluation, and provide CMS and MEDCAC a valuable tool for evaluating patient outcomes in facilities certified by different programs. In addition, several large hospitals with VAD programs have switched their accreditation to DNV and want to use, want to retain their VAD certification with the same

accreditation organization.

It should be noted that as a condition of retaining DNV hospital accreditation, DNV accredited hospitals seeking DNV VAD facility certification will have to also become compliant with the ISO 9001 quality management system. This quality management system is unique for U.S. hospital accreditation and will allow for additional objective criterion to compare VAD facilities certified by different programs. Thank you.

DR. REDBERG: Thank you. Next is Dr. Jeffrey Teuteberg, chair of Mechanical Circulatory Council, International Society for Heart and Lung Transplantation.

DR. TEUTEBERG: Good morning, and thank you for allowing me to present on behalf of the ISHLT. I have no relevant financial relationships to disclose.

There's a lot of questions before us today and there's a lot of issues that we could take up with each of these questions, but I'm going to focus today on a particular knowledge gap, and that knowledge gap is do the current indications as they're currently defined affect

our ability to assess and impede, and potentially predict these important outcomes that we're discussing today?

Bob Kormos gave a nice description of the evolution of mechanical support with the continuous flow devices, that they improved survival, better adverse event profiles and longer duration of support, and we assume that because of this improvement in technology we're moving into less sick patient populations, but we're still dealing with the old indications of BTT and DT. For the BTT trials, as you heard, patients had to be listed for transplant and they were supported supposedly for a quote-unquote short period of time, whereas DT patients were not transplant candidates and they were supported for a long period of time, but does this dichotomization really gibe with the clinical reality of taking care of these patients?

So, what does it mean to be a transplant candidate? Well, that definition changes over time. If you have a relative contraindication that's limited you earlier so

that you can't be listed at the time of

implant, does that make you destination therapy, and if not, is there a certain certainty which you have to have that that relative contraindication will get better, or is there a time frame over that, that that relative contraindication will get better for either BTT or DT?

There's also a lack of consistency both within institutions and across institutions. You can imagine two institutions across the street from one another and a patient may take a right turn into one and be implanted with BTT, and make a left turn into the other one and be implanted with DT. So what about these patients that are sort of in between, the bridge-to-candidacy patients that Lynne mentioned earlier? How big a problem are these patients, or how large of a proportion of our patients are these patients?

Well, the truth is that they're a pretty big population. This is a slightly different representation of data that Lynne showed a little bit earlier, but when you look

at patients from INTERMACS with continuous flow devices, the number above that black line,

about a third of the patients are DT patients, about a third of the patients are implanted with a device while they're listed for transplant, and the other third of the patients are BTC patients.

So if there's a collection of relative key morbidities that keep them maybe from being transplant candidates or being listed for transplant at the time of implant, we expect that their outcomes would be somewhere between the BTT and DT patients and that's exactly what we see in this data from INTERMACS for patients with continuous flow left ventricular assist devices.

The other thing that INTERMACS allows us to do is get a little bit more granularity about those BTC patients, and the centers can specifically define their assessment of the likelihood of that group of patients being transplanted as either likely, moderately likely or unlikely. And if you look at the outcomes over time and the percentage of

patients transplanted both at six months, 12 months and 24 months, the yellow bars, these progressively decline across those indications.

The other thing that's important to notice is that if you look at the group that's BTT listed, about 25 percent of those patients, actually a little more than 25 percent of those patients are still supported at two years, so they were listed at the time of transplant but they're still supported at two years. I don't know what the definition of long term is, but if you ask those patients, have you been supported for a short term or a long term, they will universally tell you I have been supported for a very long period of time.

So, how different are the patients? Well, the therapies that we use for them, and again, this is data from INTERMACS over the course of the next couple of slides, is virtually the same, some differences I think statistically significant but not clinically significantly so. What about their end organ damage? Their renal function is about the same, their liver function is about the same,

their level of malnutrition is about the same, but where they differ is some of the comorbidities that may make them a transplant candidate or not. You can see the DT compared

to the BTC have a higher proportion of vascular disease, pulmonary hypertension and social issues such as tobacco use or drinking or drug abuse, and these BTC groups actually form sort of this continuum between the BTT and DT groups.

Now ultimately, why are these patients being implanted with mechanical circulatory support? It's because they have end stage heart failure, and regardless of indication, when you look at them either hemodynamically or echocardiographically looking at LV function, RV function, these patients are virtually the same patients, they're being implanted for the same disease state.

So regardless of indication, again, the disease state is the same, it's end stage heart failure, that's why these patients are being implanted, and the therapy is exactly the same with a continuous flow left ventricular

assist device for the most part, and this BTC group actually forms this continuum of risk between these traditional BTT and DT populations with differing definitions of transplant eligibility both within institutions

and across institutions and even over time.

The length of support is also very different. You know, the DT patients aren't necessarily long term, some of them are transplanted, and the BTT patients aren't necessarily short term, many of them are on support for years at a time, and the outcomes are sort of between those two groups.

And lastly, the strategies are fluid, patients switch from strategy to strategy over time.

DR. REDBERG: Time to wrap up.

DR. TEUTEBERG: Okay. So in conclusion, I think that there is, you know, there is a knowledge gap, how these BTC patients affect the way we assess and predict outcomes on devices. The devices have evolved, the application of the technology has evolved, and maybe it's time for the indications to

evolve as well. Thank you.

DR. REDBERG: Thank you. Our next speaker is Dr. Francis Pagani. He's professor of surgery, department of cardiac surgery at the University of Michigan Health System, and he's representing the Society of Thoracic

Surgeons.

DR. PAGANI: Thank you. I'm speaking today on behalf of the Society of Thoracic Surgeons and I would like to thank CMS for the opportunity to present before the panel. These are my disclosures. The research contracts are managed by the University of Michigan.

CMS has established a general criterion for surgeon volume for center certification for implantation of ventricular assist devices for destination therapy. This criterion by itself does not address the processes by which a surgeon may obtain the required surgical experience. The lack of specifics of the process has left this criterion open to a narrow interpretation.

We believe that volume criteria alone are inadequate measures of competency, and

additional aspects of surgical training such as a patient selection and pre- and postoperative care should be documented. Although not specifically excluded by the current criteria, a narrow interpretation of this requirement has excluded a number of important pathways for a surgeon to meet these criteria. The current

system fails to recognize experiences obtained by a surgeon during an American Board of Thoracic Surgery approved cardiothoracic residency, the experiences obtained during an advanced fellowship in cardiothoracic surgery for advanced heart failure therapies, and international training and educational experiences. It is important to note that surgical experiences obtained through a cardiothoracic residency or fellowship are recognized in the accreditation pathways for surgical directors for heart transplantation programs in the United States by the network, United Network of Organ Sharing. Heart transplantation is of similar technical complexity and patient care complexity as VAD therapy.

Current interpretation of CMS criteria requires that one VAD implant be performed for destination therapy indication. We believe there is no evidence to substantiate this number as being important or relative to the overall experience of the surgeon or center.

Another important aspect of surgeon training is the recognition of preceptor or

teaching roles of a qualified surgeon with expertise in VAD therapy. Currently there is a narrow interpretation of what constitutes the primary surgeon of record. Current interpretation of CMS requirements includes only the billing surgeon as the surgeon of record. This narrow interpretation of the requirement is significantly limiting training and educational opportunities for other surgeons who are performing key technical aspects of the VAD implant procedure and participating in the pre- and postoperative care of patients under the supervision of a qualified surgeon with expertise in VAD therapy.

The STS recommends further

clarification of the CMS requirements to include documentation of other aspects of training and experience that are essential to the overall qualifications of a VAD surgeon, recognition of surgical experiences obtained through an American Board of Thoracic Surgery approved cardiothoracic residency, recognition of surgical experiences obtained through an advanced fellowship program in cardiothoracic

surgery, expansion of the definition of primary surgeon to follow guidelines outlined by the American Board of Thoracic Surgery in teaching or preceptor settings, recognition of international experiences, and most importantly, establish a pathway for certification for established board certified cardiothoracic surgeons in clinical practice without prior VAD experience. The STS recommends a collaborative process for revision of VAD surgeon requirements for certification for destination therapy to include representation from CMS, the Joint Commission or other agencies that have oversight responsibility, the American Board of Thoracic

Surgery, and the Society of Thoracic Surgeons. The STS would like to thank CMS for the opportunity and privilege to provide perspective on this important therapy for our patients with heart failure.

DR. REDBERG: Thank you, Dr. Pagani, for giving us the STS perspective on surgeons and surgeon qualifications.

Next we'll hear from Dr. Sean Pinney, who is an associate professor of medicine at

the Mount Sinai Medical Center, and he is representing the Heart Failure Society of America.

DR. PINNEY: Thank you for giving me this opportunity to speak to you today on behalf of the Heart Failure Society of America. I have no financial disclosures. The Heart Failure Society of America is a society which represents over 1,300 members. It is a multidisciplinary society composed of MDs, PhDs, nurses and PharmDs. Our mission is specifically to enhance the quality and duration of life of heart failure patients. As such, we are not organized around any specific

intervention or discipline, but rather, we are a disease-focused society. We carry out our mission by research, education and the prevention of heart failure.

We have three position statements that we would like to share with you. First, we support the national coverage decision, we do not endorse any change in the current patient selection criteria which derived from prospective randomized clinical trials. We recognize the need for further well controlled

clinical trials, including examination of less sick patients. We do not support expansion of destination therapy into these populations in the absence of randomized clinical trials.

Third, recommendations regarding VAD surgeon and center qualifications should be informed by specific volume and outcome analyses, and the recommendations of professional societies which we heard just now from Dr. Pagani, including the Society for Thoracic Surgeons and the American Board of Thoracic Surgery.

I will not go over the extensive

evidence base which Dr. Aaronson and Dr. Kirklin and others shared with you this morning other than to point out that the initial evidence base was founded upon prospective randomized clinical trials, first with the REMATCH trial which established the use of destination therapy with a pulsatile device. This was further expanded by the use of a continuous flow pump showing the survival advantage with the use of a continuous flow pump over that of a pulsatile pump.

We see that the approval of the

continuous flow HeartMate II device led to a rapid adoption of this technology and abandonment of pulsatility devices. Following the approval in 2010 of the HeartMate II continuous flow pump for destination therapy, we've seen an expansion of the use of this pump for the indication of DT. We also heard from Dr. Kirklin this morning about the results of survival for those patients receiving a destination therapy device from the INTERMACS, showing a one-year survival of 74 percent.

Nonetheless, certain evidence gaps do

exist and Dr. Stevenson summarized those very well, specifically given those patients who are less sick, what is the survival outcome of those patients who are INTERMACS category 6 and 7, and what's their quality of life, and what is the impact of mechanical support, potential impact of mechanical support in those populations? We think this is a viable testable hypothesis which is worth pursuing, and we heard from Dr. Aaronson how the REVIVE-IT trial may help to address that.

Right now there are certain specific DT facility criteria. These include that one

member must have experience implanting at least ten LVADs in the previous 36 months, centers must report to INTERMACS, they must be credentialed by the Joint Commission, and there must be patient informed consent materials and processes in place.

However, there are also other knowledge gaps which Dr. Pagani just elucidated. There are certain volume outcome relationships which remain uncertain that are certainly worth evaluating. A pathway for

foreign trained surgeons remains unclear, there is no pathway for VAD training certification, and these knowledge gaps are being addressed by position statements from the STS and the American Board of Thoracic Surgery. Thank you very much.

DR. REDBERG: Thank you, Dr. Pinney, for giving us the insight from the Heart Failure Society of America perspective. Next we have Dr. Wayne Levy, who is the medical director of the University of Washington Regional Heart Center and a professor of medicine and cardiology.

DR. LEVY: One correction, it's the

Heart Center Clinic at the University of Washington. What I would like to do is address first disclosures. HeartWare, Thoratec, General Electric, NHLBI, all of these are research funding, and the University of Washington with the copyright to the Seattle Heart Failure Model.

I would like to address point one, and that is mortality among medically treated patients, and suggest that the Seattle Heart

Failure Model will be a virtual control to describe that risk with medical therapy for patients for selection and also to describe patients who have received the device.

AHA has suggested a 50 percent one-year mortality for placement of the device, this is clearly not what is being done, most patients do not meet this criteria. CMS, unless they've changed this, to the best of my knowledge has required a two-year survival or less along with the criteria of peak VO2 of 14, but they have not provided a model to calculate the survival.

This is illustrating a curve with a 50 percent survival at two years and the NHLBI

funded trial, REVIVE-IT, will be using the Seattle Heart Failure Model for entry, and it requires 16.5 percent mortality. If we look at the Seattle Heart Failure Model, it obtains easily identifiable clinical variables including very important medical therapy. Loop diuretic doses which are not currently collected in INTERMACS are a very profound variable, with an ROT of .66 alone, it has

simple biomarkers which are last.

If we look at medication use, this is functional Class IV patients depending on whether you're on zero, one or two medical therapy, you have superb outcome, 81 percent survival if you're functional Class IV but still on two medications. This is validation prospectively on 10,000 patients, the calibration is excellent, it's now been validated with 20,000 additional patients and most data sets have shown excellent calibration if you look strictly at death. As we're now placing LVADs into lower risk patients, the event rate is higher if you're including lower risk LVAD patients.

It's a very simple online model.

Here's a patient who would be sick enough for an LVAD but if you placed them on ACE, beta blocker or aldosterone blocker they had an 11 percent mortality rather than 40 percent, and they clearly would not qualify for an LVAD.

We do not need a model like this for INTERMACS 1 through 3. For INTERMACS 4 through 7, I think it can be extraordinarily

helpful to define the risks in patients treated with medical therapy. This is from the O'Neill article showing that a peak VO2 at 14 is roughly a 14 percent annual mortality. That is not high enough risk to actually benefit from an LVAD, as we saw that average destination therapy patient is 20, 25 percent.

This is data we recently published with Donna Mancini and Keith Aaronson looking at patients with a peak VO2 below 10. This is 10-year survival and you can see that if you have a low Seattle Heart Failure risk score you have excellent 10-year survival, we're talking about 50 percent 10-year survival free from LVAD, free from transplant with medical therapy.

It does not matter if you have a high

risk score whether your peak VO2 is 10 or 18, you still have a very poor survival, and these patients should get an LVAD currently.

If you look at other things that can add to the model, risk imaging, MIBG, looking at sympathetic activation is the one that I think has the most utility, improving ROC AUC

by almost .04, which was highly statistically significant.

Does it predict outcome after an LVAD? And the Johns Hopkins University looked at it and found that it was a superior risk model even though it's not designed to predict LVAD survival, and superior to the INTERMACS risk score. If you have a lower survival with the medical therapy, you had worse survival with the LVAD. We found the same thing at our institution.

We looked at the ADVANCE trial, had the privilege of analyzing what these patients would prospectively do with medical therapy. Only 52 percent would meet the AHA criteria of less than 50 percent one-year survival with medical therapy, 74 percent would meet what I think is CMS of less than 70 percent survival.

The black bars on the left side are the intraaortic balloon pump patients that are clearly all very sick. The inotropes are across the spectrum, including some patients who actually would have predicted reasonably good survival and may not benefit from a VAD.

The people not on inotropes are more to the right side.

We can now use this as a virtual control, which could be done with INTERMACS as well. We have a blue line in predicted medical therapy, the red line is the observed outcome. You can calculate hazard ratios, and the expected hazard ratio here is in the range of an 80 percent reduction in mortality. If you look at the balloon pump patients, they are sicker, 17 percent predicted medical survival, 90 percent. If we look at the inotropes, about 50 percent, and we look at the people not on inotropes, this is the REVIVE-IT type population, they had a 92 percent survival. And if we look at the correlation with hospital days per year, people with a 25 to 50 percent mortality as predicted by the model will spend 20 to 40 days in the hospital per year. If we

look at risk stratification --

DR. REDBERG: Time to wrap up.

DR. LEVY: I would urge you to start collecting this data, in INTERMACS it will be collected and reviewed.

DR. REDBERG: Thank you, Dr. Levy, for talking to us about the importance of looking at risks in patients and your concerns about lower risk patients having a less favorable benefit-to-risk ratio and suggesting other models.

Next is Dr. Goldberg, Dr. Lee Goldberg, chair of Heart Failure and Transplant Council of the American College of Cardiology, and the medical director of the heart failure and cardiac transplant program at the University of Pennsylvania.

DR. GOLDBERG: Thank you very much. I will disclose that I have very modest speaking fees from Thoratec for its fellows training.

The ACC and AHA guidelines for the management of heart failure suggest that for patients to be considered for destination therapy for VADs, that the expected one-year survival should be less than 50 percent despite

medical therapy, but unfortunately it does not define specific criteria other than just the absolute mortality. In addition, the INTERMACS registry also defines acuity and functional

capacity but does not provide specific selection criteria.

You've heard about several prediction models so far, one being the Heart Failure Survival or the Seattle Heart Failure Score, there's also a VAD implant survival score that has also been used, but no models have been developed to predict both survival and improved quality of life, and there really is no standardized evaluation procedure for potential candidates for VAD therapy across programs to allow for collection of model covariates and then to understand subsequent outcomes.

This is probably the most important slide that I'll show, and that is what are the factors that impact outcomes, and you've heard a lot of this data in little bits and pieces, but this gets at the Medicare population that we're really focused on today and that is the concept of frailty, and which of the things do we expect to get better with LVAD support and

which of the things do we expect not to improve.

And certainly comorbidities and organ

dysfunction that's irreversible, as well as cognitive impairments, et cetera, are not always likely to get better and may very negatively impact quality of life and really decrease the value of this therapy, as opposed to some things which may get markedly better, functional capacity, et cetera, with LVAD. And so understanding this concept of frailty will be increasingly important to understand how to value this technology.

In looking at specific facility and operator characteristics that impact outcomes, clearly there are many examples that this impacts both quality as well as cost, including VADs, and the ACC supports the concept of accreditation for centers in order to provide this therapy. And again, how this is decided may need to be adjusted, but certainly understanding that accreditation is probably very important to get better outcomes, and you can see that with experience there's improved survival, and several other speakers

have shown this.

Now the goals of certification will

ensure that team members are experienced and competent within their discipline, so not just volume but also competence, for both selection and insertion, but also for perioperative, postoperative and long-term management of that patient, something that we don't have a lot of data for. We also want to make sure that there's availability of evidence-based care plans and evidence of data collection for quality measurement and improvement, not just survival and complications. And finally, that there's adequate institutional commitment and resources to support the VAD program and to report the data to the appropriate registries.

I do want to note that cardiac transplant still provides the best long-term survival, and limiting, and there is only limited VAD survival data for two years. So the ACC does support the role of transplant centers in partnering with VAD centers to ensure that patients are offered the opportunity for transplant if they are appropriate candidates, since at least with our

current technology this is a superior outcome.

The ACC also strongly supports the concept of a multidisciplinary heart care team to provide care for these patients, including a litany of healthcare providers, because all of these play a critical role in their assessment, and we believe that these should be also supported in the reimbursement strategy so that programs can provide all of these services.

In terms of generalizability to the Medicare population, there's limited data to those over the age of 70, and there are several unique challenges that need to be assessed, including the impact on caregivers, patients being able to live alone with their VADs, and comorbidities that will impact survival, quality of life, or even their ability to manage this technology even if their quality of life is good. There is very limited assessment of frailty, and then we need to address the cost of outpatient supplies and equipment and how that impacts the family, the community, as well as the providers.

