

March 22 2017 MEDCAC Meeting Transcript

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1 PANEL PROCEEDINGS

2 (The meeting was called to order at
3 8:07 a.m., Wednesday, March 22, 2017.)

4 MS. ELLIS: Good morning and welcome,
5 committee chairperson, acting vice chairperson,
6 members and guests. I am Maria Ellis, the
7 executive secretary for the Medicare Evidence
8 Development and Coverage Advisory Committee,
9 called MedCAC. The committee is here today to

14 confident are you that functional assessments,
15 e.g., six-minute walk test, VO2max, ventilator
16 threshold, A, are adequate measures which
17 reflect the patient experience; B, should be
18 included as the standalone meaningful primary
19 health outcomes in research studies; C, should
20 be included as composite standalone meaningful
21 primary health outcomes in research studies?
22 Using the following scores, again, identifying
23 level of confidence with one being low or no
24 confidence, and five representing high
25 confidence.

♀

20

1 Discuss questions for question number
2 four. Please discuss whether additional
3 patient-reported measurement, e.g., Short
4 Form 36, EuroQol five-dimensions questionnaire,
5 should be considered to capture burdens
6 associated with the heart failure therapy under
7 study.

8 Please discuss the appropriate length
9 of follow-up post-heart failure intervention

10 for assessing patient-reported measurements.

11 For some studies of heart failure
12 treatment technologies it may not be practical
13 for patients to be blinded. Please discuss the
14 impact of unblinded study participants on
15 patient-reported measurements and functional
16 assessments.

17 Please discuss how to best consider
18 the impact of adverse events associated with
19 heart failure technologies while balancing the
20 potential for improvements to meaningful health
21 outcomes.

22 Please discuss how to balance the
23 benefits and harms of therapies which may
24 improve near-term patient-reported health
25 outcome assessments or clinical measurements,

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21

1 e.g., 6MWT or symptoms, but may decrease length
2 of life.

3 This additional discussion topic
4 includes: Please discuss health outcomes of

5 interest and appropriate follow-up duration in
6 studies of technologies designed for diagnosis
7 of acute heart failure. With the health
8 outcomes and information that we have discussed
9 today, how confident are you that there will be
10 enough accurate information provided to patients
11 for them to make informed decisions? Please
12 discuss how studies can be designed to
13 accurately capture patient preferences and
14 their preferences can best be considered and
15 operationalized once the study has concluded.

16 Thank you.

17 DR. REDBERG: Thanks very much,
18 Dr. Canos. Next up is Dr. Ileana Pina, who is
19 a professor of medicine, epidemiology and
20 population health at Albert Einstein College of
21 Medicine, and associate chief of academic
22 affairs at Montefiore. She will talk about
23 this from a clinician's perspective.

24 DR. PINA: Good morning, everyone, and
25 I want to thank CMS and the panel for asking me

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1 to be here, it's quite an honor. These are my
2 disclosures, but I want to make sure, some of
3 you identify me as a consultant for the FDA,
4 and today my comments are purely my own as a
5 clinician, and I do not represent anybody but
6 the clinical community in something that we do
7 every day.

8 I've been doing heart failure
9 transplants for over 20 years and at my
10 institution we have 2,500 admissions for heart
11 failure a year. So is it a problem? The answer
12 is yes.

13 So, Daniel gave me a long list of
14 things to do, these are basically what he just
15 reviewed, but it's a little bit daunting. So I
16 thought I'd start with having the patient in
17 front of me and asking the question, what makes
18 me happy, and what makes the patient happy.
19 And I think probably what makes me the happiest
20 is when I look at the patient and I see that
21 the ventricle is essentially getting better,
22 which translates to I don't have to give him an
23 ICD, which means that I've probably medicated
24 them well enough that they feel better and are

25 doing more, and that's my happiness.

♀

23

1 What makes the patients happy is when
2 I walk in and I say to them your heart looks
3 better and you don't need the ICD, and now
4 maybe I can stretch out your visits, and maybe
5 I can cut back on some of your what I call the
6 junk medicine, my patients know I call it the
7 junk medicine, and then the important medicine.

8 But when I put all this together, we
9 really have arrows for everything. What makes
10 them happy, what makes me happy may be the
11 physiology of their interpretation but they're
12 pretty much the same goals, and keeping them
13 out of the hospital is a huge part of my goal.
14 I don't like the patient in the hospital unless
15 there's some patients that are absolutely
16 necessarily having to be in the hospital, and
17 that is a lot of our population today. And I
18 think we forget. You know, we treat the
19 admissions in the hospital as if it were this

20 whole separate thing, and it's really a comma
21 in the whole care, and that's how the patients
22 see themselves. They see themselves as moving
23 through their disease process and these are
24 time periods, but we seem to categorize them
25 with all this separateness. It's the same

♀

24

1 thing, same disease, just differently
2 manifested.

3 And I stole this slide from Gregg
4 Fonarow, not that you need to read it in
5 detail, but we've just failed, we've failed in
6 a lot of ways. And we're still failing in not
7 giving the right medications at the right time
8 for the right reasons, not recognizing patients
9 early enough when they're sitting right in our
10 wards and not knowing what's going on with
11 them. So it is a failure.

12 So let me talk about hospitalizations.
13 I don't have a lot of time and I want to cover
14 as much as I can. Hospitalizations are darned
15 important to me because of many things. I know

16 that it increases mortality, and I'll briefly
17 show you these data. It's a revolving door.
18 Very often the good drugs, our house staff, the
19 first thing they do is they stop everything,
20 and then I've got to start all over again. But
21 sometimes bad drugs are given during that
22 hospitalization.