There are several evidentiary gaps that we've already heard about, the utility and

criteria of bridge-to-decision or bridge-to-candidacy, the utilization of VAD in less sick patients. We need multidisciplinary research on end organ function and recovery with our colleagues from renal, GI, et cetera. We need end of life planning and care for VAD patients, and we need to understand how to utilize other devices, management of arrhythmias and dysrhythmias in these patients and whether they still require ICD and BiV, et cetera. We need to know what are the factors that allow successful bridge to heart transplant or to even ventricular recovery. We need to understand more about the role of anticoagulation strategies, especially age-related risks. And then the risk factors for pump thrombosis and whether there are genetic or other tests that need to be done in order to determine that. Finally, the last of the evidentiary gaps are the role of pharmacologic therapy for patients on VADs, the psychosocial impact, and the impact of right ventricular failure.

So in conclusion, the ACC supports the need for a supported VAD and advanced heart

failure registry, this data to pool across centers to allow us to analyze outcomes, identify factors for risk models, and provide evidence for best practices. Thank you very much.

DR. REDBERG: Thanks, Dr. Goldberg, for giving us the views of the American College of Cardiology and noting the importance of heart teams and data specific to age of Medicare beneficiaries.

Wrapping up is Dr. Mariell Jessup, who is the president-elect of the American Heart Association and a professor of medicine at the University of Pennsylvania.

DR. JESSUP: Thank you for allowing me to present on behalf of the American Heart Association. The advantage of being the last speaker is that I can quickly go through some of my slides as soon as they're put up. I do not have any conflicts to disclose. I think you've heard a lot of what I have on the slides and I want to underscore several important things that the American Heart Association feels strongly about.

Number one is that we've heard an

awful lot about the INTERMACS registry, and the American Heart Association feels strongly that INTERMACS has been a very useful vehicle not only to learn and look at quality issues with respect to VADs, but as a source of ongoing dialogue between clinicians, a source of publications, and has really supplemented the industry-sponsored trials. We would strongly also encourage MedaMACS moving forward because as Dr. Stevenson has said, it is critically important for us to understand the natural history of heart failure in the less sick patient population that do not get VADs.

We have a number of different criteria that, as you've heard, will predict who is going to do poorly both with medical therapy and with VAD therapy, but a lot of this criteria is based upon pulsatile flow VAD technology, and we have lots more to do with respect to risk criteria for the nonpulsatile flow VADs.

So, I think it's fair to say that the American Heart Association says when looking at the entire database, we really know who is likely not to survive with pulsatile flows, we

are learning who may not survive with continuous flow pumps, but we do not yet know who will do well, well meaning survive and with quality of life, with continuous flow VADs.

We want to talk, again as several other speakers, about bridge-to-transplant. The AHA feels the Medicare criteria should remain the same. We think that the patient undergoes an extensive evaluation to determine if they are a transplant candidate, and this evaluation is certainly sufficient to determine VAD candidacy and this will overall result in better survival for patients who might have died while waiting for a transplant.

Destination therapy, we feel the existing Medicare criteria is appropriate and there is not enough evidence to extend it to less sick patients. As we've heard, the REVIVE-IT trial is actively anticipated.

One change to consider is to remove the requirement that patients cannot be a candidate for heart transplant. We need to provide coverage for bridge-to-decision patients. This slide shows the modifiable, the

reasons why patients will not transplant

candidates. The three top reasons are advanced age, renal dysfunction and high body mass index, and it is always considered that the modifiable renal dysfunction, high body mass index and pulmonary hypertension could be modified. One-third of all patients receive a VAD under a bridge-to-decision and therefore we feel that this needs to be considered as a change in policy.

AHA supports existing Medicare criteria for the facility operator characteristics, and we just want to emphasize that there are a number of existing programs already that address training needs, specifically not surgeons but the ABIM has now begun an advanced heart failure and transplant subspecialty, there are now ACGME-approved certified training centers for these cardiologists in advanced heart failure and transplant, and the Joint Commission advanced certification in heart failure, which was created in collaboration with the AHA, incorporates the guidelines and helps advance

the whole team aspect of care for these very sick patients. Finally, the Joint Commission

advanced certification in VADs.

I want to finally finish up by saying that the Medicare population is very applicable when we talk about VADs and as you've seen, about 25 percent of the patients in INTERMACS now are 65 years or older.

I will completely finish by saying there are many many areas that desperately need research, including something that I'll highlight, the level of evaluation appropriate to determine if the DT patient is not a transplant candidate, perhaps they don't need a complete and full transplant evaluation. We need to understand the full extent of adverse events in the DT population and who is at risk for these events. We need a standardized approach to GI bleeding or infection. We need to know how to make risk profiling efforts more granular so that we understand not only survival but quality of life. We need to understand the best approach that would allow a critically ill patient to safely receive a DT

VAD; as we've heard, they don't do well. How best to use INTERMACS in premarket and postmarket surveillance. Should the

performance standards require survival longer than two years. Should there be an enforceable upper age limit, interaction between side effects, why few patients recover enough to have a VAD removed, and how to identify the appropriate less sick patients.

In summary, the current criteria for bridge-to-transplant requirements are adequate, CMS should consider revising the destination-to-bridge decision, and we look forward to many more trials. Thank you for the opportunity.

DR. REDBERG: Thanks, Mariell, for giving us the perspective of the American Heart Association on what we have learned and what we still need to learn.

Next we have four people that have signed up to do public comments, these will be one minute each. And I will say the last person, Margarita Camacho, we still need your conflict of interest form before you can speak.

The first person will be Carmelo Milano, from Duke University, and the next person is Kevin Shaw. If you want to come closer to the front, that would be great.

DR. MILANO: I'm the surgical director for heart transplant and LVAD at Duke University, and I have a conflict of interest in that I am a consultant for Thoratec as well. I had a number of comments, many of them have already been covered, but I think, you know, with regard to the first question, it's important for the panel to reflect on the types of patients we're implanting with destination therapy LVADs and what those patients' outcomes would be if we did not offer them this therapy.

In reviewing Dr. Kirklin's presentation, the majority of patients who are implanted with destination therapy LVAD are currently in the upper levels of the INTERMACS staging, they are patients who are dependent upon continuous intravenous inotropes, and these patients we know from older data sets have an extremely poor outcome without VAD therapy.

And if we look at the medical management arm of REMATCH, their survival is roughly 20 percent at one year, relative to current survival outcomes of better than 65 percent with continuous flow DT LVAD, so this

is an absolute survival benefit of about 45 percent. This is impressive compared to other cornerstone therapies for heart failure, if you look at beta blockers, ACE inhibitors, ICDs for earlier stages of LV dysfunction and heart failure, the absolute survival benefit is much smaller. So I think this is an important therapy and under the current guidelines, I think the absolute survival benefit is impressive.

DR. REDBERG: Thank you, Dr. Milano. The next speaker, the name is a little sketchy, but is it Kevin Shaw?

DR. SHAH: Keyur Shah, from Virginia Commonwealth University. My actual comments have been covered by the speakers. I do have disclosures for minor grants from industry, from Thoratec.

My concerns initially were related to

paucity of data for treating patients who were medically non-inotrope dependent, but I think speakers have covered that adequately so I have no further comment.

DR. REDBERG: Thank you very much. The next speaker is, it looks like Silvestry,

from Washington University, St. Louis, and you can reintroduce yourself.

DR. SILVESTRY: I'm Scott Silvestry, I'm the surgical director for heart transplantation, mechanical circulatory support. I also have consulting fees from Thoratec alone. I just had two comments.

One is that our program has over 100 supported patients as outpatients with over 250 patient-year lives saved at this point, and I think it's important technology. If we look back at two different populations, one is patients evaluated for destination therapy who either we decline to offer the therapy or they decline to accept the therapy at that point, at two years there's 11 percent survival.

And the second population are Missouri Medicaid patients who are only funded for

bridge-to-transplant and in patients with clear contraindications for transplant who cannot have bridge-to-transplant because of eligibility criteria, therefore they're unfunded, at two years they have zero percent survival.

I think the time has come to put the

need for support ahead of the destination of support, and treat the disease in the patients without regard to where they may or may not go. Thank you very much.

DR. REDBERG: Thank you. And our last speaker is Margarita Camacho, from Barnabas Health.

DR. CAMACHO: I'm the surgical director of the heart transplant program at Newark Beth Israel and Barnabas Health in New Jersey. I will cut this very short.

The next step is, I believe is to have trials such as the NHLBI-sponsored REVIVE-IT trial --

DR. REDBERG: Could you state your conflicts?

DR. CAMACHO: I'm sorry, I have no

conflicts.

I think the next step is to have trials such as the NHLBI-sponsored REVIVE-IT trial mentioned earlier, to assess whether VADs can benefit patients from the earlier stages of advanced heart failure. Now that this mechanical alternative exists which lasts four years and gives not only survival but quality

of life, we should be looking at VADs earlier before patients become a significant surgical risk.

With respect to two evidentiary gaps, there's no reliable predictive patient risk score, there's insufficient data to indicate the surgeon and program volume requirements. INTERMACS can really help close these gaps.

It is reasonable to continue the certification process for destination VAD therapy given the many unique features of this specialty, and due to the multidisciplinary nature and unique features of this specialty, the heart team concept should improve patient outcomes. This is supported by, as Dr. Jessup mentioned, the recent American Board of

Internal Medicine certification for heart center transplants, and the ongoing CMS-required certification, that an experienced and skilled infrastructure should improve patient outcomes. Thank you.

DR. REDBERG: Thank you very much. I want to suggest now that the speakers can move up to the front row, and we have time for continued questions from the panel. Yes, Dr.

Faught.

DR. FAUGHT: In terms of anticoagulation since bleeding is a significant comorbidity, are there new anticoagulants that are expected to improve that in any way, or any changes in the coagulation strategy on the horizon?

DR. PAGANI: Currently the recommended anticoagulation for the device is an INR of two to three.

DR. REDBERG: Your name again, sir?

DR. PAGANI: I'm sorry, Frank Pagani, University of Michigan. It's depending on the types of device, but the general recommendation for anticoagulation is warfarin INR with a goal

of two to three, and anticoagulative therapy with aspirin. There is no current data to suggest that there be a different anticoagulation profile on the horizon.

DR. REDBERG: Thank you. The next question is from Dr. Grant.

DR. GRANT: First I want to compliment all the speakers, you did an outstanding job. This is a question for either Dr. Naftel or Dr. Kirklin. In the INTERMACS it seems to capture,

what, close to 90 percent of patients with VADs, and I just did a back of the envelope calculation in the 145 centers. So, what is your estimate of what's the average number of VADs placed per center per year, because what I come up with is about 14; does that sound about right?

DR. KIRKLIN: James Kirklin, UAB. 1800 divided by 140.

DR. REDBERG: Okay. Dr. Brindis, do you want to follow up, and then next was Dr. Rich and then Dr. Schwartz.

DR. BRINDIS: I actually want to follow up on that point because Lynne very

nicely said how important it is in terms of criteria, centers of excellence, in terms of doing this safely and wisely, and the whole concept of rational diffusion of this innovative technology now at 144 centers. So when you have volume, of course it's just one indicator of quality.

I would be interested, and anybody can help me, what is the actual range in volume between centers? In other words, the median would be a more interesting question than the

mean, and has INTERMACS looked a little bit about outcomes, at least short-term outcomes related to center volume in that respect, and since we've learned from the HeartMate II risk score that there was a substantial risk related to total volume, and maybe some comments from some of the experts related to that issue.

DR. REDBERG: More than one person can address this answer.

DR. KIRKLIN: Jim Kirklin, UAB. You know, I don't have the exact numbers at my fingertip, but it would range from five to 60 or more. We have not yet identified specific

hospitals as risk factors. You know, it's early in the experience of INTERMACS, but that has not of course been a particular charge of ours. But in specific answer to your question, we have not identified to date the two years of continuous flow technology individual centers as risk factors.

DR. REDBERG: Did you know the median? I think that was the other question.

DR. KIRKLIN: If you're interested in that, we can supply that to you after the lunch break, the median number of VAD implants per

center.

DR. REDBERG: Okay. Dr. Stevenson.

DR. STEVENSON: I'll address what I think is the larger context of your question. Certainly with heart transplants, it has a very similar infrastructure to what we're talking about with cardiology, social workers, infectious disease, the surgeon, the palliative people, and so the infrastructure is almost exactly the same as what we would have for a VAD program, which is one of the reasons it has been so convenient to have the VADs in the

transplant centers, because the infrastructure is already there.

For transplants, as I recall, it has been shown as either 12 or 15 transplants per year as a clear cutoff, below which the outcomes have been worse, and I would anticipate that there would be some similar data for VADs, but we don't have the details. I think when you look at what would be required, it would be very similar to that, and frankly, trying to evaluate a center that does VADs and not transplants, right now I don't think we have a database from which to do that

very well, but clearly it looks similar to how we've made sure that the best centers have been doing transplants for the last 20 years.

DR. REDBERG: Lynne, just to follow up on that, would you say that that was related more to the volume or to the heart team concept at the transplant centers that you have previously identified with better outcomes?

DR. STEVENSON: Well, frankly, I think if you're doing fewer than 12 a year you're not going to be able to support the infrastructure

that you need to have good outcomes, because you have all those different people and if you're dividing that kind of workforce among just a handful of patients, you wouldn't be able to do it. So just the practical logistics means you would have to have a fairly large volume to make it worthwhile to have all the appropriate staff.

DR. REDBERG: Thank you. Dr. Rich, I think you were next.

DR. RICH: I just have a question for Dr. Kirklin. INTERMACS does not, the level of attribution is at the hospital, it's not down to the individual surgeons; is that correct?

DR. KIRKLIN: Yes.

DR. RICH: So that you wouldn't be able to really use INTERMACS to help us with the surgeon volume criteria. My thought and question to you would be since the STS database does go down to the level of the surgeons, has any thought been given to actually blending the two databases so that we could, one, capture the missing data, and two, get it all the way down to the level of the individual surgeon

providing criteria.

DR. NAFTEL: David Naftel. Certainly we haven't set up anything like that, and I remember when we built INTERMACS, we specifically only wanted to go down to the hospital level. That can be revisited and we could match up with the STS. We haven't done it yet and I know it's not under this panel's consideration, but the biggest issues are PHI, information confidentiality issues like that, that I hope we never have to worry about, but we do when we start merging databases.

DR. LEVY: Wayne Levy, University of Washington. Todd Dardus, who has trained with Frank Pagani, and Keith is now at our

institution, he will be joining us July 1st, he has a proposal before STS to look at patient-surgeon volume at some of the outcomes at the centers, and we'll see whether or not it gets approved.

DR. REDBERG: Next is Dr. Schwartz, and then Dr. Mock.

DR. SCHWARTZ: Rita, if you could give me permission, I have two questions that are

somewhat related actually, for a change.

DR. REDBERG: Okay.

DR. SCHWARTZ: The question I had which relates to a number of you on the panel, but it sort of picks up on what Lee said and a little bit what Mariell addressed, and it has to do with what we just talked about, ways to enrich the INTERMACS database, because it potentially has greater use. I wanted to just focus on one thing but then allow people to maybe address the broader question.

And that is, for example, as has been identified by many speakers today, the importance of quality of life, functional status and the patient-reported aspects, and also the difficulty getting that information,

and personally I agree with Lee's suggestion that this be made a core component. The question that I would have for you guys who have to kind of make this work is, what's the feasibility if there was external support or if there was dedicated support to collect this, is this just a support issue or is it a larger issue than that?

Then also the larger general question about just enriching the database in other ways, because what I'm thinking about is that it might be very useful for MEDCAC to identify, or for CMS to identify specific questions that could be addressed that would inform decisions down the road, but that depends on the capacity to generate that information in a valid reliable way.

DR. KIRKLIN: Jim Kirklin, UAB. Those are very important issues, and one of the things about INTERMACS that everyone needs to realize is that in its essence, INTERMACS is recording ongoing standard experience from hospitals. So there's not, other than a mandate to participate in INTERMACS, there is certain core experiential information they must

provide, otherwise they're out of compliance. But if there are particular studies, for example functional outcome, quality of life, that they don't deem to be part of their standard of care, then they don't have to supply that, we can't mandate that.

So that leaves opportunities for other

agencies like JCAHO and CMS to underscore the importance of that kind of information in the long-term evaluation of device therapy, and we of course think it's very important to the extent that there's an editorial article recently in the Journal of Heart and Lung Transplantation which we had worked for over a year at getting experts together, to discuss and define the role of functional outcome and quality of life data and its importance that it be standard of care in the long-term management of these patients.

So I think the reality is if we can get centers to agree and embrace the idea, or being told that the standard is to collect this kind of information, then it will be put in INTERMACS and then we can monitor it, but we can't demand it.

DR. SCHWARTZ: But outside groups that have some impact or got people's attention, might be able to help cut through this?

DR. KIRKLIN: Absolutely.

DR. SCHWARTZ: Make an offer they can't refuse?

DR. KIRKLIN: Well, it's not a matter of manpower really, because just like in the transplant world, once institutions know in order to participate in that activity or in that therapy they must supply the information then they find the resources, human or otherwise, to do it, but it has to be mandated.

DR. NAFTEL: David Naftel. To pick up a little bit further on that, everything that Jim said is obviously accurate, but we do something additional. When the coordinator does not record quality of life, say preimplant, then they have to enter what was the reason, and preimplant, the majority of those reasons are too sick. There's also administrative reasons, which is a euphemism for the coordinator was too busy, but that's more of the reason post.

But one thing that we found with a lot

of the quality of life thinking are that these instruments, EuroQol, KCCQ, they're built to hand to somebody and have them fill it out, they're not built to assess quality of life in someone who's too sick. So now we are working

with our quality of life experts to say what scores should we assign, and for the EuroQol there's five dimensions, one's mobility, and if you're too sick I think you ought to get a pretty low score, so there's a little give and take on that.

DR. SCHWARTZ: There's also some data we can talk about at the lunch break, but patients are pretty good at short-term recall, so if you ask them four days after surgery what they were doing a week before surgery, there might be ways to get that.

The second question that I had was really for Mariell. You mentioned at the end about certification and the work the ACC and JCAHO is doing, and this gets to the question we have to address this afternoon. Do you think there's any compelling reason why the ACC has to work exclusively with JCAHO, or whether the ACC could serve a similar role with other

Medicare certifying agencies or groups?

DR. JESSUP: Mariell Jessup, University of Pennsylvania. I'm a little confused because the ACC hasn't been working

with JCAHO, it's the AHA that's been working with JCAHO.

DR. SCHWARTZ: AHA, okay. I'm sorry, I'm just a general internist.

DR. JESSUP: It's just that I had my AHA hat on today too. I don't think there's any reason why not. I mean, just like INTERMACS represents an unprecedented combination of lots of agencies and industry and academia and clinicians to work together to improve the outcomes in our patients, there's no reason why we can't do that again. And I think what you've heard today was really representative of our community at large, that wants to have this technology and provide the very best outcomes.

DR. REDBERG: Dr. Mock is next.

DR. MOCK: Yeah. I'm trying not to pile on to INTERMACS here, but I did have a couple more questions if I could. When we talked about, it wasn't mentioned directly, but

the growth, to go from October 22nd to November 14th, and we added three more facilities. I guess my question is, even though there may not

be a mandate, is there a responsibility of the organization to say how many is enough, what is access, what is the ceiling, where are we going? Is 14 VADs a year, if that's not adequate, then how many more centers will we add in the next four months, six months, a year?