23 We only see about 20 percent of the
24 heart failure patients at our institution,
25 they're being seen by internists or being seen

♀

25

1 by hospitalists, many of whom are excellent
2 doctors but don't have a lot of experience in
3 the heart failure world. Once you're putting
4 them to bed, and Clinton Brawner today is going
5 to talk about that, they lose function, it
6 doesn't take long to lose muscle function. Now
7 somebody who's functioning at home needs to go
8 to a SNF because they can't go back home
9 again, they're not rehabbed enough. We're not
10 doing good physical therapy, we're not sending

11 the patients to cardiac rehab, and so the
12 length of stay business which has been
13 threatening us, and I get the care managers on
14 my head, get the patient out, the patient has
15 an extended stay, and sometimes what I need to
16 do in the hospital needs an extended stay, and
17 I can't get them out and I can't get it done in
18 four-and-a-half days.

19 So I believe hospitalization should be
20 an outcome, I believe heart failure
21 hospitalization should be an outcome, and
22 hospitalization equivalence, because I as many
23 of my colleagues who are sitting here avoid the
24 hospitalization. If I have to give IV Lasix in
25 the office, I will, and I try to keep them out

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26

1 of the emergency room and out of the hospital.
2 So those are important events in places such as
3 ours who have high volume and high levels of
4 experience.

5 We've known this for a long time, this
6 isn't new. Everybody thinks this is something

7 new and shattering. We've known that being in
8 the hospital is bad for the patients and that
9 they have a high mortality within a year,
10 within six months, it doesn't take long to see
11 it. So outcomes don't have to be two years for
12 hospitalization, you're going to know what you
13 need to know within 90 days because that's
14 where the highest rates are.

15 And when they say well, come on, you
16 know, this is heart failure, they're supposed
17 to be sick, they're supposed to die, but when
18 we put them into trials, they actually do
19 pretty darned well in trials with a very
20 controlled setting.

21 I also know that the more they get
22 hospitalized, the more the mortality. We don't
23 need to do these experiments, we know this,
24 this has been well known, but I want to give
25 you reality. This is a list of medicines that

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1 an average patient leaves the hospital with, I

2 counted them, it's 13 drugs. By the time we
3 see them in our short-term clinic which is very
4 successful, nor run by me, it's run by
5 pharmacists, we get readmission rates down to
6 80 percent and we get rid of what I call the
7 junk. The junk medicine includes the laxative,
8 the stool softener, the sleeping pill, the pain
9 pill, everything they got in the hospital is
10 totally unnecessary. How confusing, how many
11 of you can take 13 drugs in a day? I don't
12 think the patients can, but this is a real list
13 of what the medications are, taken from our
14 patients. And by the time they leave us in
15 that post-discharge clinic, especially since
16 they're diabetic and they have coronary
17 disease, I have the statins, they're down to
18 about eight drugs.

19 So what gives me confidence that I can
20 get them on guideline-directed medical therapy?
21 It's not totally impossible, and that reverse
22 remodeling should mean that the outcome is
23 going to get better. Every time we've done
24 anything that causes reverse remodeling with
25 beta blockers, the patients actually have a

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1 better outcome. And exercise therapy is safe,
2 we've done this, we've done the trials, and it
3 should be added. Capturing health status can
4 be done and I do it clinically, and I'm going
5 to show you the data.

6 And so I put the post office box here,
7 because I tell the patient, you're like the
8 little cubby holes, and I put all this
9 information into little cubby holes that will
10 give me the total picture of you, and you where
11 you are now and where you're going. They don't
12 want to see the Kaplan-Meier curves, they want
13 to hear what I have to say about how they're
14 going to do.

15 So why do I insist on
16 guideline-directed medical therapy? And I
17 thank Dr. Yancy for putting that into the
18 guidelines because I use it all the time. It
19 works, it actually works. You have to be
20 consistent, you have to be patient, you have to
21 know the drugs you're using, you have to be

22 confident, you have to have self-efficacy that
23 you know how to do this. And we do follow
24 biomarkers.

25 The inability to medicate, and this is

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1 Lynne Stevenson data, right here on the panel,
2 it's a bad outcome. If I can't get the
3 patients medicated, that is a very bad
4 prognostic sign, but by people who do this all
5 the time, not the check box. Good, I did it, I
6 gave an ACE inhibitor, check. Can it be done,
7 yes, it can. Gregg Fonarow's data from the
8 IMPROVE Heart Failure trial is real world data
9 where the addition of the medicines, every time
10 you add one you have different outcomes. So
11 we've got plenty of proof, we don't need any
12 more proof in here.

13 Reverse remodeling, we can use
14 anything we want, LVEDV, LVEDVi. I'm liking
15 LVESVi because I'm seeing a lot of consistency
16 in the literature. Ejection fraction alone may

17 not cut the mustard although it may lead to
18 eventual changing, so reverse remodeling should
19 be linked to a favorable outcome and there
20 should be some causal relationship. Should
21 that be an outcome? Yes, I think so.

22 This is stats from when I was at Case,
23 our heart failure clinic, showing you that when
24 patients are under a team approach to care,
25 guess what? We have very few admissions when

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1 they're coming to clinic, and this is a large
2 number of visits by year, and yet very few
3 hospitalizations.

4 And take a look at these. These
5 patients were sick, New York Heart Class 2.4.
6 We have a lot of women absent in many of our
7 trials, and some of you know that's one of my
8 pet peeves. And beta blockers, well done, well
9 titrated, can actually remodel. Not everybody,
10 but there are patients that can do it, and you
11 need to give them the chance to do it.

12 So this was from our old clinic. We

13 had a group of patients that had a
14 significantly improved ejection fraction with
15 peak O2s of 13.8, which is low, and an initial
16 class of 2.4. Changes in ejection fraction
17 were remarkable, as there were changes in
18 ventricular dimensions.

19 And guess what? When we did this
20 statistically, the most prominent finding was
21 the dose of the beta blocker, 139 in patients
22 who improved from a Metoprolol equivalent, and
23 98 in those that did not.

24 What about health outcomes? I already
25 heard Daniel present that you want to hear more

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1 about health outcomes. This is from our HF
2 ACTION trial that I know Chris O'Connor is
3 going to be talking more about. We can use the
4 KCCQ to show about exercise, what did exercise
5 do to these patient-reported outcomes? And
6 even though we've had a statistically
7 significant benefit within three months that

8 persisted for two years, more and more patients
9 shifted to a higher number, so we had proof
10 that exercise actually does improve health
11 outcomes.

12 And this is, again, in the clinic.
13 I've been using these for years when the
14 patients come to clinic because I want to know
15 what their status is when they walk in the
16 door, but you've got to do it the right way.
17 There is a process to get this, even in an
18 unblinded trial. It's not the people that are
19 taking care of the patients who gives them the
20 questionnaire, it's somebody in the front
21 office. I don't want to be involved when
22 they're filling it out, because I don't want
23 them to feel that, patients actually try to
24 protect us, they don't want you to think that
25 they don't like what you're doing or that they

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1 feel bad. So we give it by somebody who's
2 totally outside of their daily care, and I'm
3 not even in the room, I don't even want to be

4 in the room, and so when we take this
5 questionnaire, we do it as unbiased as
6 possible.

7 So here's a population with an EF of
8 19.8 percent, this is real, this is our clinic
9 at Case, and here are the results. And for
10 those of you who don't know the cases too well,
11 the higher the number, the better the health
12 status, not quality of life, health status.
13 And you can see that the New York Heart class
14 just really goes right down the line with the
15 value of the physical limitation and the total
16 symptom score. So that if I break it down, we
17 have a pretty good sense besides that New York
18 Heart class, which is so imprecise and so
19 subjective, but yet, pretty darned good to look
20 at outcomes, that it tracks exactly as the
21 questionnaire does.

22 And this is now today, this is now ten
23 years later in my clinic at Montefiore where
24 the KCCQ overall score is 52. That's pretty
25 bad, and those are patients leaving the

1 hospital with a pretty bad health status, even
2 though there's some wide variability and a high
3 standard deviation.

4 HFpEF, very quickly, I have no idea
5 what to do with these patients. I try to get
6 their blood pressure down, I try to get their
7 diabetes controlled, I try to put them into
8 exercise programs, I don't want them to have
9 atrial fibrillation, so I'm going to leave you
10 with a new outcome, atrial fibrillation, a very
11 bothersome, very common comorbidity that we're
12 seeing in this population. The treatment
13 guidelines are kind of non-very specific, they
14 tell us to treat blood pressure, and then the
15 new ones will be hitting the door, and Clyde
16 may be able to talk a little bit more about
17 that.

18 But what do I have a problem with?
19 It's that all the trials are different, the
20 entry criteria's been different, the ejection
21 fraction's been different, the way the
22 ventricle looks is different. How are we ever

23 going to get to this when we don't even have a
24 very good solid definition of HFpEF? And
25 atrial fibrillation is very often the

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1 presentation, and I find my colleagues running
2 to take care of that atrial fibrillation, let's
3 control the ventricular rate, but what's
4 underneath, which is the heart failure, very
5 often gets ignored, so perhaps more often
6 incidents of atrial fibrillation could also be
7 a health outcome.

8 And yes, I use spironolactone because
9 right now that's the best data that I have from
10 the NIH-sponsored TOPCAT trial.

11 Exercise, highly ignored, and yet we
12 do have data, they're smaller trials, they're
13 not the big large randomized trial, but we do
14 have data that the HFpEF patients do well with
15 exercise, and I've got some of them walking in
16 the hall, walking around their dining room
17 table, because in the Bronx at this time of the
18 year you can't always go out and walk, it's a

19 little cold now with ice and snow on the
20 streets, so I have them walking around the
21 dining room table and telling me how many times
22 they can go around. It's still exercise, it's
23 just not on the treadmill.

24 And then my key points for outcomes in
25 HFpEF, reduction in all cause hospitalization;

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1 improvement in objective function, their
2 ability to actually rehab; well captured
3 symptoms, which is very hard to do; and the
4 absence of AFib.

5 And then finally, devices for HFpEF,
6 what do I want in a device? I want it to have
7 biological plausibility, I want it to improve
8 physiologic parameters, and notice, I'm not
9 that interested in long-term mortality but I am
10 interested in hospitalizations, and my ability
11 to up titrate drugs and to continue therapy
12 even with the device on board.

13 So let me finish up here, because I

14 don't have a lot of time. ADHF, acute heart
15 failure, again, a comma in the process of care
16 where we deal with the iceberg, and there's so
17 much more going on underneath. Why do we think
18 that 48 hours of a treatment is going to
19 reverse this? We have failed in many of our
20 acute heart failure trials, and it's time to
21 look at it appropriately. Again, it's a comma
22 in the whole disease process and when we ignore
23 the disease process, we're ignoring everything
24 that has gone on underneath until the patient
25 now comes in with orthopnea and fatigue.

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1 So with those thoughts, I leave you
2 there. Thank you, Danny.

3 DR. REDBERG: Thanks so much, Ileana,
4 a great perspective from a clinician. Next
5 we'll hear from Dr. Philip Adamson, vice
6 president of medical affairs and medical
7 director at Abbott, which was formerly St. Jude
8 Medical. He's representing AdvaMed.