Let me be more specific. Is there discussion in your leadership, or do you anticipate formulating a concept around a center of excellence that would provide adequate numbers for the surgeons and for the team, and show that those outcomes equaled constricting the utilization of this implantation across the country?

DR. KIRKLIN: Jim Kirklin, UAB. So, that's a very complicated question, as you know. In brief, it's important to understand that our initial charge from the NHLBI was a scientific one, and there has been a gradual evolution, of course, to wanting to supply quality assurance, which really addresses your

concern.

It is always a delicate balance

between, for example, trying to get as much information as you can from the community at large, not all of which participate in destination therapy, and therefore are volunteer members of INTERMACS, and yet trying to be beneficial to the greater good about really what is appropriate in terms of numbers, volume, experience, et cetera.

So in short I would say that INTERMACS would welcome a collaboration with anyone, whether it be CMS or other aspects of federal government, insurance carriers, to in a responsible way try to identify risk factors to whatever level was desired. I think that currently we don't have quite enough information to begin that pursuit because of our short period of interval follow-up, but clearly we are open to exploring anything that would improve the overall lot of patients and the allocation of device therapy, but it's a challenging concept.

DR. STEVENSON: I'm going to step up, not because I haven't answered but because I

want to prolong the time and attention that

your question gets. If we look at cardiac transplantation, it is a very limited resource because of the number of donors and so it's very important that the utilization of that resource in terms of the fairness of distribution and the ability to learn how to do it better be concentrated in centers.

For VADs, I think initially it was assumed that the number of VADs is infinite. However, I think we can make a good case that the resources required for VADs, it's not infinite either, and I feel very strongly and personally that it's our responsibility to make sure that they are used as best they can be used, and that the learning curve is as efficient as possible, and there's clearly a limit of the number of centers that should be doing it. I hesitate to use the word certificate of need, but that's the sort of thing that's in my head in answer to your question.

DR. MOCK: Will you allow me one more follow-up?

DR. REDBERG: Sure, one more question,

and then next is Dr. Pina.

DR. MOCK: It takes me back to a comment I think I heard today about an audit that takes place, and an example that might have been used was if a patient came in and had an implantation and then died within 48 hours, that would be an indicator for follow-up on the audit. But one of the things that was perplexing to me is I think I also heard that the audits take place every five years unless there's a flag of need.

So if we put that in perspective, as the number of facilities rise and the resources that are required to do audits, where do you find that follow-up justification?

DR. KIRKLIN: Jim Kirklin, UAB. Well, the audit process, first of all, is geared by design in INTERMACS to be an audit of the quality of data, not quality of performance in terms of survival after VADs. Now the quality assurance aspect is designed to inform hospitals very specifically how they are performing in terms of outcomes, survival, compared to the rest of INTERMACS. And it is very important, of course, the auditing for

compliance and quality of data is not necessarily separate and distinct from the quality of the program, since if you were doing a bad job you might not want to put your data in.

But we do have, in answer to your question about once every five years, we audit 30 centers a year. We do have constraints about costs because we have so much money to work with, but we have altered that in this second five-year context to in addition offer extensive telephone audits rather than just site visits. So we have an array of study nurses who are very aggressively calling many centers every week, so that it is not just a matter that one site gets examined every five years or whatever that number would be, they are examined very frequently, and that's a cost effective way to us to increase the quality, but we don't have the money to be able to audit every center every six months with a physical visit.

DR. REDBERG: Dr. Kirklin, I just wanted to kind of follow up, because I think of audits as when we're checking that what's

entered in the registry is actually what occurred in the medical records. So I'm curious what information is gotten by calling the centers, and also on those every-five-year audits, what percentage of the patients that were entered are included in the audits?

DR. KIRKLIN: Well, when they physically visit the center, and correct me, David, if I'm wrong, 100 percent of the patients over some specific time period are examined. Please.

DR. NAFTEL: David Naftel again. I'm glad you bring up this point. With apologies to everyone who has been involved with auditing, we believe the traditional audit process is severely flawed. To go in and say okay, at three months the database said creatinine was 1.2 and we found out it was 1.3, that's a nice thing to fix, but we're so much more concerned about a top down. So what we do when we go to the institution, we go through ever single patient and say first of all, we want to make sure we have all the patients, then let's hit the top things, death, transplant, device malfunction, bleeding,

infection, get the big stuff on everybody. And then we do a five percent complete audit, five percent of the patients to get all of them, and that's the onsite visit.

The phone calls that are every two months to the hospitals, the nurse calls and she -- they're all shes, she has in front of her the quality assurance report for the hospital and the data quality report, and she goes through that and she says okay, now, you have a patient who's out two years and nothing has happened, we need to sit down and talk about that patient, you know, adverse events, whatever. So we go through each patient like that and we get a good idea of what's going on.

So, we think it's an efficient way to actually perhaps do a better job at auditing than the traditional look for every scrap of information in a few patients, we would rather get the good stuff in all patients.

DR. REDBERG: Thank you. I have next Dr. Pina, then Dr. Feinglass, then Steinberg, then Heseltine.

DR. PINA: First of all I want to

thank all the presenters, I think you've done

an outstanding job of putting the field out there. My questions have to do with gender. I haven't heard much of the differentiation between men and women, particularly in the adverse events under INTERMACS, so that's one question.

And then the follow-up, since now that we have a larger database of pVO2 on women with heart failure, should we be thinking of lowering that less than 14 pVO2 to a different level for women as opposed to the men? Maybe Jim or Dave, you can start.

DR. KIRKLIN: Well, at least in a multivariable sense, gender has not been identified as a specific risk factor, so the outcomes in women have been similar.

DR. PINA: Including AEs, like bleeding, stroke?

DR. KIRKLIN: Yeah, so I'm going to ask David, would you comment on what knowledge we might have about AEs that you may be more familiar than I in terms of gender, is there any?

DR. NAFTEL: So, we're going through the adverse events one by one and we almost

always perform a risk factor analysis. I cannot off the top of my head recall gender coming in.

But if I may back up a little bit, and this will probably be the concluding remark at the end of the day by INTERMACS, but with apologies. You know, the partners are NIH, CMS, FDA, but NIH has driven the whole INTERMACS effort, but we've said from the beginning that we want to engage CMS or we want CMS to engage us, and that's why we're so pleased to be here. So we're making a list of everything that's being asked and we're hoping we can continue to work with all of you in making very specific reports, and Ileana, especially go after this question. We have a couple extracts of gender but there's a lot more to do, so I'm looking forward to a collaboration, so keep asking the questions and every time we say no, or we don't know, we will make a note and talk about it later.

DR. REDBERG: David, I just want to

follow up. I believe we published, the FDA study that HeartMate II was approved on at least had higher rates of bleeding and

complications in women, and I think that's true in others. But following on your comment that it's NIH driven, as you know, a lot of the NIH databases are now open access. Is this going to -- I don't believe it's currently open access, is that correct, so is it going to become publicly accessible?

DR. NAFTEL: Yes, that's a great question. So as Jim said, we started out as a scientific database, and we have made provisions and have handed the INTERMACS data with deidentified data to researchers. That's as far as we've gone. There certainly is the mandate that NIH, who owns the data, that we hand all the data to NIH, NIH does make it available, but that's usually tied to the end of the study and we don't want to be at the end of the study, so we don't have any provision that I know of. I know NIH is represented here today and they may have a different answer, or a better answer.

DR. REDBERG: Thank you.

DR. AARONSON: Keith Aaronson, University of Michigan. There are data, as you mentioned, for bleeding, there's also data for

stroke in some of these databases for increased risk in women.

In terms of the pVO2 question, this may be kind of a strange answer, but this question is fairly complex and I'm not sure I know the answer, but the oxygen consumption is a function of the exercising muscle mass in part, and so for a woman, a 65-year-old woman with a pVO2 of 14 is actually not bad, it's probably 60 percent or more predictive. So if those numbers were derived from studies of middle-aged men, and using something else would probably make more sense if you were going to use pVO2 as a criteria.

DR. STEVENSON: Lynne Stevenson. I just want to underline the issue of I don't think we're doing the right thing for pVO2 right now for either transplant or VAD. The original landmark data from Donna has really guided us, but that was back in 1991 before we

used beta blockers, so I really think the pVO2 needs to be reexamined both for transplant and for VAD, and I suspect the number will come down.

Additionally, it's one of those things

that will allow us to better assess the benefit of VAD and transplant, so we need the data post-VAD the same way as we have it post-transplant, to be able to anticipate what the delta will be.

DR. LEVY: Wayne Levy, Seattle. If you look at the data, we have a pVO2 of over 1,200 patients and ten-year follow-up, and the ROC change was .008 and that was added to the Seattle Heart Failure Model which was almost useless. At NHF Action we presented data that the pVO2 was about a .01 change, it was not statistically significant at one year in 2,300 patients, neither of which affected efficiency or exercise duration. So it can be guiding, but I think we have other ways that we really need to assess risk beyond pVO2.

DR. STEVENSON: But I do have to say, the difference between pVO2 and any risk score

is that pVO2 has intrinsic validity, it says what you personally can do, as opposed to a risk score that has no physical translation. So I think the pVO2 will remain very useful, it can tell us whether people can do the square dance, whether they can golf with a cart or

without a cart. I think it has very interesting implications to be able to tell patients what they can expect with the therapy.

DR. REDBERG: Thank you.

Dr. Feinglass.

DR. FEINGLASS: So coming on the tails of Dr. Schwartz, my question is about criteria for certification. It sounds as if CMS and JCAHO have somewhat different definitions of that, and I would posit that we probably need one criteria. I would be curious to hear from those of you that spoke to this, what should that criteria be and can the groups get together to figure out what that should be.

DR. AARONSON: Keith Aaronson, University of Michigan. The STS is in active discussions with the Joint Commission regarding some of the elements that were mentioned today

with respect to surgeon training and criteria, so that process is ongoing. So we hope to have future meetings, in fact some are planned, to address some of those issues.

DR. FEINGLASS: In the near term or long month, within the next few months we might get resolution on this, or longer?

DR. AARONSON: I would hope in the near term would be our goal, yes.

DR. JESSUP: Mariell Jessup, University of Pennsylvania. I would just give you one other example. The American Heart Association in conjunction with JCAHO tried to come up with certification of advanced stroke centers similar to what an advanced VAD program would be, and you know, it involved a number of different stakeholders, which would be necessary here, and it wasn't simple. It took a lot of time and a lot of will, but I think people are very much in our community for that, as long as there was a voice from all stakeholders.

DR. SCHWARTZ: Can I add on to that.

DR. REDBERG: Is it related to this?

DR. SCHWARTZ: Yes, directly. Is there anybody here, including physicians from Duke or other surgeons, who don't believe that the issues raised by Dr. Pagani are, if not needed, are at least reasonable to consider? Is there anybody here who thinks that the current criteria are appropriate, or should we be taking as a given that they need to change?

Is there anybody that feels they don't need to be changed.

DR. AARONSON: Well, I think the bigger issue is really a dichotomy as to what is currently acceptable for transplantation, what we are currently doing in LVAD therapy, so you have to have some kind of melding of those expectations. Because right now the training experiences that one receives in residency are adequate training for what constitutes heart transplantation, so why should we be more strict and hold a different opinion in the arena of VAD?

DR. SCHWARTZ: It strikes me that there is a logical or practical pathway for people to become certified. It seems like a

Catch-22 if you have to do ten procedures before you can be certified in the procedure, so you have to build.

DR. KORMOS: Well, maybe one of the reasons you might want to consider that is there's a limitation on hearts to transplant; however, there may not be a limitation on implantation procedures.

DR. AARONSON: But if residents or

fellows are able to get those volume requirements in training experiences even with heart transplantations, you would think that the number would be lower, and it's not, it's actually higher, and they may still meet those expectations.

DR. GOLDBERG: Lee Goldberg from the University of Pennsylvania. I do want to make the plea that it's not just about the surgery, that making sure that you have a heart care team that includes cardiologists that are certified, because it is patient selection, it is long-term follow-up. It's critical what happens in the OR but that's only four hours of the life of a patient who has to live with

this, so it is the concept of certifying not only the surgeon, who is one integral part of the team, but actually a health care team that includes cardiologists that are trained and social workers and financial staff and whatnot, and so similar to what we've done in transplant, creating a model that is a village around these programs is absolutely critical for long-term success. So it would be, I think it's just critical that we don't focus only on

the surgeon, because it's not just about the surgeon, they are critical, but it's all of them that is actually needed.

DR. SCHWARTZ: The intent of my question was the broader sense.

DR. REDBERG: Thank you. The next question is Dr. Steinbrook.

DR. STEINBROOK: Somewhat related, I was hoping that several people might address the issue of heart transplantation, what is the overlap between the centers, and I think there are 144 or 145 which are doing these devices, do we know anything about volume issues and overlap of volume, do we know anything about

the whole heart transplant enterprise and whether that seems to be related in a big picture sense to how well one does with these procedures? You see what I'm getting at?

DR. KIRKLIN: Jim Kirklin, UAB. So, there are, 113 of the 140-some that are designated as destination therapy centers, I don't have the exact number in my head, but I can tell you with confidence that it would be less than ten, less than 12 that would be destination therapy alone without a transplant

program, so it's very uncommon.

DR. STEINBROOK: But with the new ones which are coming along, is the overlap staying tight together, or is there anything which can be said about the volumes and things of that sort?

DR. KIRKLIN: Well, I'm not sure about the new programs that are coming on line, whether they will more likely be DT-only, is that the question?

DR. STEINBROOK: Yes, if the growth in the ones which are DT-only has been separate, but maybe historically had been limited to

places with transplant, but not as much now.

DR. KIRKLIN: I think even in the initial stages of INTERMACS there were a small number of programs, I don't know if it's statistically important, but there were a small number of programs in the beginning as there are now that were destination therapy only, but it's a very small number.

DR. REDBERG: Next we have Dr. Heseltine, then Kormos, then Sedrakyan, Brindis, Donovan and Faught.

DR. HESELTINE: Thanks. I too would like to thank the speakers for their clear presentation, it has been very valuable. I have two questions really for Drs. Kirklin and Naftel. The first probably is fairly straightforward to answer and that is, because your trial is in fact a registration trial or registration, registry, not a utility or obviously not an RCT, my question actually speaks to the fact that in three periods, 2007, '9 and '12, you lost about 15 percent or so of the hospitals participating, and I would like to understand what that does to the data in

your opinion.

And my second question really speaks to our question one, which is if we look at the group 4 classification, your group 4 classification, it seems to me that I don't see the breakout of the benefit versus the adverse events as clearly as I would like to, and perhaps you and others might speak to that.

DR. NAFTEL: The chart that I showed that had those dips in the hospitals, that is 100 percent an artifact of protocol amendments. So you know, you heard a lot of talk about who's in, who's out under compliance, but

there's no discussion about a current IRB. So that is totally, when we have a new IRB amendment, we give the hospital 60 days and at the end of that you're inactivated, you're not kicked out, not by any means. We do everything we can to get you back activated and back active, and do everything we can to have no data lapse during that period. So you see in each case, it comes back up, and it's that bunch coming back.

So I think throughout the whole

experience, I believe we lost one, maybe two hospitals, one stopped their VAD program and I forget the other one, but I know it's been a maximum of two that we've totally lost.

DR. HESELTINE: Can you speak to the second point, really the INTERMACS classification 4 patients.

DR. KIRKLIN: Well, the information that I showed you, you can refer to those slides. There's not a great difference in adverse events at least as we've looked at it to date, except in levels 1 and 2. So if you are seriously ill, then some of the adverse events are more common, but otherwise there

seemed to be, if you will, greatly related to the device and the experience of being on the device itself as opposed to how ill the patient was when he came into the setting and received the device.

DR. HESELTINE: That's really my point, the adverse events rate is not greatly different in that group, so I'd have to look at the benefit versus that adverse event group, that's really what I would like to speak to.

DR. KIRKLIN: Yes, and of course that -- I'm sorry. For some adverse events it is, but for things like pump thrombosis, bleeding, neurologic events, driveline infections, it's really not different, but of course as Keith and Frank can speak eloquently to, that's the reason for REVIVE-IT, to examine the risk-benefit ratio in those patients who are more ambulatory but importantly impacted by heart failure. And of course this is one of the challenges of, even in comparing things like the quality of life that Lynne Warner Stevenson was referring to in a medical group versus a group with a device, because eventually we're going to have all together

come to some common definitions about when a patient decides which is worse for you, coming to the hospital six times during a six-month period, or walking, or never coming to the hospital but constantly having a driveline infection, for example, or the possibility of suffocation versus the outlook of could I have a stroke from a thrombotic issue. So it's of course extremely complicated, because it's not

like the same adverse events are going to occur in one group more frequently than another, it's a completely different set of adverse events in transplantation, device therapy and medical therapy.

DR. HESELTINE: So would you agree in that group we don't have sufficient data yet to be able to determine that risk factor?

DR. KIRKLIN: I would agree.

DR. REDBERG: Thank you.

DR. KIRKLIN: It's an ongoing process.

DR. LEVY: Wayne Levy, Seattle. I would propose that we should record the Seattle Heart Failure Model score as a virtual control which would allow you at least an estimate of the mortality benefit. It will not estimate

adverse events or other things, but for each individual patient or groups of patients, you could at least say this group would have had a 50 percent survival with medical therapy, they're actually 75 percent. They have a 50 percent reduction in mortality, you may be able to estimate that and see whether or not the benefit is fixed or whether it varies based

upon their baseline score.

DR. REDBERG: Dr. Teuteberg.

DR. TEUTEBERG: Jeff Teuteberg, University of Pittsburgh. Kind of in answer to your question too, I guess the question is how different do we know INTERMACS profiles 3s and 4s are, although there's sort of a Rubicon of these processes being inotrope-dependent, it's very different from center to center. You may go to one center and that same person who might get started on an inotrope and be very stable, may be at profile 3, and maybe at another center would not be on inotrope, just be at home, and they may not feel as well, but they're not an actual profile 4. So the question is sort of how much drift there is between these two categories too, and whether

that may be part of the reason for such low numbers.

DR. REDBERG: So as I understand it, there is inter-center variability in those classes.

DR. TEUTEBERG: Yeah, so it's subjective. I mean, most of us would roughly

agree with when someone is inotrope-dependent, but I think we could walk down the line and say when does someone become inotrope-dependent, and I think that would vary from patient to patient, so there may be some fluidity between those profiles. I think the closer you get in these profiles, they are a little more subjective.

DR. STEVENSON: I just want to clarify. I think between 3 and 4, we wouldn't disagree that a person on inotropes is 3. What we might disagree on is would you put them on inotropes or not.

DR. TEUTEBERG: Right.

DR. STEVENSON: You might, I might not, et cetera.

And I think it's important to point out also that for the profile 4, our current

understanding of their survival is that it's significantly less with the VAD, I'm sorry, with medical therapy than with the VAD. So as soon as we move beyond the resting symptoms to somebody who is comfortable at rest but has symptoms with exertion or activity, there I

think it becomes less clear that there's a benefit. But I agree, the transition point is somewhere in there in the ambulatory patients.

DR. REDBERG: Dr. Kormos was next, and then Dr. Sedrakyan.

DR. KORMOS: So, I want to follow up on this variability in implant rates in various metropolitan areas, because you can go to cities with the same population and see implant rates that vastly differ between those two cities, and I know there's regional differences in heart failure, but we're not talking about that. So this is really a question for Mariell and Lynne. There are accepted standards for medical therapy of heart failure, and one of the entry points is very clearly delineated in the coverage decision, it's failure of medical therapy. So is there in fact consistent agreement on what medical, optimal medical

therapy is, and more importantly, how broadly is that applicable across sites? Because if it isn't, then we've got a huge amount of variability, and how do we address that point?

DR. JESSUP: Mariell Jessup,

University of Pennsylvania. To answer your question, is there a broad agreement about what constitutes advanced heart failure, I think was your question, I could point to a written statement by the European Society of Cardiology several years ago that was published that outlined criteria, Lynne Stevenson outlined several criteria, but like everything else in medicine, there is the science and then there's the art, and I think there are many doctors who will see a patient with severe heart failure symptoms who will say this is end stage when in fact they haven't even been adequately treated at all.

And I think similarly to when you present a patient to surgery and say we want to do bypass surgery, and they'll say this is a really sick patient, I'm not going to do it, whereas another surgeon may say boy, this is a routine case for me. So I mean, the short

answer is we like to think that there's a standardized criteria, but so much of this is the art of medicine and so there's not.

DR. KORMOS: But then this becomes

really critical when you're moving onto the transplant centers and the non-transplant centers, which is inevitable, so how do you equate all this? Because like Jeff said, if you turn left you get a bridge-to-transplant VAD, if you turn right you get a destination VAD. How do you level the playing field?

DR. JESSUP: Well, I completely agree with you, I think this is why me personally and the American Heart Association feel that it's very critical to examine the team and to recognize that there is, by having a team filled with experts, both surgical experts, cardiac experts, nursing experts, and patient advocates on the team that's going to determine whether they get a transplant or palliative care, there needs to be a consensus of experience and training, and putting the patient in the center of care, and I think that is the only way we're going to do it, which is why I personally, but I'm representing the

American Heart at this moment, feel that it's very critical that we have strict criteria standards of VAD centers as we move forward,

and I would defer to Lynne.

DR. STEVENSON: I agree completely. I don't want to mix up sort of the science with the art. I think this is part of the reason why we want to certify the cardiologists at these centers as having advanced heart failure training. If you take someone who is certified in advanced heart failure, take them out of a transplant center, put them in a center that does only VADs, they still have the skill to identify a patient in fact that has failed medical therapy.

I would venture to guess that of the heart failure cardiologists up here in the front row, we would probably do the same thing in four out of five patients. In the fifth maybe I might try a little longer to do something else, but it would be a relatively narrow margin. I think it's the experience that determines the caliber.

DR. REDBERG: Does INTERMACS collect data on the medical therapy that the patient's

on prior to VAD or whether they were on optimal medical therapy? I'm seeing people nodding

yes. Dr. Teuteberg.

DR. TEUTEBERG: Jeff Teuteberg, University of Pittsburgh. And Bob, you know we see this. Of the patients who have advanced heart failure in the community, if they make it into a center which has advanced heart failure specialists, then I think they will get adequately triaged. With the different rates of VAD across the country, there may be centers, there may be cities where those patients never make it to the advanced heart failure center and we never see them, and so they never get an option for advanced heart failure therapy. The question is whether there are a lot of people that are hiding out there in the communities, so to speak, with questions, do we actually get to see them?

And I think I would agree with Lynne, that we would all generally agree on who has failed advanced medical therapy for these very sick patients, but in the community for the people who haven't been seen, I think it's very very low.

DR. REDBERG: You can answer briefly,

we have about three minutes left.

DR. GOLDBERG: Lee Goldberg from the University of Pennsylvania. I do want to say one thing about optimal medical therapy in the stage 3 patients. As Dr. Stevenson mentioned, many of these patients are not tolerating optimal medicine. When we record the data on INTERMACS forms they're not on a beta blocker or ACE inhibitor because they're in shock. And so it is very difficult post hoc to say well, were they on it in the past, we don't capture that, we just know what they're on at the time, so I just want to put a caveat that that data may not be as helpful as you would like.

DR. REDBERG: Just one.

DR. STEVENSON: I think this is very important, that when we look at it we look at not only what they're on, but INTERMACS also captures what have they been on, so basically you can tell if they have been on optimal therapy and then deteriorated to the point where they can't tolerate it.

DR. REDBERG: Okay. I didn't find it at least in the presentations, but we can come

back to that after lunch perhaps. Our last question before lunch is my vice chair, Dr. Sedrakyan.

DR. SEDRAKYAN: Thank you, Rita. I guess the benefit of being the vice chair, I can ask the question or be way off.

I think most of the discussion focused on this facility and surgical learning and the criteria. So Dr. Aaronson, you reported that most recent literature shows much better outcomes and you attributed that to increased learning. The same as Dr. Goldberg, you also treated it year by year outcome improvement through surgical learning. And then we heard from Dr. Steinbrook that in fact a lot of these centers are also transplant centers, so they're not naive to these patients. So how much of that improvement do we really attribute to learning versus you attribute to lowering the thresholds, getting to INTERMACS 3-4?

DR. AARONSON: This is Keith Aaronson, University of Michigan. By learning, I would attribute it to a surgical learning curve, but also the learning curve with respect to patient selection, which I guess you're sort of getting

at in terms of critical illness. Clearly there's been less INTERMACS 1 and progressively less INTERMACS 2 as time has gone on. The number of patients in 6 and 7 hasn't changed all that much, but the ratio of 1 to 2 versus 3 to 4 has gotten smaller with time.

I think we've learned a fair amount about patient management that we didn't know initially, and continuous flow devices are better than pulsatile devices, and I think all those things are contributing. Quantifying that is another question.

DR. SEDRAKYAN: Another question. Is there more patient selection that you can share with your colleagues rather than them really learning by doing more?

DR. AARONSON: I can't quantify the difference. I mean certainly if you look at the trials, sometimes we see very early on investigator experience plays a role in the first outcomes, but when the center has put in their 20th versus their 40th, or the 40th versus the 70th, it's not clear.

There was some work by Kathy Liepzis some years ago suggesting that volume made a

difference with the XDE experience. But relating -- all these things are changing simultaneously, so to be able to say how much is changes in what the surgeons are doing, how much is changes in what the cardiologist does, the VAD coordinators and even, frankly, the support groups where the patients are getting together and talking to each other, I don't know how we can tease that apart really.

DR. REDBERG: Quick comment?

DR. PAGANI: Yes. The other issue is when you talk about the number of VADs you're not talking about at the specific surgeon level. So if the center did 15 VADs, there may be three surgeons putting those 15 VADs in. So any number, in any of these data experiences that they've talked about are not talking about specific, you're talking about a program number that accomplished that.

DR. REDBERG: Thank you. We will wrap up this morning, and I will thank the panelists and the speakers again, the speakers for great presentations and the panelists for a very stimulating discussion, and obviously there are a lot of issues identified.

I will just highlight I think some of the ones we will particularly come back to, because we do have another hour after lunch, are questions about what are the volume outcome criteria or other criteria that help us to identify best outcomes, what facility-specific and patient criteria there are, the role of the heart team, because I think we've heard a lot from all of you about the importance of the heart team, and what considerations there should be in accreditation to get the best outcomes for our Medicare beneficiaries.

So, I will thank everyone. We have cut into lunch a little bit because we're still coming back at one o'clock, because we're going to have a lot more questions after lunch. Thank you.

(Luncheon recess.)

DR. REDBERG: I would like to welcome everyone back from lunch, hope you enjoyed the Thanksgiving festivities, and we will resume our panel discussion and questions, and actually Dr. Brindis is up next for our questions.

So we will have basically, I will just

go over the format for the afternoon. We will have an hour to continue open panel discussion with more questions, and then we will focus in on the voting questions which Dr. Smith went over this morning. Focusing on the voting questions is particularly helpful, and I will point out if we can try to focus our discussions on particular outcomes in Medicare beneficiaries, so persons over 65 as well as persons under 65, the total population who are also covered by Medicare, because that is the charge of this committee.

As well we can focus, as I said before, on the heart team, the accreditation, and a lot of the very interesting issues that have been raised, and then we will take the vote and then we'll continue to have discussion after that, and we will end no later than 4:30.

And all our presenters, if you can come back and sit in the front row, because we are not done.

DR. BRINDIS: Thank you, Ralph Brindis. My question is a clinical one. I

want to learn a little bit more about the whole complication of aortic insufficiency with

continuous flow pumps. I remember seeing one slide saying the frequency may be as high as 25 percent but sometimes it may be of clinical importance. And so as we approach an era where we may be using more destination therapy on patients who are at so-called lower risk, I want to get a flavor for how significant is this clinically, aortic insufficiency.

Two, is there, I guess intuitively and I could be wrong, is this a time-related phenomenon, do we have to follow patients now with continuous flow pumps long enough to understand if it gets worse over time, and maybe some understanding of AI.

DR. PAGANI: Aortic insufficiency is a significant concern with long-term support depending -- there has been a number of studies that have been reported and the incidence may be as high as 20 percent at two years of some degree of AI that's new, and it can lead to complications such as recurring heart failure and need for reoperation for the valve, so it

is of concern.

There is some potential contributing factors. Having the aortic valve continuously

closed may lead to a higher incidence of aortic insufficiency at least, and how you manage blood pressure.

DR. BRINDIS: So the timing of destination therapy and relationship, is that also predictors of somebody's underlying aortic valve in terms of patient selection, have we learned anything related to that in aortic insufficiency here?

DR. PAGANI: In terms of a surgical approach for the valve at the time of operation, depending on the surgery, but there is a general consensus that with moderate degrees of aortic insufficiency on board, you would certainly have to address the aortic valve at the time of the operation of the LVAD, because if you let moderate aortic insufficiency grow more, that would obviously get worse with implementation of the LVAD as the LVAD drops the pressure and then increases afterwards, so that would be addressed at the

time.

With respect to long-term support, it's approximately 20 percent at two years to develop some degree of aortic insufficiency

that is de novo, that they didn't have at the time of operation.

DR. AARONSON: I don't think in terms of more than mild, it's just plain mild. Aortic root dimensions are a predictor, blood pressure is a predictor, and the valve opening.

DR. REDBERG: Dr. Donovan was next, then Dr. Mock.

DR. DONOVAN: I think this question is primarily for Dr. Stevenson. In your presentation you did mention the concept of a standardized informed consent. I'm convinced that this is a very complex area, we've already heard that you can drive down the street, turn right, turn left, and have a different outcome in terms of procedure. Certainly information that's presented to patients could have the same effect. Are you aware of any mechanism where a standardized informed consent could be employed for patients who are candidates for

ventricular assist devices or can you imagine any at this time?

DR. STEVENSON: I think this is absolutely crucial. At the moment as I understand it, the certifications only include

that you have a standard informed consent, meaning a standard for your own site. As we all know, those informed consents vary greatly from center to center, they're usually completely unintelligible to the layperson.

And furthermore, I think there's an assumption by many patients, particularly older patients, they have what I call the fly or die illusion, that they will either fly out of the hospital in great shape or they will die on the table, which in many cases is not that frightening to them. They don't understand that there's a very large continuum in between which they may not want. I would think that it should become part of the standard criteria but that specific pieces of information should be included. Furthermore, it should be included in a language that patients will understand, even though they may have limited numeric

literacy, which may in fact require a diagram with a hundred happy faces and 30 sad faces, for instance.

I think that the implications of this actually go far beyond VADs, they should be there for transplants, for any other cardiac

surgery, for TAVR, for ICDs. I think this is one of the very few areas in which we might both improve care and decrease costs by not doing things to patients that they wouldn't want if they knew what they were.

DR. REDBERG: Thank you, that's a really important point, we want to improve care.

Dr. Faught, I think you had a question, and I didn't want to skip you.

DR. FAUGHT: It's a little bit of a more general question. I'm concerned about the screening criteria for the procedure. Now we're all accustomed to a fairly rigorous screening criteria for transplant procedures, which usually involve not just creatinine, but also some sort of cognitive screening, psychological screening, looking at the social

situation, so forth. How congruent is that with what's required for the VAD centers and should it be made more congruent or more systematic?

DR. TEUTEBERG: Jeff Teuteberg, from Pittsburgh. I mean, I think all of our patients we're assessing for destination

therapy, for any VAD therapy, get that evaluation as part of that, they get sort of the full transplant evaluation, and I think there may be some --

DR. REDBERG: I'm sorry, are you speaking for your center or for everyone here?

DR. TEUTEBERG: I'm seeing a lot of nodding heads, that when you get evaluated for DT you very rarely get evaluated for DT alone, you're getting evaluated for advanced heart failure therapies, are you a transplant candidate, are you a VAD candidate, or is there something else we can be doing for patients, they mostly get all this stuff. I think there may be some patients who clearly would not be transplant candidates, if they had colon cancer two years ago so you would not transplant them,

but they would still get a lot of that evaluation anyhow because so may of those things are important to how patients do over time.

DR. STEVENSON: Lynne Stevenson. I think in the majority of transplant centers that I'm aware of there is a standard evaluation form for transplant and that has

been amended, in some cases even lengthened, to be a sort of a standard evaluation form that includes everything needed for VAD as well.

DR. FAUGHT: Right. One of my concerns as well is that it's going to spread outside of transplant centers, and I'm just wondering what should be mandated in terms of the screening criteria.

DR. AARONSON: Keith Aaronson, University of Michigan. One of the things I think I heard you ask about was neurologic assessment, emotional assessment, psychiatric assessment beforehand, and as you know, that's standard in transplant evaluations but it's equally important in the VAD world, that these folks, the emotional burdens of mechanical

support are substantial, the need for family support or other means of support, so we will do, have a neuropsychological battery test, five or six-hour testing over a couple of periods is done fairly commonly if there's any question, particularly more in the DT population, the older population.

DR. REDBERG: Actually I was going to ask a question next, and then get to Dr. Mock.

My question is not so much on the specific treatment of patients, but in preparing for this meeting I went back and reviewed the pivotal trials and started with REMATCH, because in particular our voting questions have to do with how does VAD plus optimal medical therapy compared with optimal medical therapy alone, and that was the only randomized trial I found that actually had a medical therapy arm. I was glad to hear MedaMACS was starting. So going back, I realized that the trial was 2001, but all the trials that have come after that were just comparing one device to another without a medical therapy arm, and especially in light of what we've heard about VADs moving

into a lower risk population where clearly medical therapy would visibly have better outcomes.

So my question, I was struck in REMATCH that the two-year survival in the medical therapy arm was eight percent, which is very very low, and certainly in none of the later trials would I have expected the two-year survival to be so low, and then of course in the device arm it was 25 percent. But in the

figure that, the Kaplan-Meier analysis, you know, at 24 months there's only five people left in the LV assist device group and three people left in the medical therapy group, and that was the only long-term data I could find.

And not only that, in the actual trial that didn't account for everyone in the trial. As you know, there were 68 people in the device group, 61 in the medical therapy group, and the trial was ended at 92 deaths. So if you add 92 and this, that doesn't account for what happened to the rest of those people. And there are little X's that say censored, but there's nowhere in the message that says why

they were censored. In the inclusion criteria it stated that you had to not be a candidate for transplant to be in this trial, so I would have thought maybe they were censored, and I don't know why I should be guessing, I thought it would be in there but I couldn't find it.

So I'm just wondering, number one, what happened to the rest of those people, why were they censored, and do we have any additional data that, because now we're talking about long-term destination therapy, you know,

two years or more, and I find very little data to compare that to medical therapy. So I was wondering if anyone could help me understand this trial and where we are now. Lynne is one of the authors, so I would ask you first.

DR. STEVENSON: In the REMATCH trial, at the time I think we all agree, it was a very small database, as you noted. Having been involved in that trial, I can tell you it was the hardest trial I've ever done in my life, because to take people who are INTERMACS profiles 1 or 2 and say it's a VAD or nothing, is something that we would never do again, I

personally couldn't do it, and I don't think really any of us could.

To answer your question about what happened to them, some of those actually ended up moving over to VAD after their two-year follow-up. A couple did get transplanted although at entry they weren't transplant candidates. I can't tell you exactly what happened to all the little X's, it's clearly a very small group.

However, I think now with the VAD survival being as good as it is at one year,

that no one would ever feel the need to document the survival of INTERMACS 1 and 2 without a VAD, but as you say exactly, it highlights the need to have the survival on medical therapy for the less sick patients before we begin to embark on putting VADs in there, and I think this is really a crucial thing to do, and REVIVE-IT is a good example of how that will happen.

DR. REDBERG: Do we have more data on that now to inform us, because I didn't see medical therapy arms in the other trials, and

obviously INTERMACS doesn't have a medical therapy data component.

DR. STEVENSON: I don't think you'll ever get a medical randomized arm for INTERMACS profiles 1 and 2, I think it would be very difficult to do.

DR. REDBERG: But I'm not restricting that to just 1 and 2. You're saying 1 and 2 because that's what REMATCH --

DR. STEVENSON: I'm saying that for 3 it would be home inotropic therapy, which I think there are enough experiences with home inotropic therapy to show that the survival has

been less than 25 percent at a year, so I don't think that people would feel comfortable randomizing to home inotropic therapy either, which puts us at INTERMACS level 4, which is about where we're trying to get more data in the medical arm.

DR. REDBERG: Dr. Mock? Thank you.

DR. MOCK: I would like to go back for a couple minutes if we could on patient selection. As I'm thinking about getting the best care for the right member at the right

time, and I'm again thinking about the explosion of the numbers of centers that are doing VAD implants, 10,000 members a day aging into Medicare, and then we have the population that's most vulnerable, the special needs clients, the disabled members that for whatever reason have heart failure at younger ages.

As I look through the INTERMACS criteria, I think I saw two questions that go to what you were saying earlier today, Doctor, frailty and socio, I think it says psychosocial issues, yes or no. So my question is, are we asking the right questions in INTERMACS, or when you, the leaders in this field, are

sitting here, there's not 144 of you here.

As an industry, when we look at our answers, is this applicable to the CMS population, we have to be able to answer that with some security. Are the questions appropriate, are we asking the right questions to put these procedures in the right patients, and is the information that you presented today something that we can apply to the Medicare population?

Is that -- I'm sorry, did you get the question? And just to be specific, if you can help us in answering the question in the form of the question that we need to answer today, that would be probably most helpful.

DR. STEVENSON: We've actually done quite a bit of work with the INTERMACS team trying to define what we would like to know about patients in terms of some of the factors you mentioned, specifically frailty, and Joanne Blumenfeld has done a lot with that. We tried to look into how to incorporate some measures of frailty into both MedaMACS, which we are able to do because that is a research study specifically, and into INTERMACS, but there's

no easy way, as you've heard, to have 8,000 people to be able to support the kind of data entry it takes to assess frailty, you know, without some kind of reimbursement to the sites for support staff to do that, but I think frailty is critically important.

The issues of psychosocial status, the cognitive ability, those as you've heard are routinely evaluated in terms of both transplant

and VAD. I have to say that it's not something that we have been able to quantitate in a way that I think I could enter on a data form, but it's certainly something that we discuss every Wednesday morning at our VAD meetings where we often have the neuropsychiatrists evaluate patients and help us know, would this person be able to change their batteries, et cetera, but I don't know a score that would easily go into a data form.

DR. MOCK: And could you just help me understand, since this isn't my primary field, give me a feeling of the average VAD patient that's in the Medicare population, whether they're young and frail or whether they're a bit older, how long are they going to be in the

hospital, how many days do they spend in the ICU, when they leave acute care do they go home, do they go to AIR, do they go to SNF, kind of help me understand that.