9 And I'll just add that we'll have a

10 few minutes at the end of all the presentations
11 for any Q&A from the panel. Thank you.

12 DR. ADAMSON: Thank you, Professor
13 Redberg, members of the coverage committee,
14 particularly Dr. Canos and Dr. Chin for this
15 invitation. I'm honored to speak in front of
16 such distinguished folks on a committee and a
17 panel.

18 Ladies and gentlemen, I'm here to
19 express the opinion of industry on behalf of a
20 common group called AdvaMed that represents all
21 of industry that is responsible for the
22 development of novel interventions and
23 technologies for patients with heart failure.
24 I'm Phil Adamson, I'm a heart failure
25 cardiologist, and as Dr. Redberg mentioned, I'm

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1 medical director at now Abbott, and involved in
2 many clinical trials to evaluate novel
3 technologies to improve outcomes in our
4 patients with heart failure. And really, my

5 task here is to describe the industry's
6 scientific rationale for identifying
7 appropriate endpoints for clinical trials, and
8 it's clinical trials testing novel
9 interventions to benefit Medicare patients.

10 We are focusing on which meaningful
11 patient-centric outcomes are appropriate to
12 evaluate new interventions, because we are
13 actually seeing some improvement in
14 longitudinal care and disease management of
15 patients with heart failure, and this is giving
16 us new goals, it's giving us new therapies and
17 new ways to allow patients to remain stable in
18 their own homes and avoid hospitalizations.

19 Today is very important. The
20 assessment of endpoints and outcomes will help
21 us to maintain the progress that we've been
22 seeing in management of these patients, and to
23 ensure that success will continue as we manage
24 these very very symptomatic and difficult
25 patients to manage. And frankly, we all know

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1 that heart failure is an exploding pandemic,
2 with expectations of the prevalence to double
3 within the next 15 years. So we really, I
4 think, have to have a concerted effort to guide
5 how we develop novel tools to manage patients
6 with heart failure and deal with the problems
7 that are associated with this chronic disease.

8 You know, I spent the last, nearly
9 half my life as a cardiologist taking care of
10 heart failure patients, and those patients have
11 taught me a lot about how this disease affects
12 them and what they want, and I've had
13 innumerable lessons taught me from my patients.
14 And I've also learned in the last two years a
15 lot about industry. As a member of industry,
16 I've learned that one of the most important
17 things is that industry finds really no value
18 in innovation that's made just for the sake of
19 innovation. In fact, our goals align with CMS
20 and other organizations such as the American
21 Heart Association. Our purpose is to provide
22 solutions for unmet clinical needs, providing
23 the highest levels of patient-focused
24 scientific evidence to improve the quality of

25 health care for Medicare beneficiaries. And in

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1 fact we agree with CMS, and we agree with the
2 American Heart Association, that heart failure
3 hospitalizations are very important, and this
4 is a very important clinical endpoint to
5 manipulate and to change as technology
6 improves.

7 Frankly, heart failure
8 hospitalizations are horrifying to patients,
9 they're potentially deadly, and these patients
10 who otherwise have reasonably stable heart
11 failure syndromes are faced with the
12 possibility of death, drowning in their own
13 juices, and this stress and trauma doesn't just
14 affect the patients, it affects their families,
15 their caregivers and their long-term outcomes,
16 their psychology, their socioeconomic status.
17 Heart failure hospitalizations are devastating,
18 and worthy of our attention.

19 As Dr. Pina mentioned in some of her

20 slides that were published, patients when asked
21 if they could stay out of the hospital and
22 avoid symptoms, would that be better than
23 staying alive longer, most answered yes, please
24 make my symptoms better and keep me out of the
25 hospital, don't just prolong my life.

♀

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1 Therefore, I think there's clear alignment
2 between CMS and AHA and the most important
3 group, our patients, that preventing
4 hospitalization is a worthy endpoint to
5 validate novel clinical technology.

6 I want to spend a little bit of time
7 going through the process, because successful
8 innovation processes must first focus on the
9 end result. The end result is the ultimate use
10 of clinically meaningful and appropriately
11 validated tools. Industry is called upon to
12 produce the highest level of scientific
13 evidence to satisfy rigorous regulatory,
14 reimbursement and coverage approvals. The
15 process involves discovery and clinical

16 development, which for most technologies
17 culminates in a pivotal trial that evaluates
18 the novel innovation, and it's important to
19 note that in these clinical trials many times
20 the control group itself receives better care
21 than in the community.

22 That's why discussing endpoints is so
23 important, and why the common goal of assessing
24 safety and effectiveness is a rigorous process.
25 However, it is important to note that industry

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1 continues to gather data after FDA approval and
2 after CMS coverage, and uses that information
3 from this period to ensure that ongoing safety
4 and effectiveness in generalized use of the new
5 intervention is present, and to use this
6 information for revision, rediscovery,
7 redesign, which are mandatory for any product
8 that's designed for the benefit of the heart
9 failure population, because many breakthroughs
10 are concomitant and simultaneously occur over

11 time, so where you end up may be different than
12 where you start, so it's an ever-changing
13 landscape in health care delivery for patients
14 with heart failure that's very important to
15 assess and reassess. So with this in mind, the
16 proper selection and agreement on appropriate
17 endpoints for validation of novel clinical
18 tools is critically important to the
19 sustainability of this traditionally successful
20 cycle of development.

21 You know, heart failure is really a
22 syndrome that can be described as a journey and
23 is associated with several different phenotypes
24 which we all know, several different etiologies
25 and comorbidities, and unfortunately there

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1 really isn't a one size fits all endpoint that
2 applies to all aspects of this heterogenous
3 journey.