DR. STEVENSON: I would say that the VAD patients that we prefer to do, which I consider the, sort of the goal would be a 72-year-old man who has had heart failure for

six or seven years, has gradually deteriorated but has not yet malnourished, still an ambulatory patient. May have had a recent ICU admission but is not in the ICU now, in fact hopefully has been able to go home, think about this for a while so he is making a reasoned decision within his family to schedule him electively to come in for an assist device, maybe in a few days before that to tune up a little bit for the surgery, then optimally would go home at 14 to 21 days and would go home with his wife. That's what we hope for. How many exactly fit that, I would say certainly no more than half and probably less than that. Mariell, do you want to add anything to that?

DR. REDBERG: Can you quote what you

would tell him would be the adverse event chances? You were telling us about the little smiley faces and the things; what would you tell him to put you on the spot, Lynne?

DR. STEVENSON: I don't have all the data for that. I would tell him that he has probably, in terms of smiley faces, I would say

that his chance of being here a year from now is 70 smiley faces out of a hundred, I would say that his chance of a stroke is 11 sad faces out of a hundred. If it's the ambulatory patient that we discussed, I would say that the chances are four out of five that he will go home directly after the transplant. That would give you an example but I have to admit, I don't have all the data to make the whole chart of smiley faces that I should have.

DR. HESELTINE: Isn't the patient you described a level 4 patient?

DR. STEVENSON: Yes. Frankly, the level 4 patient is the patient right now, I think, that I would be looking at, someone who's truly miserable with their current life but still ambulatory, for destination therapy.

DR. HESELTINE: But your point was, I

think, that we don't know what the outcome is for those patients compared with the complication rate compared with their overall survival rate on medical therapy.

DR. STEVENSON: The profile 4 patient in fact, I think from the data that we have, if

they have symptoms at rest, we're talking about a less than 50 percent one-year survival, if they truly have symptoms at rest for the profile 4. It's when we move out of that that I have more difficulty. If it's a patient who has symptoms at rest on medical therapy and I'm beginning to think, gee, if I can't do a VAD, is this someone I might think about putting on continuous inotropes, it's right in that level. But I am pretty comfortable with someone who has symptoms all the time, even at rest, that their chances of both survival and quality of life are better with a VAD.

DR. KIRKLIN: Jim Kirklin, UAB. I think it's fair to say that in most of our experiences for patients who are either rapidly deteriorating or in shock, then there's no issue, they're not going to survive. But the vast majority of other patients actually have

some time to reflect and say I want the device, that would be 90 percent of the patients that we operate on, they would have some time to reflect about it and say I'm unhappy enough with my lifestyle, quality of life, and

although they're interested in knowing about, in the levels that we're currently implanting, that is basically 1 through 4, that they are unhappy with their quality of life whether they're 50 or whether they're 73. They're either tied to inotropes or having repeated admissions to the hospital, or are unable to do anything meaningful, and they are actively asking for the device.

And so in the current way that mechanical support surgery is practiced, and I think most would agree here, that it really, in general terms, it doesn't take convincing of the patients. Now there are some patients that are not interested and then there's no further consideration, but for those 1,800 patients who have been implanted, they're either critically ill or they're actively seeking mechanical support.

I think when we talk about levels 5, 6

and 7, now that's a whole different issue in which it becomes incredibly important to look at the various markers of quality of life and so on. But just in brief, you'll remember that

the little information we have on quality of life shows that those who are seriously affected are dramatically reduced after a year after device implant, and that's basically true through level 4.

DR. JESSUP: Mariell Jessup, University of Pennsylvania. I completely agree with what they said but I felt compelled to say that unlike somebody that wakes up and has a heart attack, heart failure in general is a process, and I think that's why you're also hearing us say that in the best possible setting, a patient that has progressive heart failure, they end up in a center that has a variety of options to offer this patient. So whether they're 72 or 52, you know, you can present a series of things, you know, you may get better with medicine, we may be able to put CRT in and you'll get better, you may need a transplant, you may be only a candidate for a VAD. And I think it's a continuum, so it's

rarely just a VAD or no VAD, and I think that's the important issue about criteria that makes me feel compelled to say, remember the data

that we've all showed you, that a third of the patients get a VAD because we're not sure which way they're going. So yes, that means our criteria may be a little squishy, but it means that the relative contraindications to many of these things are just relative, and it takes time to manage them to decide what to do as well, which is, I think, also why it's good to only do this in centers where they've got all the options.

DR. REDBERG: Dr. Steinbrook and then Dr. Sedrakyan and then Dr. Kormos.

DR. STEINBROOK: So, I wanted to get back a bit to the issue of volume and center-surgeon comparable experience. What if we came up, and I think this would be of special interest for Dr. Stevenson, Dr. Kirklin or Dr. Kormos, is the relationship between the INTERMACS data and the universe of ventricular assist devices which are being implanted. In other words, and again, this isn't my specific field, but it seems like there's a lot of

clinical trials going on, and that's good because the technologies are getting better and

that's good for the patients.

But I'm wondering kind of at a macro level, if there's 1,700-odd ventricular assist devices a year which are getting into INTERMACS, how many more are actually being implanted, and could there be some way to capture that information in terms of center-to-center experience, because there may be issues with particular devices, the proprietary issues within these trials, et cetera, but that is a surgery and there is some experience there if those numbers are sufficient.

DR. PAGANI: For destination therapy, I mean, the two, the one active trial or two active trials that are in process now are the HVAD trial for destination therapy, and that enrolled 450 patients over a period from August of 2010 to May of 2012. Then there was the BTT to CAP series, which enrolled about 330 patients, right, over a period of 18 months, and that started -- let me see -- 340 patients. And then there was the Dura heart-lung trial which only enrolled 63 patients. So you know,

there is roughly 700 patients, 800 patients

over two-and-a-half years.

(Discussion off the microphone.)

DR. STEINBROOK: So 1,700 to 1,800 in the database each year, correct, new additions?

DR. PAGANI: Over the last --

DR. STEINBROOK: Over the most recent years, so that's a substantial number?

DR. KORMOS: Right, but there will be new trials, I mean, there will be ongoing new trials that will be continuing to enroll patients.

DR. REDBERG: Thank you. Dr. Sedrakyan.

DR. SEDRAKYAN: Thank you. I have a question about the functional outcomes and quality of life. Many speakers highlighted that this is really a critically important outcome, and I really need your opinion, how trustworthy you think the data is that you have right now. Dr. Kirklin, you have shown a slide on visual analog scales, and it has shown that from preimplant levels there was substantial improvement at three months and then it stayed constant. Then I'm comparing that with the

eighty percent of people progressively getting major adverse events at two years. So there seems to be a lot more people cumulatively getting these adverse events, and yet it's not reflecting on their function and quality of life. Do you have any comments about that?

And I might also tie that to the question about six-minute walk because Dr. Aaronson, you reported on one of the slides that for HeartMate II, you compared it to CRT of 30-40, but your baseline for that population started from 150. So, can you clarify this for me?

DR. KIRKLIN: Well, we have a paucity of data, and this is one of the reasons that we are in desperate need of a mandate from the medical profession and from the regulatory profession about making requirements to collect certain kinds of information on every patient. Our quality of life data beforehand has been crippled partly by the fact that it overestimates the quality of life because those patients who are too sick aren't participating. Afterwards the variables are, we really can't even qualitatively analyze the variables which

predict which patients are going to be enrolled in a quality of life questionnaire, it's somewhat determined by the level of resources available at the center because it's not considered standard in their follow-up.

So I think the degree of difficulty of getting valuable information is very difficult. We've had endless conversations about strategies and whether we pay the centers, incentivize them one way or another. But at the end of the day, INTERMACS reflects the actual practice of care for patients with VAD therapy, and so to the extent that the standard of care is to get this additional information, then we would be able to provide very useful information to you and the scientific community in general, but we are hampered right now because if you look at the numbers on the quality of life, and the numerator and denominator is almost depressing in terms of what we're collecting.

DR. REDBERG: Also, while you're here, did you also say earlier that there was almost no change, or maybe someone else did, between peak VO2 in the preimplant data and the

postimplant data, or was that --

DR. AARONSON: There was -- this is Keith Aaronson, University of Michigan. There are no peak VO2 data in the clinical trials post, we're going to actually do it in REVIVE-IT, but that wasn't captured.

DR. REDBERG: So we do not know the impact of VAD on VO2?

DR. AARONSON: We do from individual centers, we have some data from VAD centers, but it's not in the clinical trials.

The improvement of VO2 is not that dramatic. It actually is disproportionate to the improvement in six-minute walk, the improvement in six-minute walk is actually larger in general relative terms, but you're thinking as sort of a heart failure doctor what the six-minute walk is compared to the VO2.

The six-minute walk, to get back to Art's question, in the HeartMate II later study we did distinguish between patients who didn't walk at all at baseline and their comparative improvement, and patients who did walk initially were less sick, and they still improved a lot, about 200 to 350 meters. So

it's certainly inflated by indicating a value of zero in the six-minute walk, but even if you limit it to those who did walk, there's a huge improvement in walk distance.

I think the question about how does quality of life improve when adverse events occur is a fascinating question, and there's strong literature showing that patients rate their quality of life very differently when they have adverse events and actually experience them than what they thought they would have had before they had them. If you look at the REMATCH study, you know, the patients lived eight months longer but five-and-a-half of those months were spent in the hospital, yet they rated their quality of life as substantially higher, and the survival effect. But even among the survivors, they had these adverse events, but that's quite well known.

There's a classic paper with a statistical analysis looking at surgery with radiation therapy, and it was very clear afterwards that in fact the whole process was

faulty because when patients lost their voice,

they thought it would be terrible beforehand but they actually didn't think it was so bad afterwards, so there's -- what's that?

(Laughter.)

DR. REDBERG: So, the reason I was interested in VO2 is because I was struck by Lynne's comment that that was the only objective measure, because I don't know how subjective or objective six-minute walk is, but clearly we're talking about non-blinded comparisons. You've got one patient that got incredible benefit from the procedure and yes, they felt better, they thought it was wonderful, but the other person clearly didn't feel that same kind of investment in them, so I'm trying to separate subjective from objective criteria.

DR. AARONSON: There's data showing that for heart failure patients, six-minute walk generally gets to about 85 percent of predicted VO2, or let me rephrase that, 85 percent of what they would do on a maximum test, but obviously that is variable

and there are people who don't make that effort. The improvement in peak VO2 that we've

observed has been around 3.5 or 4 mills per kilo minute among those who were actually able to exercise at baseline.

DR. LEVY: One brief answer which may help. A 100-meter improvement in six-minute walk is a one point change in NYHA class, so when you're talking about 150 to 200 meters, you're talking about 1.5 to two changes in NYHA class, so both the NYHA class and the six-minute distances are very concordant.

DR. REDBERG: Dr. Pina, and then Dr. Mock.

DR. PINA: I want to clarify that the pVO2 data that we have, we have it from, I think it was called EVADE, wasn't it, it was post the pulsatile devices, and the highest peak VO2 was 14.5, and that was like over 12 or 15 years ago, we don't have anything newer than that.

DR. REDBERG: Okay. Dr. Rich, yes.

DR. RICH: I have a clarifying question for Dr. Kirklin. I believe this is

true, in that no data from clinical trials ever gets to INTERMACS, INTERMACS is a total post-commercialization database. Can you get

the data in there post hoc and you add it to INTERMACS later, or do you just do meta-analyses between the INTERMACS data and trial data?

DR. KIRKLIN: Initially during the genesis of INTERMACS, we had planned actually with Thoratec to put their clinical data trial into INTERMACS and they were very anxious to do so. Unfortunately as you can imagine, if the database during the clinical trial is not the exact same variables and the same programming, then it is a whole new set of programming that has to be done to make translatable their clinical trial and the elements to be put into the database. I could just tell you from experience, that just never happened and I don't think it will happen because it's expensive, takes a lot of time, and everybody is very very busy with INTERMACS and in the company to be able to allocate that amount of time, X number of months to do the

translational programming. So as of right now we do not have, unless the study is done through an INTERMACS platform, then we don't have the ability to get clinical trial data

really into INTERMACS even if the company wished to.

DR. REDBERG: Dr. Kormos, then Dr. Steinbrook, then Dr. Schwartz and Dr. Brindis, and then we're going to focus on voting questions.

DR. KORMOS: So, this is actually a question I want to direct to Mr. Scott. There's a lot of discussion about how a regulatory body that enforces certain standards and sites interpret what the requirements are from CMS. I mean, it's really left up to that regulatory body. How do you see moving forward if you were to do this, how do you see working with CMS and/or other academic societies, for example, to help define the criteria for what is an appropriately trained cardiac surgeon and/or cardiologist, because it's not -- I mean, you stated your requirements here, and thank you for sharing that, but again, they're

broad and they can be interpreted many different ways. So how do you work, I mean, how are you going to work with societies to help nail that down? We've heard some discussion from STS but there is no mechanism

currently that's acknowledged by Joint Commission right now for training a cardiac surgeon, so how do you move forward with that?

And the second part of that question is, do you do this universally, because heart failure is of course without borders and there's translation of physicians and surgeons between borders all the time, so how do you -- for example, are you considering doing this in Europe as well?

MR. SCOTT: Thank you, Darrel Scott, with DNV Healthcare. The program as we have submitted and as you have the requirements for, is one that has been developed with the field, it has been developed with clinical consultation with Johns Hopkins, and has been submitted for comment with two large VAD centers and has been peer reviewed, and we view that as a continuum, ongoing process, as a

document that can continue to be refined as the field, as the clinical field is refined. And so it's not a program that is stamped and fixed forever, it's a program that has evolved in constant consultation with our clinical partners and that's how we're going to do it.

In terms of will we transport this to Europe, our main focus is doing it first in the United States and then depending on the demand for it and how it evolves, that certainly is a possibility, because as you know, DNV is a worldwide certification organization. So that certainly is a possibility, but our main focus now is the initial approval for the United States.

DR. REDBERG: I think, Robert, you were next.

DR. STEINBROOK: Just to briefly follow up on Dr. Rich's question, the response, it's really more of a comment, but it may require a push from the government, CMS or FDA, but it seems like there are a lot of missed opportunities by not making the registry data as broad as possible, both from the standpoint

of the center experience, the surgeon experience, the volume issue, and also from all these other things that we're talking about, and there's obviously a lot of experience now which we didn't have five or ten years ago in terms of what questions you want to ask, what things to collect, and standardization of

things. I mean, even if industry data was somehow not available until after the trial was done and an FDA decision was made, there are a lot of opportunities, I think, to move in that direction and be able to harness that for the benefit of patients going forward.

DR. KIRKLIN: Jim Kirklin, UAB. Of course you're preaching to the choir and we agree with that in spades. And just by way of explanation, you know, for us it's the art of possible. So NHLBI in their wisdom, and we agreed with it initially, was that they couldn't mandate, they felt uncomfortable mandating that clinical trial data with all the privacy issues and so on would be automatically mandated into INTERMACS, so we lived with that.

The next is missing patients with

informed consent. Initially this was a scientific database so we had to get informed consent. So now NHLBI is putting their full power behind getting an initiative to waive that, so we're moving in that direction. And the FDA is doing their part in trying to encourage companies to put their clinical trials through the INTERMACS platform, but they

can't force that. So we're trying the best we can and I think we're making progress in greater representation of the vast database of VADs out there to be collected, but we have a few barriers.

DR. REDBERG: At this time I want to read the voting question one so that we can focus any additional comments and questions that people want to resolve before we vote on this question. And so it is, how confident are you that there is adequate evidence that specific patient criteria can be used to prospectively identify clinically meaningful changes in health outcomes, improved, equivalent or worsened, that are likely to be experienced by patients who receive a VAD in

addition to optimal medical therapy compared with optimal medical therapy alone?

And CMS has defined the health outcomes of interest as the clinically meaningful changes that we're particularly interested in deciding on of mortality, adverse events, patient function and quality of life.

So with that, if there are any comments from the invited speakers from today

or from our panel.

DR. SEDRAKYAN: I have a question related to our first voting question. Dr. Stevenson, you mentioned particularly in the context of the standardized consent, it's important to translate this information into an understandable format for a variety of subgroups of patients, so patients like me. Have you ever done any work, say, profiling the ten most common patients that are part of the INTERMACS now, or anyone here among the presenters, to quantify those benefits and potential adverse events and harms so that we can compare to objective performance goal with medical therapy? Is there anything that would

be a Decision A format currently that we can use for voting on question one?

DR. STEVENSON: No.

DR. SEDRAKYAN: So, because most of the information --

DR. REDBERG: The answer was no, for the reporter.

DR. SEDRAKYAN: A lot of the information was about risk ratios and showing three-time, four-time higher chance of

mortality or event occurrence, but it was very hard for us to put it in a context of a profile of patients over 65 with renal failure, with INTERMACS 4, what would be the event occurrence. So some common scenarios that could help us answer this question in a patient-centered way? And so the answer is no.

DR. REDBERG: Yes, Dr. Mock.

DR. MOCK: Maybe, Dr. Aaronson, you would be in the best position to answer this. I want to make sure that I understand the inference that was just made regarding readmissions and quality of life. So my question for any of you that can answer is what

would be the 30-day readmit rate for a Medicare eligible member that underwent a VAD implant, and then is that five-and-a-half months out of eight is in the hospital? That was what I thought I heard. The inference I was making is five-and-a-half months out of eight in the hospital might not be seen as a good quality of life.

DR. AARONSON: That was with REMATCH with the XVE where we were expecting -- this is a pump that's no longer made, and technology is

going to be mandated in patients who were substantially sicker than those who now on average get implanted, but those data are historically interesting when read in the context of that even patients who suffer a really negative adverse event profile still view their quality of life as better given the point improvements of heart failure symptoms, but it's not relevant at all in terms of this question.

DR. MOCK: So I still would be very interested, then, in an answer to the first part.

DR. KORMOS: Well, so, that -- let me just make a comment here. We're actually in the midst of analyzing the readmission rates in INTERMACS. It's a fairly complex analysis for a variety of reasons. But I think at six months, I think we're looking at about 30 to 40 percent free of readmission, so about 60 percent of patients would have had at least one readmission within the first four months.

DR. MOCK: And those are 3s and 4s, or 5 through 7, or all?

DR. KORMOS: I don't have that

information.

DR. AARONSON: We've looked at our data at Michigan and it looks like the average patient would have eight days in the hospital following the initial hospitalization, one of which would be on the ICU and seven would be on a regular floor bed.

DR. REDBERG: When you say the average patient, what age is that average patient?

DR. AARONSON: This is the average of all the patients who are at the University of Michigan. You know, our average

bridge-to-transplant patient is probably in their early 50s, their actual -- the trials, the average bridge-to-transplant patient is in their early 50s and the average destination therapy is in their low to mid 60s, lower end of 60s. In our center I think those would still hold, maybe a little bit older, but reasonable.

DR. REDBERG: So would it be fair to say for the average Medicare beneficiary who was mostly over 65, that the majority are women, and it might be longer?

DR. AARONSON: It might be fair to

say, but I don't have those data.

DR. REDBERG: Does anyone else have those data?

DR. MOCK: Would you think in the future it would be beneficial to segregate that information so that we could have that information about Medicare members?

DR. REDBERG: So, Dr. Heseltine.

DR. HESELTINE: So, let me make sure that I'm getting this right. I'm focusing now on, my question is focused on patients who are

likely to be Medicare eligible who are in the 3 and 4 group, levels 3 and 4. Now I understand that the initial mortality or initial complication rates which you've shown primarily are driven in large part by level 1 and level 2. But as I see it at the end of the year, you've really only got about 30 percent of patients who have not had some sort of complication, at the end of two years you've got only about 20 percent of patients who have not had some sort of complication.

So if I look at, particularly the class 4, but even some of the class 3 patients and I ask myself the question, can I compute to

some extent the complication rates for living with medical therapy versus the VAD, that's where I'm struggling to try and balance the data that you've demonstrated to us.

DR. LEVY: Wayne Levy, Seattle. So if you look at the Seattle Heart Failure Model, it's roughly ten days per year per 10 percent for annual mortality, so if you're putting them in with somebody with a 50 percent annual mortality with medical therapy, you'd expect

them to be in the hospital 50 days per year, so if the hospitalization was 12 days, they would have four hospitalizations during the year in the type of patients we're describing.

If we're looking at the less sick patients it might be 20 days a year with two hospitalizations, so they would have a very high readmission rate with medical therapy alone.

DR. MOCK: Does the Seattle classification take into account socioeconomic or education, or all call, no age?

DR. LEVY: The variables are age, gender, ejection fraction, blood pressure, medical therapy, and simple lab variables like

hemoglobin and lymphocytes, which actually go down with age, along with uric acid and cholesterol level. So there is no socioeconomic status or other things included.

DR. STEVENSON: I think it's still important just to remind ourselves that the INTERMACS data that we have currently, more than half of the patients are profile 1 and 2, with a one-year survival estimated at less than

five percent for one, less than 20 percent for two, so I think the issue of kind of readmissions in that group is really not relevant because they're dead, so it's pretty cheap.

DR. MOCK: Quality of life, Doctor, that was the question.

DR. REDBERG: That will be our last comment before the vote on question one, so I'm going to read the question one and then I'm going to ask each of the voting panel members to vote, and then you can each --

DR. GRANT: Can we pose some questions about question one?

DR. REDBERG: We did just pose them.

DR. GRANT: No, I just had a question

about the way it's framed, that it's saying specific patient criteria, so are we talking about INTERMACS as a classification, are we talking about sex, are we talking about age? For example, what we've heard about some of the INTERMACS groups, is that considered a specific patient criteria?

DR. REDBERG: I can kind of help.

I'll interpret it and then let Art comment, and if anyone else from CMS wants to comment, please do. I interpret specific patient criteria to be just what, if you were a physician and deciding how to advise your patient, you would look at these criteria and say based on your age and your sex and your renal condition and your, you know, overall health, and perhaps in a few years but we don't have it now, frailty, I would advise that your outcomes from this procedure would be X.

So you're asked to say currently, do you feel there's adequate evidence that we have that we can identify these specific patient criteria in order to prospectively identify, to advise a Medicare beneficiary or patient, this is just patient, clinically meaningful changes

in the health outcomes listed. Does that answer your question?

DR. GRANT: The question is does it apply -- I mean are we talking about all, are we talking about INTERMACS class 2, are we talking about 2, 1, or are we talking about 4?

DR. REDBERG: We're talking about all

patients who receive VAD.

DR. GRANT: All patients.

DR. SEDRAKYAN: Yeah, absolutely. My understanding is the same as Rita's, 1, 2, 3 INTERMACS, renal failure, any characteristics that prospectively can be identified. At this point it's more general, the next question is more clarifying and we can discuss in the next question if there are any specific criteria that you think are able to help us.

DR. HESELTINE: I don't want to belabor this but I tend to agree with you, but the question here is being driven by two facts. One is that we know that half the patients are levels 1 and 2, and the others are level 3 and 4, or maybe even higher. So to answer this question, I can do it I think based on some data for some patients, but not for the great

majority of patients, or at least if I've misheard data, so that's the struggle here.

DR. REDBERG: I understand that, but this question is to address the general question of a patient for VAD, and then as Art said, it will become more specific. Is this

another short clarifying question?

DR. BRINDIS: Yes, because I also have extra nuances for this question, in that I think that we might be able to do a lot of these things if we may have infrastructures, tools that we could do these things, but they may not have been totally applied. And so the question is, can it be used? Well --

DR. REDBERG: No. How confident are you that there is adequate evidence right now, is there adequate evidence that specific patient criteria can be used to prospectively identify. We're talking about right now, can you do that, not what can be in the future.

DR. BRINDIS: Well, let's say we have the criteria -- I apologize. The criteria is there, it's not being fully collected at this time.

DR. REDBERG: You're answering the

question of what you can do now.

DR. BRINDIS: Okay.

DR. REDBERG: I'm just going to remind you that you would vote one to five. One is that you have low confidence that there is

adequate evidence to answer this question currently, five would be you have high confidence to answer this question currently, and obviously three is intermediate. You can vote one, two, three, four or five, and then after the vote we will discuss, each panelist can discuss why they voted how they did.

DR. SCHAFER: And real quick, I'm sorry, I call your attention to adequate evidence. So is the evidence adequate, that's the first question that we're asking, and then you can go talk about the specifics.

MS. ELLIS: I just need to say for voting purposes, what I need everyone to do is to basically push the button that is on your keypad one through five, whatever your vote is. You can hit the button as many times as you want. The last score that you choose is what will be displayed. Once everyone has voted, the next step will be for everyone, for us to

go down the line and state your vote, and this is including the nonvoting members also. There will be two scores at the end of the meeting, okay?

So again, we need you to state your name and your vote, because again, this is being webcast, okay?

Could you just hit the remotes one more time? Someone did not push the button.

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

MS. ELLIS: Thank you.

DR. REDBERG: So the vote was a mean of 3.22, and at this time I'm going to start with Dr. Sedrakyan and we'll discuss our vote.

DR. SEDRAKYAN: Art Sedrakyan, three.

DR. BRINDIS: Ralph Brindis, three.

DR. FAUGHT: Ed Faught, four.

DR. GRANT: Mark Grant, three.

DR. HESELTINE: Peter Heseltine, three.

DR. MOCK: Curtis Mock, three.

DR. RICH: Jeff Rich, four.

DR. SCHWARTZ: Sandy Schwartz, three.

DR. STEINBROOK: Robert Steinbrook,

three.

DR. FEINGLASS: Shamiram Feinglass, three.

DR. DONOVAN: Kevin Donovan, three.

DR. KORMOS: Bob Kormos, three.

DR. PINA: Ileana Pina, two.

DR. REDBERG: So at this time you can see, there's a discussion question. If there is at least intermediate confidence, and we do have at least intermediate confidence because the mean score should have been greater than 2.5, then we're going to discuss what prospective patient criteria predict, one, clinically meaningful improvements in health outcomes; two, equivalent health outcomes; and/or three, clinically meaningful worsening of health outcomes.

So for all of you who voted, do you want to make any comments on what specific prospective criteria you had some confidence would predict these health outcomes?

DR. SEDRAKYAN: I think my understanding was that the INTERMACS criteria, particularly 1, 2 and 3, have substantial face validity and evidence behind it. I'm less

convinced that starting from 4 we have adequate evidence for us to make a proper decision based

on the criteria that are part of the, let's say 3.8, starting from 3.8 or 4.1.

So in addition to that, there are a number of risk factors that were discussed, including renal failure and right ventricular function, so those were identified as important potential predictors of outcomes or worsening of outcomes. Older age certainly has been associated with worse outcomes in terms of survival. I was less convinced that we have enough evidence to understand how quality of life and functioning is changing based on these risk scores, aside from probably again INTERMACS 1 and 2, and maybe 3.

And I was unsure if I can differentiate these risk factors from bridge-to-transplantation with destination therapy. I mean, I think the risk factor profiles seemed to be similar for both of these conditions in terms of worsening or improving of the health outcomes.

DR. REDBERG: Dr. Brindis.

DR. BRINDIS: Rather than being

repetitive, I'm going to just focus on a couple

comments. I think that we understand issues related to heart outcomes related to mortality, but I'm more interested in our challenges that we have related to PROs or patient-reported outcomes, and I appreciate that we have some infrastructure tools that can get us there, whether it be from Seattle or pVO2, or other patient-reported outcomes, and we need to devise and empower our INTERMACS registry to have a stick that is dressed up as a carrot to be able to assess this for us going forward.

I'm also concerned that we need further expansion in our understandings of chronic complications. I think that I'm a little less confident about some of the chronic complications, in this case related to neurologic and maybe even aortic insufficiency, but again, trying to assure our population going forward how we can best assess that, and again, empowering INTERMACS with kind of the infrastructure tools and the carrots and sticks to do so.

DR. REDBERG: Thanks very much, and thank you for that reminder also, Dr. Brindis,

that we don't need to repeat a point even if you agree with it that's already been made, but just anything additional. Dr. Faught.

DR. FAUGHT: Yes, this is Ed Faught. I'm very pleased that we have this kind of tool, we certainly don't have it in a lot of disease states, and I felt really that there are several very concrete criteria that I heard that are useful in determining possible outcomes. I would like to see something in between quality of life and more physiological measurements, something like activities of daily living, Rankin scores, something like that. It's always easy to ask for more data from the people that are doing the surveys, I understand that, but I think some better understanding of some of the functional outcomes would be useful.

DR. GRANT: I won't repeat anything obviously, but I will say I was tending actually toward voting a two, and I'll try to explain a little bit why.

I mean, I think first is the issue about the decision-making here, which all of you I think have illustrated quite well, the

decision-making surrounding using these devices is very complex, and so it's just, it takes a lot of different factors, it's a big huge network, that's one piece.

The other thing is the structure of the evidence, and I was thinking of what would happen if I went to systematically review this evidence and draw conclusions about it, and I think for the higher risk INTERMACS stages it's pretty clear. But as Rita alluded to before, what we have is we have one randomized controlled trial that is old where we are asked to compare optimal medical therapy to best medical therapy. In every study we have non priori comparison subsequently, and then we have single-armed trials, and the premise of identifying predictors in these single armed studies from my perspective is to say that we know, if you believe whether we can predict it or not, what would transpire for these patients if in fact they did undergo that.

That kind of evidence is very difficult in my mind to synthesize and to judge unless the outcome is absolutely certain. So when you move up those stages it becomes in my

mind very difficult, and even more difficult to identify these specific predictors.

And I wanted to just reiterate something that Art spoke to before. The other part that's missing here in my mind in terms of presentation of evidence is there's a lot of relative risks, you know, and they're good, you know, they're informative if you have this disease. But what drives decisions are sensitivities and specificities, and false positives and false negatives, and those are the kind of data that really allow making an informed decision based on evidence from my perspective. In this case, the only identified predictor is just the patient should have a VAD and this one, you know, given this particular class.

DR. HESELTINE: Peter Heseltine. In addition to my colleagues' comments with which I agree, I wanted to focus for a moment on the lessons we've learned in other spheres of medicine which we could apply here. In doing cancer trials for 35 years, and we've been doing registry trials for a whole host of chronic illnesses, it seems to me that while

there is an appropriate emphasis on PROs, none of these or very few of these have actually been evaluated. What I would really like to see are validated PROs in this field specifically relating to VAD, that would allow us to interpret what patients really feel about it and what, in terms of their things that are important to their life, actually seem to have a difference, not just being alive.

The other part about this is that I also have real concerns about the technology creep aspect of this. As physicians we tend to do things because we can, and so I need to be absolutely sure that I'm not in fact creating adverse events which I don't perceive to be particularly important, but the patient may well perceive it to be important. These would include not only infection, but also things like thrombus apart from stroke and heart attack, and the other more obvious ones. So again, I think that we need to focus and reach out to other standards in other areas of medicine and apply them here, rather than think that we're in a bubble and we can invent it all

ourselves.

DR. REDBERG: Thank you. Dr. Mock.

DR. MOCK: Curtis Mock. I have to say, I'm walking away from here thinking that VO2 is a pretty valued predictor in success of implantation. I would have to say that the way this question is formatted to include the outcomes that CMS asked for makes it a challenging simple answer. Certainly there's been great presentations over the day that showed that survival is a metric that is clearly comparable. However, on the other end of the outcomes we're being asked about, the quality of life is not so well supported. So as we move forward in an important aspect in the care of our Medicare membership, I'm just hungry for more information and more data that would be specific to those aspects of their care and their life, and as you mentioned, Doctor, their caregivers and their life at home.

DR. RICH: So, I do agree with your opening comment about the ambiguity of the question, and so I've personalized this.

Working in a center doing 50 VADs, seeing level 1, 2 and 3 INTERMACS patients all the time, I

don't see all the other levels, so I answered it on the basis of the way I practice my medicine and the way I implant things, so I felt like it was really good evidence.

But I do agree that the second half of the equation is that quality of life and functionality is extraordinarily important, and I think we've had really deep discussions when we were talking about transcatheter aortic valve replacement, so you can put a transcatheter aortic valve in a 90-year-old but if she ends up with a stroke or you have to amputate her leg, is that a good outcome? No, it's probably not a good outcome. So I'm on the, with high technology like this with a lot of dangerous and serious adverse events, I do think we need that extra additional information, but I answered it from the facts that I have for my patient population.

DR. REDBERG: Jeff, I'm just going to ask you because we have a second part to that question, so I'm going to let you start with

the second part and then we'll come back, so you will have the first opportunity to crack this one. Do these criteria vary if the

intended use of the VAD at the time of implantation is one, bridge-to-transplantation, or two, destination therapy? And just add that and the rest can answer both of those at once, and then come back to Art if he has anything.

Do you want to add anything else on whether it would differ if it was BTT or DT, those criteria?

DR. RICH: The way I had answered it?

DR. REDBERG: Yes. What you just answered, do you think of it differently when now specifying a VAD for bridge-to-transplant or specifying a VAD for destination therapy or do you think of it all similarly?

DR. RICH: I kind of bring it together, I think of bridge-to-candidacy, it's so homogeneous now with patients that you can't tell when you first meet them whether they're going to be a transplant candidate or they're a destination therapy candidate, so you're kind of stuck in that middle ground. So I try to

evaluate the patients fairly and openly, and let them ultimately move in whichever direction physiologically they go after they start the therapy.

DR. REDBERG: Thank you. Sandy.

DR. SCHWARTZ: Well, I neither currently or in the past have cared for these patients, so --

DR. REDBERG: So you have nothing to say?

(Laughter.)

DR. SCHWARTZ: But I think it's based on what I read in preparation for here, and the information presented here, as well as talking to some people who have experience about their clinical experience. My thoughts largely, I don't really have anything significant to add to what's been said before, I will leave it to Art, Ralph and others.

I gave it a three, I think there is, you know, we can make reasonable clinical decisions, but as you get into B, then I think the more you parse that, the more we get into subsets, the more we look at interactions

across clinical parameters and variables, the less confidence I have. And so I think by the time it gets down to individual decision-making in some patients I think we can feel more comfortable than in others, and I think there's

a -- intermediate to me means we can get by, you know, should we offer it to patients for whom the people with clinical expertise based on the evidence feel that they can make a reasonable decision in conjunction with the patient, but we certainly have a high priority for developing better evidence in these areas.

DR. REDBERG: Thank you.

Dr. Steinbrook.

DR. STEINBROOK: I just want to focus on B and specifically destination therapy. We didn't have much discussion on this, but it stands to reason that if people fortunately survived longer with these devices in place that there will be a set of questions related to device failure and long-term complications and whether device A as compared to device B is what to be concerned about after four years. Of course, to be at four years is doing

reasonably well, so that's a good problem to have, given this situation. But I think that the people in the field, as I'm sure you already have, need to be thinking about some of the things which are going to become relevant as the data continues to evolve and people are

followed.

DR. SCHWARTZ: And Rita, one other thing. I think there's a real need to understand at the individual level the tradeoffs between likelihood of benefit and likelihood of harm given the high rate of serious complications that occur, both in patients who are not treated with this and who are treated with mechanical assist devices, so I think it's really important to start being able to come up with more individual clinical predictors to guide the clinical decision-making.

DR. REDBERG: Thank you.

DR. FEINGLASS: Shami Feinglass. I would add here that I'm fairly confident that this is the right thing to do for levels 1 through 3. I think there's some question for

all of us for anything greater than level 4, and I commend the speakers for the comments on what you all are doing to gather more evidence in that area, but I think that is less clear than 1 through 3.

DR. DONOVAN: The only thing I would add about the first question was it was

supposed to be a comparison with medical therapy, and I think we've heard enough that the optimal medical therapy is somewhat variable and that really makes the comparison a little less compelling.

I was also concerned about what appears to be a false dichotomy between bridge-to-therapy, destination therapy, and I'm not sure that those categories serve the best interest of the patients, and I think they perhaps should not exist.

DR. REDBERG: Thank you, Dr. Donovan. Dr. Kormos.

DR. KORMOS: Well, I'm kind of torn. I mean, I'm on both sides of the fence here as everybody sitting here knows. Having said that, I think we have good evidence that

survival benefit exists in some classes of patients who get this therapy. Can you do harm, absolutely, but I think that's the challenge of some of the newer trials that are going to be coming up here, to understand in these less sick patients whether we can produce harm or not produce harm.

I struggle with the quality of life

information as to how we get to that, because I really don't know how much more cardiac output produces a better quality of life. Does it really get rid of the heart failure state, or is once somebody is tagged with a heart failure state are they always going to have exercise limitations because of some of the very things we discussed, such as frailty and deconditioning, and attitudinal differences of how you're going to live with heart failure. There's just so many factors that influence your ability to do an exercise test. So I think we need the information, I think it's just going to be hard to really nail it and that's going to require some work.

I honestly believe that we can

identify who's a transplant candidate. After that, I'm not so sure. There are those that are in between and you can call them bridge-to-candidacy or whatever the hell you want, but they're just not transplant candidates. So I think we've got two classes of patients that we're really looking at, those that are listed and those that are something else, and maybe they're DT, maybe they're not,

and that's where perhaps a heart failure indication has more relevance than this sort of kind of intellectualized subset of classes that was really developed by industry to help them qualify their devices, it has nothing to do with the reality of how we work.

DR. PINA: I'm also on both sides of the fence here and I voted a two, and I'll tell you my reasons why. The clinical trials that were done to get approval for these devices was for a different population than what we're seeing now in INTERMACS. It was a very carefully chosen population for a clinical trial, and even in those trials we felt the pain of missing quality of life information,

missing functional assessment, on whatever is out there is based on a lot less in number than were actually enrolled in the trial.

We don't have a great quality of life issue for these very sick patients and I think Jim Kirklin said that, and I know that we've been talking about getting one and trying to validate it, and it is a lot of work, because for these patients just getting out of bed may be an improvement in quality of life if that's

all that they've been is in bed, so I am not confident that I can say who these are going to be. And so as we move more and more into the Medicare population, which we're seeing a lot of, things like frailty, things like a low albumen showing malnutrition, things like anemia are going to have a much much bigger bearing on the results, even though the surgery may be done well and how they recover postoperatively. So in this older population, I am not confident that we have enough criteria.

And I also agree that the lines are blurred, that this, you know,

bridge-to-transplant, bridge-to-destination are blurred, and I don't think it's ever been the intention of the Agency or the FDA to make those distinctions, it really needs to be done by industry, and I would be much more in favor of a bridge-to-decision, or a bridge to whatever happens next.

DR. REDBERG: Thank you, and on behalf of the panel I'm going to say I thought we had a great discussion, and we were really grateful to the speakers, I think we all feel like we

have the world's experts here in heart failure, use of ventricular assist devices, and cardiac transplantation, and so that we were really able to evaluate the data where we are.