4 This figure actually outlines a very
5 simplistic view of heart failure progression,
6 but might be useful to identify where some

7 unmet clinical needs exist, it shows how
8 endpoints are dependent upon where the patient
9 is in the journey. So let's start at the
10 beginning with a hemodynamically stable
11 ambulatory heart failure patient with
12 reasonable functional capacity, reasonable
13 quality of life, and mild to moderate
14 persistent symptoms, and actually this
15 represents the vast majority of patients with
16 the diagnosis.

17 And you know, we've learned a lot,
18 we've learned a lot over the years about this
19 phase of heart failure, and at least for
20 patients with reduced ejection fractions,
21 guideline level evidence supports drug and
22 device interventions to prevent disease
23 progression. Unfortunately no clear guidelines
24 exist, as Ileana just mentioned, for patients
25 in this Phase I portion of this journey who

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1 have preserved ejection fraction heart failure,

2 despite several clinical trials evaluating
3 promising interventions.

4 Many patients eventually experience
5 worsening symptoms and transition to seek
6 urgent care, and many times are hospitalized to
7 receive the IV rescue therapies. And, you
8 know, we've learned a lot about this transition
9 period from hemodynamically stable ambulatory
10 patients who transition into the decompensated
11 state requiring hospitalization. In fact, it's
12 a process that takes much longer than what we
13 originally thought. It's characterized first
14 by early increases in filling pressures that
15 can be detected weeks before patients develop
16 symptoms, leading to a presymptomatic
17 congestion, hemodynamic congestion phase which
18 is associated with changes in cardiac autonomic
19 control, and eventually interstitial edema,
20 shortness of breath, lack of rest, pulmonary
21 edema and the need for hospitalization. And in
22 fact, over 90 percent of patients who are
23 hospitalized for heart failure exhibit severe
24 symptoms of congestion in the presence of
25 excellent perfusion of their body, so it's the

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1 congestion that tends to drive hospitalization.

2 Unfortunately, consistent prospective
3 randomized clinical trial outcomes testing a
4 variety of methods to monitor patients using
5 daily weights and early detection of symptoms
6 with the hopes of preventing hospitalizations
7 in this transition period have failed, and it's
8 probably due to the fact that the transition
9 from stable ambulatory to decompensated is
10 characterized by this significant
11 presymptomatic stage in which we can't see with
12 signs and symptoms that the patient is
13 worsening, and the patient doesn't know because
14 he doesn't have symptoms developing. Weights
15 change, symptoms develop, but they may be too
16 late to provide effective guidance to prevent
17 hospitalization.

18 A clearer understanding of this
19 transition from stable to decompensated
20 discovered an unmet clinical need. New
21 interventions tested in this transition phase

22 should be expected to identify patients when
23 they develop hemodynamic compromise without the
24 development of symptoms, and should have the
25 goal of preventing subsequent hospitalization.

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1 So when we test things in the transition phase,
2 knowing what we know now about that process,
3 heart failure hospitalization prevention is a
4 very important outcome of those evaluations.

5 Now once hospitalized, patients
6 transition to Phase II in this diagram, in
7 which typically high dose IV diuretics are
8 delivered as rescue therapy, and again,
9 multiple clinical trials evaluating several
10 promising interventions at Phase II, once
11 patients are acutely decompensated and in the
12 hospital, have consistently yielded negative
13 results, and Ileana touched on that in her
14 talk. Even recent trials testing novel matrix
15 proteins have failed to impact clinical
16 outcomes, so it seems that stage two actually

17 may be too late in the course of this

18 progression to congestion, and little can be

19 done to alter the course of progression.

20 As patients transition then into the
21 number three there, we've unfortunately learned
22 that after about an average of five days in the
23 hospital for rescue therapies, over half the
24 patients are discharged with continued
25 congestion, the same that brought them into the

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1 hospital. This Phase III transition from
2 discharge to home is an incredibly important
3 time because 25 percent of patients who are
4 discharged are actually readmitted within the
5 next 30 days. In fact if you look longer term,
6 50 percent of patients are readmitted in six
7 months, and over 70 percent of those patients
8 are readmitted after a year. Clearly stage
9 three of this journey represents an unmet
10 clinical need to more appropriately discharge
11 patients and provide more effective followup.
12 New technologies introduced at this time point

13 to demonstrate a reduction in readmission rates
14 is a meaningful outcome.

15 Frankly, this admission-readmission
16 cycle is difficult to stop, and each time the
17 patient cycles through this process their
18 disease worsens and progresses. Many patients
19 who repeatedly decompensate eventually
20 transition into a totally different
21 pathophysiology we now call advanced heart
22 failure or refractory Class IV Stage D heart
23 failure shown as number four in the diagram.

24 Heart failure pathophysiology now
25 changes to include poor systemic perfusion,

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1 which is a very serious problem requiring very
2 serious interventions. Therapies and outcome
3 testing for this phase are completely
4 different, and include providing implantable
5 mechanical circulatory support systems or
6 transplantation for appropriate patients.
7 Importantly, for patients unable to receive

8 advance therapies, identification of them as an
9 advanced patient should provide an opportunity
10 for palliative care, as near-term death is
11 really hard to avoid.

12 So the ultimate goal, then, for
13 management of patients with chronic heart
14 failure is to manage and maintain stability,
15 and avoid decompensation. Novel interventions
16 being tested for this purpose should prevent
17 the ill effects of decompensation, which
18 include progression of cardiovascular
19 remodeling, leading to chronically elevated
20 cardiac filling pressures and poor systemic
21 perfusion with progression of their disease.

22 Clearly, as Ileana has mentioned,
23 we've been shown this data from Professor
24 Stevenson's lab and led by Dr. Setoguchi.
25 Patients who have multiple hospitalizations are

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1 at higher risk for mortality. In fact,
2 patients experiencing just two admissions are
3 nearly twice as likely to die compared to

4 patients admitted only once. More recently,
5 though, very interestingly, it became clear
6 that no matter how decompensation was treated,
7 whether it's in the traditional hospitalization
8 or emergency department visits, or even
9 outpatient intensifications of therapy,
10 decompensation leads to higher long-term
11 mortality.

12 This data from the PARADIGM HF trial
13 demonstrates a threefold greater mortality in
14 patients experiencing decompensation regardless
15 of the venue for rescue therapy, and let me
16 orient you to this slide. The solid black
17 diamonds represent death rates in patients
18 without a clinical decompensation event, and
19 that's compared to the red diamonds, which are
20 patients who had intensification of therapies,
21 the green diamonds, ER visits with IV care, and
22 the blue diamonds are traditional
23 hospitalization.

24 And look at the mortality associated
25 with these events. The mortality differences

1 between no events is dramatic, but the
2 mortality difference between experiencing
3 decompensation are very similar, regardless of
4 the venues in which rescue therapies are
5 delivered. In fact, in this trial which ended
6 somewhere in the 2014 range, it became clear
7 that clinical practice is evolving to rely on
8 more extended outpatient hospital visits to
9 provide IV therapy, which is represented on the
10 second bar of each of these pairs. So you can
11 see over time that clinical practice patterns
12 have evolved to rely on less hospitalizations
13 and more outpatient-based rescue therapy
14 treatments of decompensation.

15 The decision, then, about what
16 endpoints are appropriate, is dependent upon
17 where the patient is in their journey, and when
18 the innovative treatment is introduced.
19 Clearly heart failure hospitalizations and
20 decompensation events are associated with very
21 poor long-term outcomes, but let's focus more
22 closely on the components of the journey. It's

23 certainly desirable, and a patient-preferred
24 outcome, to maintain stability and avoid
25 decompensation altogether.

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1 As mentioned, multiple interventions
2 tested in clinical trials while patients are
3 acutely decompensated and already hospitalized
4 have produced really consistently disappointing
5 results. The benefits of maintaining stability
6 are now clear, and it should be apparent that
7 heart failure hospitalizations are important
8 targets as primary endpoints in heart failure
9 clinical trials.

10 And as clinical practice evolves,
11 another important measurement of success may be
12 to prevent ER visits requiring an IV rescue
13 therapy in short hospital stays that do not
14 qualify as traditional hospitalizations as
15 we've defined them in the past.

16 As is always the case, clarity of
17 endpoints that depend upon exercising clinical
18 judgment can only be achieved with careful

19 evaluation of each event. This requires
20 thorough unbiased blinded expert adjudication
21 of events as part of the routine clinical trial
22 design, and it should include confirmation of
23 the patient's clinical status at the time of
24 the event, documentation of all therapeutic
25 interventions provided, additional -- and

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1 interestingly, additional careful medical
2 record review should identify investigator
3 involvement in the decision to administer IV
4 diuretics or provide hospitalization,
5 especially in single blinded trials.

6 I think it's important to capture
7 all-cause hospitalization and include them
8 either as secondary endpoints or used as
9 observational data, to ensure that a change in
10 heart failure hospitalization is not really
11 just a shift in resource utilization or
12 diagnostic coding.

13 Finally, combining decompensation

14 events with mortality as a composite endpoint
15 is reasonable. However, if mortality is not
16 included in a composite primary endpoint,
17 mortality rates must be monitored to ensure
18 complete assessment of competing risks.

19 So let's consider, now, patients who
20 develop a need for an advanced therapy shown as
21 Phase IV in this diagram. And it's important
22 that endpoints chosen in clinical trials should
23 be disease-specific. Patients with refractory
24 advanced heart failure many times are acutely
25 unstable and require prompt intervention to

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1 survive. I think we all remember the startling
2 difference in mortality seen in the REMATCH
3 trial between medically treated advanced heart
4 failure patients and those receiving mechanical
5 circulatory support. It would be really
6 difficult to envision another trial examining
7 medical management in this group.

8 However, once the advanced therapy is
9 delivered, then it's also important to

10 recognize the disease state in patients who
11 receive advanced therapy is different, vastly
12 different than ambulatory heart failure. For
13 example, post-transplant immunosuppression and
14 rejection represent many poor outcomes in
15 transplant groups.

16 Patients living with mechanical
17 circulatory support also have a unique
18 pathophysiology which includes coagulopathy,
19 systolic events, device-related infections and
20 device malfunction. How do these patients
21 start in their journey to mechanical
22 circulatory support with totally different and
23 severe baseline conditions, which is associated
24 with very high mortality using medical therapy
25 alone. In this regard, new iterations of

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1 mechanical circulatory support focus primarily
2 on restoring functional capacity, improving
3 quality of life, and decreasing complications
4 associated with the pathophysiology that's

5 acquired with the chronic device implantation.
6 In fact, hospitalizations for acutely
7 decompensated heart failure are rare after a
8 bad implementation and may not be a meaningful
9 short-term endpoint. Hospitalizations for
10 bleeding, infection, device malfunction,
11 however, would be key elements of measuring
12 success in these patients.

13 Particularly important for this
14 context is that currently available quality of
15 life measurements are designed for patients
16 with chronic heart failure and may not be
17 specific to this new pathophysiology that
18 exists post-VAD support. While established
19 quality of life measurements document
20 improvement from baseline in patients receiving
21 MCS, the remarkable post-VAD clinical
22 improvement is compared with their severe
23 baseline. In this regard, new disease-specific
24 quality of life markers are likely needed to
25 evaluate the durability and the magnitude of

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1 specific components of quality of life that
2 capture the unique challenges of patients while
3 they live with mechanical circulatory support.