The consistent themes I heard listening to the voting panel were that while we certainly have specific patient criteria and INTERMACS is a very valuable registry, there is a crying need for more patient-reported outcomes and in particular for really meaningful quality of life and functional status measures, you know, things that would mean something to any of us if we had to make

that decision for ourselves or for a loved one, you know, how much more could you do, would your life be in doing things that we enjoy or in a hospital bed, and then have it individualized with benefit and harm, and we will talk about this a little later with question three about how this can be generalized for our Medicare population.

And so with that, we'll now turn to voting question two, and I'll read it and then we can have a discussion and then the vote. So now we're going to look specifically at, how

confident are you that there is adequate evidence that one or more facility and/or operator characteristics predict clinically meaningful improvements in health outcomes for patients who receive a VAD in addition to optimal medical therapy, compared with optimal medical therapy alone? So we're really looking now at facility and/or operator characteristics.

Did any of our speakers have any comments or anything they wanted to add to address this question? Okay, we can vote on

that. I think we did have a lot of discussion about these particular questions, so if no one has any additional comments or questions, we can take the vote. So now we will vote similarly on question two which I just read, I don't need to read it again, the panel has your clickers, and then there are discussion questions for these as well.

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

Okay. So now we have a mean of 2.33, so there is less confidence, in fact that would be intermediate to low confidence in this

question, and actually if I read this correctly we are not going to have the discussion questions now because it says only if there is at least intermediate confidence, and we fell below the 2.5 cutoff. Actually, I'll let -- so we can discuss, thank you, B and C. Okay, let's go back and get the vote, and then we'll do that, thank you.

DR. SEDRAKYAN: Art Sedrakyan, two.

DR. BRINDIS: I voted four, Ralph Brindis.

DR. FAUGHT: Ed Faught, I voted three.

DR. GRANT: I voted two, Mark Grant.

DR. HESELTINE: Peter Heseltine, I voted two.

DR. MOCK: Curtis Mock, two.

DR. RICH: Jeff Rich, two.

DR. SCHWARTZ: I'm the reason we're not discussing this in more detail, I voted one. I would be glad to increase my vote to discuss it, because there's a reason for that.

DR. REDBERG: Don't worry, we'll have a discussion.

DR. STEINBROOK: Robert Steinbrook, three.

DR. FEINGLASS: Shami Feinglass. We can't do .5 increments, right? I was between two and three, so three.

DR. DONOVAN: Kevin Donovan, two.

DR. KORMOS: Kormos, two.

DR. PINA: Ileana Pina, two.

DR. REDBERG: And so now we can discuss the vote, and in addition we can discuss the discussion questions B and C, so I will read those. Please discuss the role, if

any, of facility VAD specific certification to assure attainment and maintenance of any characteristic identified in question 2.A, and please discuss the role, if any, of the heart team concept in the management of patients who receive a VAD. So really trying to drill down on facility characteristics and also talk more about the heart team, which we have all talked about this morning and this afternoon.

DR. SEDRAKYAN: I voted two, and mostly because I think I would want to see more information in INTERMACS with some analysis of the facility level data to see if it really has an impact. I think the fact that a lot of these centers are already transplant centers

was reassuring to me that these centers have experience of dealing with these patients, at least 90 percent of them, and in light of that, yes, it makes sense that the heart team and multidisciplinary care would probably improve the outcomes, but we don't have the data from VAD, we don't have the data from INTERMACS. I think it would be very important for us to have some data, whether it's a volume outcome or any

other information, number of people who have done fellowships, with fellowship training, number of surgeons who are, who have done more than ten surgeries in the past three years, some information, I think that would have helped us maybe rate this higher. But at this point I think there is really a paucity of evidence related to this question.

DR. BRINDIS: So, I need to defend my four. I took the question literally, is there at least one facility or operator characteristic, and we heard overwhelming evidence that the volume of the center is a predictor of outcomes, I think it was two to one in terms of outcomes, or in terms of mortality, we also heard that level of

experience over time led to better outcomes, so I think there is good data related to the volume relationship.

The challenge is that everyone else feels, is the issues of the data being in trials, and I would be very interested in understanding exactly what the Joint Commission does, that is, how much of their certification

is based on systems, how much is it related to process, and how much is it related to outcomes. I'm getting the feeling it's not related that much to outcomes, but I would like to be told differently.

What is the frequency, for example, of the certification looking at the outcomes? We were all disappointed, although I understand the challenges that INTERMACS has, of not having a spread of all the 145 hospitals and their volume-outcome relationship, that's a flaw. And for us as clinicians going forward, we need transparency related to result of the centers to make informed decisions, so those are additional issues in addition to Art's comments.

DR. REDBERG: At this point, there was

also a question on the heart team concept. Did you want to add anything on the importance of that?

DR. BRINDIS: That is as close to motherhood and apple pie as you can get.

DR. FAUGHT: I voted for motherhood and apple pie, but I voted a three primarily on

faith, I'd have to admit, because I believe the places that do heart transplants will probably do this well, as in the same level of quality. However, as was mentioned, we don't have enough quantitative evidence to select the training centers or surgeons, or to really know what constitutes a well-trained surgeon in this area yet, I think.

DR. GRANT: Mark Grant, I voted a two, primarily for the reasons of what I felt was in general lack of evidence. That said, I think the speakers conveyed to me that they all have a good if not completely clear idea of what all these characteristics would be, and my guess is when you do examine the value, you will probably not find too many surprises.

I think it's quite reasonable to extrapolate some of this stuff. I mean, the

evidence on transplant surgery probably will apply here, so I don't think we're completely left in the lurch, but at the same time it would really be important to have those analyses done for transparency purposes.

DR. MOCK: Peter.

DR. HESELTINE: Peter Heseltine. I voted a two because I don't see data to tell me the characteristics given that I'm obviously not going to refer a patient to somebody who doesn't have a hospital or hasn't got a program going.

But to my prior point in the last question, once again, we have international standards for risk management in medical management of patients, 14971, although it falls under 9001, it's really 14971 that we need to be paying attention to if we're going to look at the ISO standards, and I think that that concept of the risk-driven approach to managing these kinds of patients really allows us to then present inevitably because if you're doing this, you're involved in it, it enables you to benchmark yourself against an external standard, which I think is so important in

medicine for us to do, and not just be persuaded because we have a colleague who believes this who is persuasive to you when they talk to you.

DR. MOCK: Curtis Mock. I certainly

feel as though, when my neighbor or my aunt or my brother or my sister goes to a facility for this phenomenal advancement in therapy, if they ever do, I would like to know how that facility performs and how the agent performing the activity performs, and not just the agent but the interdisciplinary team that's taking care of them. I think this is a new day and the results that have been displayed today are an example of that, and I think part of this is personal, because part of the new day is transparency, and for us to have 15 percent of those members not reported is I think not where we want to be. Optimally if it's not, if a facility is not able to record the members that are involved in this therapy, then I can't imagine why they would be reimbursed for performing that. For us to have the transparency and have the mandate that you may need to show these outcomes, I think that's the

place where we need to go.

DR. RICH: Jeff Rich. I voted a two and unlike the first question, I did personalize this. I personalized it, I can

tell you what characteristics at my institution have made it an excellent place to have a VAD implanted, but I don't know that I could articulate that to the rest of the world and say with non-transplant centers doing VAD, this is the set of characteristics that I think are important to assemble a program and be successful from the get-go.

I do believe with respect to the heart team with Ralph, this is what we're promoting and I think the ACC should come out with guidelines for that as they've done with coronary revascularization, I think it's the new way of delivering cardiovascular care, not only in our country but in Europe, so I think it's extraordinarily important. That would be the one piece that I think is pretty solidly established.

DR. REDBERG: Thank you.

DR. SCHWARTZ: Sandy Schwartz. I gave it a one because while I strongly, I'm sure

that there are characteristics, operator and institutional characteristics, for example my suspicion is I'd rather be operated by a

surgeon than a non-surgeon, you know, and things like that. Seriously, I focused on the word adequate evidence, and while I agree with Ralph in terms of the associations that have been demonstrated and the strength of them, having worked on panels like this before, I really think that to have adequate evidence we have to look at the potential confounders, we have to look at the interactions, and to really get an understanding of what's driving this.

So to me with the adequacy of the evidence, I was putting a hat on, if I were a regulator or if I had the jobs of some of the other people in this room or at this table, could I confidently come up with regulations, what is the volume, you know, and the answer is I wouldn't be able to, so I think what I want this decision to mean is that we really have to make this a priority for research.

Regarding the questions B and C, the same sorts of things. You know, I agree with what Mark says, and I think it's going to be a

dog bites man, not man bites dog story when we find out what's going on, we're not going to

find a lot of surprises here about what's going on. The experts, from my experience, are right far more than they're wrong when we get that empiric data to understand what they're saying, and I think what the people think is going to be the case. But in terms of what Medicare and CMS needs to guide their decision-making, I think they need much more specificity.

And similarly for the heart team concept, besides motherhood and apple pie, it's just got so much face validity to anybody who's ever either been a patient or taken care of patients, but can we specify what the really needed criteria are? Even if we look across our institutions, there are significant differences in how we structure these things and that may be fine, but we should find out the incremental points, especially as we're entering an era where there are going to be more constrained health care resources, we really need to know what the incremental benefits are of how we construct these things and how they operate and things like that.

So to me, it was really the adequacy

of the evidence in being able to answer the subsequent questions that we would be forced to answer.

DR. STEINBROOK: Robert Steinbrook. So, in terms of the adequacy of the evidence, I was caught between a two and a three and I had to choose something, I chose a three. I think some of that comes from some inference from other areas of medicine and what we know about other aspects of cardiac surgery, so that's evidence in one sense, but not evidence in the sense of what we sometimes think about on this committee.

But I did have a couple specific comments related to the discussion. Number one, I think we've heard fairly clearly that some fairly rigorous evaluation by someone with very good expertise in heart failure, medical management, really ought to be a first step before anybody goes down these sorts of pathways regardless of what the center was and what sorts of other procedures they do, so I just wanted to say that for the discussion, number one.

Number two, I think we heard and some of the comments on the earlier question reinforce this, that the notion of bridge-to-transplant, destination therapy, that where we are now, it sounds like from people in the field is that that's not as meaningful a distinction. And I think if we're talking about implanting a left ventricular assist device, basically any center which does this, regardless of what happens six months or a year down, ought to be part of registries, part of databases subject to public reporting, et cetera. I think that there are some centers which don't get into the universe of INTERMACS, but I don't know how many there are.

And finally, I think in terms of the outcomes, public reporting, internal quality assurance, you name it, and this is not at all a criticism of INTERMACS, but I think in terms of where things are going, we really need to get every single left ventricular device in there, from registration of the device at the time before it goes into mobilization and track all that. I'm not saying go back and redo everything which has been done over the last

number of years in 8,000-plus devices, but going forward to have a much broader data collection and reporting starting from the beginning.

DR. SCHWARTZ: Rita, there was one other thing that was triggered by what Robert just said about, you know, the thorough medical evaluation by a cardiologist who has significant expertise and experiences. I think the other thing that we haven't talked about today with the institutional competence or the team is the ability to manage the complications that are going to occur, that we know are going to occur. And since we know that the overwhelming majority of people are going to experience at least one major complication, just like with organ transplantation in general, this really requires an institution that can respond across the board, and that should be formally evaluated somewhere.

DR. REDBERG: Okay.

DR. FEINGLASS: Shami Feinglass, I voted a three. As you heard me say earlier, I was between a two and a three. I would agree with the original statement by Dr. Brindis that

this is motherhood and apple pie when you're looking at the heart team concept and I do actually personally agree with that, but I would say if you're asking the direct question, do we actually have evidence, do we know what those end points are, I don't think we do. However, I'm not so sure we need that.

In this case you can take the notion of best practice and look at what are the best functioning groups that you think you have at this point, pull your best practices out from that. You can certainly do some studies off of that, but if you look at the time that has been spent already studying this, and I think it has been time well spent, we're at a tipping point of certainly knowing a lot more than we did several years before, and I think everybody has stated up here already that we think that there should be teams that know how to deal with this stuff really well, that it cannot be everywhere, that there is a heart team, that there is an experienced heart failure staff there before any of this was going on. So again, I would point us to the notion of best practices, not so sure that the nature of this

question lends itself to what I think we need to achieve with it.

DR. DONOVAN: Kevin Donovan, I voted a two for reasons everybody else said. I would not want to take my motherhood and apple pie either, but I do think there would be some value in demonstrating the usefulness of the health care team and exactly what that should constitute, because I'm sure that varies from center to center. But the research has to close the knowledge gaps when we have these problems with an evidence base, and until that happens, maybe we should be restricting VADs to transplant centers.

DR. KORMOS: So, if the question would have been how confident are you that there's adequate evidence that if you have a driver's license you're not going to have as many car accidents, I would have voted two on that one too. I think that part of the reason there's no evidence is because every meeting you go to, and a lot of this, you know, industry has done a tremendous job of educating clinicians in this, it's always about team building. I mean,

this is just harped on so often that it's

drilled into everybody that even wants to do this. And you are a transplant center, you've grown up with this concept, so in some sense it's a question that there is no evidence for because you can't test a null hypothesis.

Now it might be that, you know, having a driver's license doesn't get you into a NASCAR race, so as we move forward and get more advanced into less sick patients again, and we're talking about going into centers that are not transplant centers then we may have evidence at that point, I don't know, it's hard to say.

I think that the heart team concept is just a natural. I see this as a real opportunity, because the opportunity here exists between, there's so many quality initiatives that are built into societal efforts, so STS, AATS, American Heart, Heart Failure Society, all of these societies have tremendous quality initiatives built into them, I know that STS does. This is an opportunity again where we can combine some efforts into

looking at how to measure quality initiatives because I don't know, and personally I want to

lay the burden on INTERMACS to be the adjudicator of sites as to whether they're doing a good job or not. We may want to somehow spread that nasty responsibility out into a broader realm, but I do believe that transparency is paramount, I mean, it's in every other facet of medicine that we do, and it has to be here as well.

DR. PINA: I won't belabor the point, I voted a two, and having seen this develop through the years, to me it's just another arm of heart failure care that requires the expertise of heart failure to take care of these patients. And what happens beyond the VAD we haven't really discussed a lot here today. A lot of these patients don't go home, they go to skilled nursing facilities, you must have a relationship with them to teach them how to take care of these patients. So it's much more so than just what happens in the hospital, it's what happens beyond, and I was raised with the team concept, so I don't know anything

other than the team concept, and I don't think that I could function outside of that team concept, so I think that is absolutely

critical.

We actually do have some information about what constitutes teams, our committee at American Heart, Mariell has already gone, I believe when she was chair, we sent out surveys to heart failure programs all over the country to try to find out what the team was really composed of, and I just thought of that as I was sitting here talking to Bob, and I don't see it in our literature we were sent. But it talks about, you know, how many nurses do you have, how many dietitians, what composes the team, and it was specifically for heart failure programs but the committee is called heart failure transplantation, so I think that we do have some idea of what's going on around the country. Now this was a few years ago, but it's probably not that different.

DR. REDBERG: Thank you all, and I thought that was, again, a great discussion. To summarize what I heard, and particularly the

themes I heard repeated, is that as Ralph said so eloquently, the heart team, we all agree, is like motherhood and apple pie. I would speculate, and this would be speculating, that

perhaps because it's not specifically stated in the disability criteria, but you all took it as a given, and perhaps it is because the VAD did grow up in these transplant centers where clearly there was a team, but I think it probably is much more of an issue now because my understanding is that there, and we heard that there are more VADs going to non-transplant centers to do the destination therapy where they may not have a team and it may not be in the culture as it is for what you're used to. And therefore, specifying what a team consists of and how important it is in terms of patient care would be really important to outcomes. And certainly when we saw the rapid growth in the VAD centers, it suggested that it is spreading a lot more rapidly. I don't know, Jeff, if you know how many heart transplant centers there are in the U.S. currently?

DR. RICH: Maybe 20.

DR. REDBERG: 20, so clearly there are VAD centers that are outside of transplant centers. Pardon?

SPEAKER: 120.

DR. REDBERG: 120, so if it's 145 and there's more adding every week, it seems, it is going to be more of an issue.

The other things I heard repeated were the importance of public reported outcomes, public open data, and again we get back to that INTERMACS registry data should be publicly accessible and available for clinicians and researchers, and that, I heard some suggestions that the facility data should be available, you know, perhaps specifically on hospitalcompare.gov, so that patients knew and physicians knew what the results were at the facilities in their area. So, I think that was all a very helpful discussion, and now we can move to the --

DR. SEDRAKYAN: If I could just add one thing, and this is for Dr. Naftel. Given the data that Dr. Pina has, it shouldn't be

that difficult to add that to INTERMACS in terms of the information about heart teams and also other facility characteristics, and do analysis on that. Am I right or is it a bit more complex than that?

DR. NAFTEL: We do that in the NCDR.

DR. REDBERG: Okay. So now we'll get to the third voting question which we have kind of alluded to already, but I will read it. It's how confident are you that these conclusions are generalizable to the Medicare beneficiary population? And again, I will ask if any of the invited speakers or if any of the panelists have any particular comments or questions on this voting question. Robert.

DR. STEINBROOK: This is related to INTERMACS. Could you remind us what the median and mean ages were of the patients in the registry, particularly in the last year or two?

DR. KIRKLIN: The one slide had the age of 64 for destination patients.

DR. REDBERG: And that was mean; is that correct?

DR. KIRKLIN: I guess so.

DR. STEINBROOK: Well, but -- mid 50s, or 64?

DR. REDBERG: Dr. Kirklin, do you want to go to the microphone?

DR. SEDRAKYAN: We calculated from your data that a third of the patients were over 60.

DR. REDBERG: Yeah, it looks like 60 to 79, or 60 to 74.

DR. STEVENSON: I'm sorry, I don't want to sign off on this number, but the last report that we had circulated among us from INTERMACS, 41 percent were between 60 and 79.

DR. REDBERG: Okay. And then a few percent, I presume, are over 80.

DR. STEVENSON: Yeah, a half of a percent over 80.

DR. REDBERG: Thank you. So with that, we can take the vote, and so you can use your clickers again.

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

MS. ELLIS: We're waiting on one vote. There we go.

DR. REDBERG: Okay. So for this vote we have a mean of 2.8889, so pretty much right on intermediate, and now we'll start with Art to talk about your vote.

DR. SEDRAKYAN: Art Sedrakyan, three.

DR. REDBERG: And also -- well, we can go down and do the vote.

DR. BRINDIS: Ralph Brindis, three.

DR. FAUGHT: Ed Faught, three.

DR. GRANT: Mark Grant, four.

DR. HESELTINE: Peter Heseltine, three.

DR. MOCK: Curtis Mock, two.

DR. RICH: Jeff Rich, three.

DR. SCHWARTZ: Sandy Schwartz, three.

DR. STEINBROOK: Robert Steinbrook, three.

DR. FEINGLASS: Shami Feinglass, four.

DR. DONOVAN: Kevin Donovan, four.

DR. KORMOS: Kormos, four.

DR. PINA: Ileana Pina, three.

DR. REDBERG: And for the discussion question, it's which conclusions are likely or unlikely to be generalizable to the Medicare

beneficiary population? Do you want to start, Art?

DR. SEDRAKYAN: I voted three just based on the strength of the data that has been presented related to INTERMACS 1, 2 and 3. I think that's probably very generalizable to the elderly populations unless convinced about other factors. Certainly, again, I would like to see the profiles of elderly patients over 65

and event occurrence based on a variety of profiles of patients over 65 to make a more informed decision and understanding of how generalizable these data can be for the Medicare population.