4 In this regard, then, disease-specific
5 quality of life measurements are now recognized
6 as one of the three pillars of quality health
7 care delivery, along with clinical
8 effectiveness and safety. The most clinically
9 validated instruments, as Ileana mentioned, are
10 the Kansas City Cardiomyopathy Questionnaire,
11 and the Minnesota Living With Heart Failure
12 Questionnaire. Although these instruments are
13 not perfect, favorable changes in each of them
14 independently predict a favorable outcome, and
15 are robust enough, in patients with chronic
16 ambulatory heart failure at least, to represent
17 a meaningful clinical outcome.

18 Longer-term assessment, however, of
19 quality of life using these instruments becomes
20 confounded with the comorbidities that commonly
21 accompany the heart failure syndrome.
22 Furthermore, questionnaires assume that the
23 patient has sufficient cognitive function to
24 understand and provide accurate answers, and

25 the prevalence of cognitive dysfunction in

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1 patients with heart failure may be
2 under-appreciated. Assessment of quality of
3 life beyond one year from an innovative
4 intervention is probably problematic. But
5 developing novel quality of life instruments
6 that focus on patient-specific defined worst
7 symptom or psychosocial stressors along with
8 locus of control issues are risky in the
9 context of evaluating a new technology. A
10 negative result with a new quality of life
11 marker may actually be due to the new quality
12 of life marker itself rather than the new
13 technology. So I think we need creative ways
14 of evaluating new quality of life measurements
15 that are meaningful and obligatory endpoints in
16 clinical trials that match the disease that's
17 present.

18 So how about functional assessment?

19 Changes in functional capacity are also

20 important markers for a successful novel
21 intervention. All functional assessments,
22 however, assume and are limited to patients who
23 can participate in the measurement without
24 confounding impairment from comorbid conditions
25 such as arthroscopy, amputation or paralysis.

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1 Certainly the easiest and most widely used
2 marker is a simple six-minute hall walk test,
3 which remains a good measure and a good measure
4 of functional capacity with appropriate
5 diagnostic and prognostic value.

6 More sophisticated cardiopulmonary
7 stress testing with the goal particularly of
8 measuring VO2max provides an excellent measure
9 of exercise capacity, but we believe should be
10 performed under specific conditions such as
11 core lab oversight or interpretation of
12 borderline tests using observatory or objective
13 methods intended to validate tests that would
14 otherwise be considered inadequate.

15 Additionally, statistical analysis is

16 planned to account for patients who
17 subsequently are unable to repeat the tests for
18 reasons unrelated to the fundamental question
19 being tested. Functional improvement is a
20 patient-centric preferred outcome of any
21 intervention tested in the heart failure
22 community.

23 So how about surrogate markers or
24 intermediate markers? They certainly are
25 attractive for use in clinical trials since

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1 shorter-term changes may reflect that the
2 intervention is successful and may give rise to
3 conclusions about long-term benefits. For
4 example, it's reasonable to consider a
5 reduction of valvular regurgitation or stenosis
6 as an appropriate endpoint for a novel valvular
7 intervention. Reversal of adverse ventricular
8 remodeling, as Ileana mentioned, is a very
9 gratifying thing to see, and usually measured
10 as an improvement in left ventricular and

11 systolic or diastolic indices, and directly
12 correlated with improved survival. But
13 reversal of adverse remodeling is known to
14 occur with successful drug and device
15 interventions and should be considered a
16 measure of success.

17 In patients with acute cardiogenic
18 shock from acute myocardial infarction or
19 myocarditis, temporary mechanical circulatory
20 support may prolong survival long enough for
21 improvement in ejection fractions to occur, and
22 that may be a situation in which the left
23 ventricular ejection fraction may be an
24 appropriate intervention.

25 And finally, favorable changes in

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1 biomarkers such as NT protein, C or B type
2 proteins, or ST2, may provide sufficient
3 evidence to support further investigation of a
4 novel intervention. And particularly
5 applicable to patients with reduced ejection
6 fraction heart failure, congruent improvement

7 in biomarkers, functional capacity and quality
8 of life as a composite is now a means for
9 expedited regulatory review and potential early
10 FDA approval, with the expectation of further
11 real world evidence development in the
12 post-approval period.

13 In that regard, then, fairly recent
14 development of credible real world databases in
15 very large populations also provide meaningful
16 opportunities for continued evidence
17 development. Data objectively extracted from
18 these databases have the potential to
19 corroborate the results of randomized clinical
20 trial data, and have the potential to provide a
21 so-called cultivated cohort, which may provide
22 appropriate concomitant comparison groups.

23 Multiple databases are now available
24 from several sources and may provide novel
25 means to more fully evaluate generalizability

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1 and, importantly, clinical effectiveness of a

2 novel intervention after it's made available
3 for clinical use.

4 In summary, then, disease-specific
5 non-mortality outcomes are scientifically sound
6 methods to evaluate novel interventions for
7 patients with heart failure. Preventing
8 decompensation events regardless of the venue
9 in which therapy is delivered should be
10 considered as appropriate in clinical trials,
11 in heart failure clinical trials. The goals of
12 allowing patients to remain stable and at home
13 is patient-centric and appropriate. Stability
14 many times improves quality of life and
15 especially in those patients whose baseline
16 condition is characterized as quite severe.