Also, patients with renal failure, certainly that's another population that has been reported and they have, you have some data that patients with prior renal failure have worse outcomes. Again, I would need to see a bit more frequency based information rather than just risk ratios, and a comparison to not having renal failure, but some of the information is certainly generalizable to the Medicare population and that's the reason I

voted three.

DR. BRINDIS: Maybe you should have the other end go first sometime, but had an intermediate vote of three for all the reasons that you said, Art, and with the particular appreciation in the sobering fact that Lynne told us earlier, that the average age of people with heart failure is 74, and that's not necessarily the average age of the patients in the registry. So we have a lot to learn about

comorbidities and patient profiles appreciating age as an independent risk, particularly as we get older.

DR. FAUGHT: This is Ed Faught, I voted three. I was encouraged by the curves in the hazard ratio suggesting that age by itself is not a really strong factor in adverse outcomes. For example, for death it's 1.24 in the INTERMACS data, which is not too bad, so that's encouraging.

On the other hand, I had some reservations about, for the same reasons, particularly comorbidities and adverse effects. You know, the stroke risk, does it go up more

with older people, you would think it would, and the other adverse events I would like to see those stratified out by age a little more. But overall, we have quite a few older people in the registry, so I was confident that we could make some conclusions.

DR. GRANT: Mark Grant. I voted four and the reason, I felt the representation of elderly patients in trials and registries was substantial. I get the, what I sense is that, or judge that selection among older patients is

a probably a little bit different than it is for younger patients, and so it's not every heart failure patient who is elderly is necessarily a candidate here, but I didn't see red flags to say there was considerable effect modification anywhere, that things should be that different based on what was presented and what I've read, and I think that summarizes it.

DR. HESELTINE: Peter Heseltine. I voted a three also. While I agree that there were very little differences by age alone, I think that's probably selection bias, as several of you pointed out. So the other side

of that coin, which is if we were to apply this to the general Medicare population, would we in fact encounter more side effects, would we in fact encounter less survival if in fact there was less selection bias for patients? Those are things we don't know, and so that's why I voted it as three and not four.

DR. MOCK: Curtis Mock, two. Again, the average age of 74 hit me this morning. Whether that's the mean of 59.6 or 54, I think the question is Medicare beneficiary and that doesn't necessarily mean over 65, it could mean

younger, and I think the data that we were presented today didn't explain to me that these were Medicare beneficiaries, irrespective of age.

DR. RICH: Jeff Rich, I voted a three. I was impressed with the hazard ratios presented by Dr. Kirklin showing that there wasn't much of a difference for mortality at least with respect to age, there was early on, but not later.

I, again, personalized this one, because I do select patients differently in the

older patient population, I use a different set of criteria, but I learned that different set of criteria from having all the other experiences, so I don't do INTERMACS 1 patients, I just don't do that, there's an increased risk and they're doomed to fail, it's futile. So I do think there's enough data from the INTERMACS database and through my own personal experiences to think that we can generalize this to the Medicare population, at least on a level of three evidence.

DR. SCHWARTZ: Sandy Schwartz. I voted a three, it was really between a two and

a three. You know, in general, I think to generalize to that, I think we saw data that showed that, I think we saw data that suggested there might be important differences, early mortality and, you know, more severe patients. And even something I will check with the Alabama folks offline sometime, while the absolute difference is larger percentage-wise, there was a difference in the shape of the curve and the elderly population looked like it might be a 50 to 75 percent increase in

mortality rate.

I've talked to the surgeons and doctors around here, and just clinically, you know, I think implicitly people know this well, and make future decisions. So I think what they're really saying is that it applies generally, but again, I think this is one of the opportunities we have to get more research.

I just would want to say one thing about INTERMACS, because I have to go a little bit early. A lot of us have spent time telling us what we would like INTERMACS to do more of. I think this is, from my perspective, is really just respect for what you've been able to do so

far and the capacity you have with extended resources to do more. And I think when people are asking for more, what we're really saying is we like what you've done and like what you have developed and we, you know, we're academics and researchers and clinicians and we always want more, like my kids used to, or still, and they're grown.

(Laughter.)

DR. STEINBROOK: Robert Steinbrook. I

voted three, nothing to really add to the comments on the three vote, or maybe one comment.

We saw a slide, quality and survival, getting at the issue of reasons why people, what people value, why they choose to do this, why they perhaps choose not to do this, so I think that at some point this data may already exist, but would like to know more about in the Medicare population as well as patients more generally, as to what are the reasons which go into a decision to proceed with an assist device, what are the reasons why people choose not to, I think there could be perfectly good reasons and that might inform either way in

patient decision-making.

DR. FEINGLASS: Shami Feinglass, I voted a four. I would say ditto to Mark Grant for his rationale for that. I'd also say that when you look at the Medicare population, the one thing I would highlight is looking at the quality of life outcomes and being able to get a little bit more information on that, I think would make it even easier to vote higher on

this.

DR. DONOVAN: Kevin Donovan. I voted a four instead of a three in a burst of unaccountable enthusiasm for the data that was presented.

(Laughter.)

DR. KORMOS: Kormos, four, and I'll second that. I really don't have anything more to add.

DR. PINA: Ileana Pina. I voted three, and I interpreted this question to be how confident are you that the conclusions are generalizable, meaning my conclusions before, of which I wasn't very confident, so that addresses that.

DR. REDBERG: Well, I think we heard

an array of interesting comments on how everyone interpreted the question and the data and the consistency, again, that I heard is that it would be helpful to have specific data for particularly over 65. We made some extrapolations based on the age, but it wasn't clear that we were, that particularly since the age of the INTERMACS registry is quite

different than the average age of the Medicare population, that that was a reasonable extrapolation. And in addition all of the things that we're evaluating, quality of life, functional status, adverse events are going to occur at different rates in older people, and the Medicare population in particular have more comorbidities.

Ileana mentioned earlier and I'll remind you that the Medicare population is 60 percent women and the INTERMACS registry was less than 20 percent women, so it is clearly a different population than our average Medicare beneficiary, and we don't have a lot of sex-specific data either. But having said all that, the committee overall felt intermediate confidence in being able to apply the data to

the Medicare beneficiary.

And so, that moves us to the last question, which is, how confident are you that clinically significant evidentiary gaps remain regarding the use of ventricular assist devices, and again, we can vote one through five, and then have a discussion.

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

So the one person who voted four can raise his hand. No, I should say the mean was 4.6667, and Art has a suggestion that we each focus on particularly one evidentiary gap, because I think we heard a number alluded to, and that way you can each pick one.

DR. SEDRAKYAN: I'll focus on a gap and I'm hoping all the others will be covered. It was quite exciting that 20 percent of the population that was analyzed in INTERMACS had outcomes at two years. That was similar to transplantation. Dr. Kirklin reported that and that's very interesting to me. I was looking and I was reading a transcript of his presentation at the AATS this year, and you were asked a direct question, if you will tell

your patients or transplant patients, some of them who are similar in your data or in the INTERMACS data to get an LVAD, and you said yes.

That to me is a very important evidentiary gap there. How many of the

transplant patients, if those 20 percent of INTERMACS would correspond to 60 percent of the patients getting transplantation now, 80 percent, 10 percent? Because it's 20 percent within INTERMACS, those without prior cardiac surgery, how many of these patients would be currently getting the transplant? I think that's an interesting gap that I think hopefully will be part of the clinical trial, so that we understand more if LVAD can be an alternative to transplant in the future, that's one gap that I thought would be good to highlight.

DR. BRINDIS: So, my gap is going to be how do we actually identify the --

DR. REDBERG: I'm sorry, Ralph, it was my oversight, but we do need to state our scores, and we can do it at the same time.

DR. BRINDIS: Ralph Brindis, five.

DR. SEDRAKYAN: Art Sedrakyan, five.

DR. BRINDIS: So, I'm choosing how do we appropriately identify the less sick patient, and this is actually becoming more philosophical but then on the ground with it,

we have the REVIVE-IT study to help us out. But I mean, basically we're looking at finding the sweet spot in terms of, if you will, destination therapy in the patients who are less sick, and the challenge for the sweet spot is that it's going to be changing as the technology changes, as our experience changes, and that will be a huge challenge for us. It's also going to be changing because I think it would be applied, and particularly since we're here at CMS, to patients who are older, and I do think that although the data we have related to mortality is encouraging, there are other issues other than, that are morbidity-related that we need to identify in the elderly.

DR. FAUGHT: Ed Faught, I voted a five. You know, there have been a lot of things identified. I would just say that I would like to see more data on outcomes in terms of functional status, not just how far

they can walk, but getting in and out of bed, do they need a cane, sort of more detail in terms of what people, the quality, or not just the quality, but the texture of people's daily

life after this compared with before.

DR. GRANT: Mark Grant. I voted a four for the following reason. First, I couldn't vote five because when we do these large, or even not so large evidence reviews and we say gosh, there's all these evidence gaps, you just don't know what you're doing, and I just don't have that mood to make that judgment here. I think the story is an extraordinary one, frankly.

But I would share Ralph's point, and the point is how far up the ladder do you go with the benefits and risks, when might that tradeoff really just not make sense. That in concert with, it's a personal decision, and I think a lot of the efforts in that realm about presenting those risks to patients is important, because sometimes people will choose differently, but I think these people need to have a choice.

And I think the issue of frailty is

always close to my heart as a geriatrician in the not so far distant life. And I think you folks are, I think the evidence is sensitive to

that generally, but it certainly does need to be addressed too.

DR. HESELTINE: Peter Heseltine, I voted a five, apologies, because I think there are some very specific gaps and they concern me. I'm particularly concerned that we make decisions about what benchmarks we're going to achieve before we make assumptions about what VAD is doing for patients. Specifically as I mentioned earlier, not only PROs, but looking across medicine and asking the question, so I think this is a good outcome measure, but is it similarly, is it comparable in cancer trials, is it comparable in other chronic disease trials, so at least when I go to the payers, I can give them some sense that we're approximately as physicians on the same page, our patients agree with us, we agree internally, whether it be cardiologists or cardiovascular surgeons, but also that your colleagues who are referring to you actually believe those outcomes are valid, appropriate,

and that you're meeting them. That's to me a gap that we should be able to manage, and we

must.

DR. MOCK: Curtis Mock, I voted a five. Thank you again so much for your presentations today and your work on this exceptionally important topic. I undoubtedly think that there are opportunities, and the reason I know that is because I heard those comments from you today. I heard that there are gaps in the literature and, you know, the integrity that you bring to this discussion and what you do for our patients and members every day should not be forgotten, and thank you for that.

I think it's all about access, but not just the procedure. It's about quality, it's about having the right team do the work, it's about having it done in the right center, and it's about picking the right patient to have the procedure, and I'm leaving here today thinking that all of you are looking toward that path, and I thank you for that.

DR. RICH: Jeff Rich. So, unlike the other end of the table, when I voted I had a

great intellectual and emotional depression, so

I voted a four instead of a five, when I couldn't justify it. We've talked about a lot of gaps today, all of them clinical, we're great clinicians, but what we did not talk about today was costs, and I think that it bears a burden on the payment systems to have these kinds of technologies placed into elderly patients, and I think we have to be sensitive to that. I'm particularly sensitive to it, we've been on Medicare fee for service for the last years of the Bush administration, there were things that we talked about, and not that we would make clinical decisions based on cost, but I think it's important to design the right payment system to support this technology and if we don't get it right up front, we may lose the technology.

DR. SCHWARTZ: Sandy Schwartz. I voted five. I agreed with what Mark said, I think, and in fact looking at other things, while we're all cognizant of all the gaps that exist here, just beyond what was said, I think it's a very important area given the nature of the clinical problem and both the health and

resource implications and the impact this has on people's lives, so it's very important to try to rectify that.

On the other hand, I think we would be negligent if we didn't note that there has been a lot more work done in this area than there has in most other areas of medicine. We were much more aware of our gaps because there are gaps, in other areas they're chasms. You know, apply this to most noninvasive procedures that are done, there's a large body of evidence that's been generated and degenerated. So my five doesn't indicate the lack of knowledge that's been generated, it's just the need to try to hone in on what we think we know, what we all want to find out.

You know, my major emphasis, Rita, will be thinking about this from a patient perspective, what would I want to know as a patient, what's my likelihood as an individual, the chance of success and the chance of having a significant complication, and how would that translate into, you know, my ability to function in a way that I would want to.

Those are the key things that I would

be interested in, so I think when we have this aggregate data now, when we're learning a lot about broad, you know, 10,000 feet parameter things, and now we need to generate more information to help interface between the physician and the patient.

DR. STEINBROOK: Robert Steinbrook, a five. Two comments.

Number one, to echo what Sandy just said, I've had the privilege of serving on some other MEDCACs in other areas of medicine and I can tell you that at this time of the day we were often in a one to two evidence free zone. In this whole field there's a lot of data, there's a lot of meaningful data that we've heard today, and everybody's commended for that, but that's why we can see what gaps are there and need to be looked at for the future.

I want to make a comment about certification. I don't feel that I know enough to say what value is added by certification in this entire process given everything else, whether it makes more sense to have one group doing certifications, two groups, many more groups, but I do think that would be an area

for CMS's people to do. We have some idea as to what we're trying to get to, we've spoken generally about this team, all these different resources which are needed for technical expertise and given these complications later, some idea of where we want to go with those sorts of things, but where certification or other things fit into that, I think needs to be sorted out.

DR. FEINGLASS: Shami Feinglass. For me, it's really at the end of five. The reason for that five is not because I think there's any problems with what you guys are gathering. We've heard down the row, you guys are really a bright spot for device trials, you really are a group that if you can take this and plop this down to the way other devices are developed, it's going to help those other devices.

That said, I think you have all identified very clear gaps. I don't think these gaps should stifle the innovation in this device at all, but I think they can inform how that changes and grows. I think you've clearly delineated that there are problems, or not problems, but there is information still needed

in this level 4 and greater, whether you're doing a VAD or medical management. I think you are addressing those issues with some of the studies you're putting in place, and I commend you for doing that.

So again, my five is not that this whole area should be tanked, and I don't want people to walk out with that. My enthusiastic five is you've identified what those gaps are, let's deal with those gaps, but as Medicare considers it, they need to consider where you have good evidence without the gaps, and direct their coverage decision possibly in that direction.

DR. DONOVAN: Kevin Donovan. I voted five. I would also like to add my thanks to the panel of speakers, I think you should have been labeled educators because you did such a fine job. The only thing I would add is that with patients making personal decisions in the face of evidentiary gaps, informed consent I think then becomes crucial. An informed consent approach, as was mentioned before, should probably find a way to become

standardized as much as possible and if we can

do that, we should also include the caregivers, because the burden falls on them almost as much as the patients. Thank you.

DR. KORMOS: Bob Kormos, I voted five. So, I'm going to get passionate here because we all want information. I've heard about five different gaps and six different gaps here, that we want these people, and I'm going -- here's my conflict of interest, I never stated it, but I am a PI of INTERMACS. Who's going to pay for this? This is data that is critical to the field, it's absolutely important to get more information and we have a mechanism, but you know what, it doesn't come for free. You've got coordinators who are burned out at sites trying to get the basic information in, you've got INTERMACS people busting their butts trying to get analyses out for a myriad of issues, things that come up. So whose responsibility is it?

I mean, the NHLBI has been wonderful in supporting this now for, at the tune of, I don't know how many million are we up to, guys,

six, 12, plus another four? I mean, the reality is they've got us off the landing

strip, okay, we're flying, but we cannot maintain altitude unless we have ongoing support. So I'm looking at CMS, I'm looking at FDA, I'm looking at all these government agencies that want to improve the care of patients and want to improve survival, and they want the best quality of care and outcome for individuals from very costly high technology.

So how do we fix this? That's the gap that I see, is the ongoing support that's necessary to keep this information flowing.

DR. PINA: Ileana Pina. I voted a five, and Rita, you had asked us to hone down on a few areas of gap. Some of these patients who are older and come in hopefully in the future as bridge-to-decision may also ultimately get transplanted, and it would be really interesting for me to know how those patients do, the ones that are near 70 or even 71, 72 that are currently getting transplanted, and I don't think we know that.

The other thing we didn't talk a lot

about was device exchange. Some of these devices don't last forever and some of them do malfunction, some of them do thrombose, and I

don't know if age had a relationship to device exchange, we didn't really talk about that.

And then finally, and going a little bit into what Dr. Kormos was saying, the use of medical services after the VAD implantation seems to be to me fairly large, and the costs involved in that. I don't know, but it seems, just from looking at it at a distance, you're looking at people who aren't transplant candidates to start off perhaps for a myriad of reasons, including comorbidities where you're going to be using renal services, the older patients need a nutritionist much much more perhaps, the exercise therapists, and these are going to be very high cost to Medicare, and I don't know that we have a handle on that, and I don't think that INTERMACS can give us a handle on that, but the Medicare database may be able to, the administrative database.

And I want to help really in congratulating all the INTERMACS folks, Jim,

Lynne, Mariell, David, because this has been just an incredible project that, it's so satisfying to see where we are. And I know that we're not perfect, but boy, we've come a

long way from knowing very little to knowing a lot more than we did five, six, seven years ago.

DR. REDBERG: Thank you. I also want to add my thanks, I heard a lot of, and I echo the commendations to our invited speakers and really for the work of, I think what really came through, I think everyone in this room really wants to figure out how to give the best care to our Medicare beneficiaries and our patients in general with advanced heart failure and the role of ventricular assist devices.

We really heard a lot of evidence, both from INTERMACS as well as the clinical trial data, and we heard the evidentiary gaps, and I agree, I think it's really a tribute to your work to have identified what we do know and what we still need to know. I think we clearly heard a great suggestion besides the endorsement of the heart team and looking at

volume outcome, I think we also heard suggestions for an informed consent form and specific things that should be included, patient-reported outcomes on an informed consent form. And certainly the cardiologists

and other people, I think it's not just for VADs, but oftentimes we could do a better job of informing our patients what the benefits and what the risks are for these procedures so they have a clearly informed decision and an individualized decision. If we give them the benefits and risks for them personally, obviously everyone will weigh that a little differently. So, I really thank you all for an excellent presentation that was very informative and educational.

I want to offer the opportunity at this time if anyone on the panel or any of the speakers has any random thoughts related to VADs or advanced heart failure that we haven't already covered, than you want to make at this time.

DR. SEDRAKYAN: If I could add, I also would like to commend CMS for bringing this

issue up, this patient centeredness that we all care about. I think this was a great MEDCAC. It's very different, as Jyme alluded to in the beginning, that we're really getting into not only patient-specific or facility level, this is part of patient centeredness and providing

patient-centered care, so I think this is really a tribute to CMS being visionary as well.

DR. RICH: I just wanted to return to Bob's comments earlier about certifying agencies and who's going to create the criteria. I think it's really the professional societies' responsibility to create that, working together with the hospitals to do like we did with TAVI, and create a document for all the professional societies, and float that out in joint publications. I think it's our responsibility and no one else's to come up with those criteria, and I think that would be very helpful.

DR. SCHAFER: So, Dr. Rich, we will look forward to that document.

(Laughter.)

I too want to thank everyone, it has been a terrific discussion today. Presenters, panelists, you've given us a lot to think about. The transcript from today will be posted on the website. Any further action or national coverage analysis, obviously that will be posted on the Internet, and we look forward

to continuing discussion on this topic. I think I've heard today, you know, we really should meet again in another couple years and see where we're at at that time, and we'll continue our discussion.

So thanks, everyone. Safe trips.

(Whereupon, the meeting concluded at 3:25 p.m.)