17 Functional improvement is an important
18 outcome, very important assessment of
19 innovation, and can be considered as primary
20 endpoints under certain conditions and
21 circumstances. And certainly combining
22 congruent improvement in biomarkers, quality of
23 life measures and functional capacity is a very
24 strong signal for overall health outcomes.

25 We applaud the efforts of CMS in

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1 stimulating this discussion about how to
2 measure success with novel interventions that
3 are designed to improve the patient experience
4 with heart failure. Alignment of non-mortality
5 endpoints as a criteria for regulatory and
6 coverage decisions is critical to ensure
7 sustainability of clinically meaningful
8 progress in innovation, with the hope of
9 providing meaningful solutions for addressing
10 unmet clinical needs. Thank you very much.

11 DR. REDBERG: Thank you, Dr. Carroll.
12 I'm sorry, thank you, Dr. Adamson. Looking
13 ahead. I would like to introduce Dr. John
14 Carroll, professor of medicine at the
15 University of Colorado School of Medicine, and
16 director of interventional cardiology.
17 Dr. Carroll.

18 DR. CARROLL: Thank you, Dr. Redberg.
19 It's a pleasure to be here this morning and to
20 share with you some thoughts on what health
21 care outcomes should be of interest to CMS in

22 studies for heart failure treatment
23 technologies. I have no financial disclosures
24 relative to this topic. My institution and I
25 are investigators in a variety of clinical

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1 trials in this space.

2 So, the goal is to provide CMS with
3 the ideal health care outcomes and research
4 studies in heart failure treatment technologies
5 and appropriate follow-up duration, and I will
6 try to stick to the topic. My perspective is
7 perhaps different from others here. I'm an
8 interventional cardiologist and my areas of
9 expertise relative to this are heart failure-
10 related valvular heart disease and other
11 transcatheter approaches to valve replacement
12 and repair, and CHF related to cardiac shunts
13 treated with a variety of different
14 transcatheter technologies, that's my
15 perspective.

16 Clinically significant valvular heart

17 disease is really becoming prevalent in our
18 aging U.S. population as shown here. Moderate
19 to severe mitral valve disease, aortic valve
20 disease obviously increases with age, and
21 notice that the final age is greater than 75,
22 and certainly now we have many many of us
23 living beyond that point. So there are major
24 issues that we have to discuss and make
25 explicit that are confounding in outcome

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1 assessments and one of them is the issue of
2 advanced age, and the other is socioeconomic
3 status.

4 And certainly in this area of heart
5 failure in general and also in the areas I
6 work, the focus is on the elderly, it is a fast
7 growing segment of the population.
8 Cardiovascular disease is the leading cause of
9 morbidity and mortality in these people and
10 they have the presence of significant
11 comorbidities and different forms of cognizant
12 dysfunction, social support, diminished

13 functional status. All these things influence
14 our decision-making and treatment outcomes.

15 Furthermore, we have to deal with
16 certain realities that life does have a finite
17 expectancy and as we age, that the expected
18 life expectancy drops, and that's relevant when
19 we talk about therapies that apply to
20 80-year-olds versus 50-year-olds. And the
21 survival benefits of some of these treatments
22 do have, and have been shown in randomized
23 clinical trials, are important, but the other
24 benefits are extremely important in predicting
25 the value of transcatheter therapies, such as

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1 clinical status, quality of life, and freedom
2 from hospitalization.

3 And these outcome assessments must be
4 put in a broader context of the patient's daily
5 existence, and there are a variety of social
6 determinants of risks and outcomes for
7 cardiovascular disease that we all confront on

8 a daily basis, and include some of these items
9 demarcated on the left, and these markers of
10 socioeconomic position often are not captured
11 when we do clinical trials and we assess
12 long-term outcomes, and are key issues that are
13 under appreciated but have a huge impact on
14 outcomes.

15 So in preparing for this, I tried to
16 be very explicit about the different domains
17 about things that need to be considered,
18 survival but also objective assessment of the
19 disease-specific anatomical physiologic
20 variables that the treatments address. The
21 presence or absence of treatment complications.
22 The improvement, or lack of, in
23 patient-reported health status. The objective
24 functional assessments and the freedom from
25 hospitalization, and lost of independent

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1 living.

2 So in terms of the objective
3 assessment of disease-specific anatomical

4 physiologic variables that the treatment
5 addresses we have to have a time frame, and
6 typically the time frame for assessment is
7 immediate to 30 days. One year is important if
8 durability is a central issue for the
9 treatment.

10 I always hesitate sending movies as
11 part of the talks, but on the left is a patient
12 with an aortic bioprosthesis that has generated
13 severe regurgitation and on the right is after
14 the implantation of a transcatheter valve
15 within that, and the two videos show severe
16 aortic regurgitation on the left and the
17 absence of aortic regurgitation. So that's the
18 assessment of the treatment effects.

19 We can further assess the outcomes
20 directly related to the disease process by
21 other measures noninvasively or invasively, and
22 this shows the pre and post impact on cardiac
23 aortic pressures, also respiration of the
24 competent aortic valve.

25 Outcome assessment like cardiac

1 ultrasound is central in the heart failure and
2 the transcatheter and surgical valve area. The
3 preprocedure documentation has severe mitral
4 regurgitation that must be paired with the
5 postprocedure documentation with the degree of
6 reduction using standardized methodology that
7 we have arrived upon.

8 Next, we must assess the presence or
9 absence of treatment complications and the time
10 frame of that is really throughout the
11 patient's life, but starts with the immediate
12 to 30 days. One year is important because
13 there are some late complications that are
14 unique to different treatment modalities.

15 So we've learned a lot about
16 assessment of physician and hospital
17 performance that's relevant to looking at
18 outcomes, as CMS wishes to do, for example an
19 isolated surgical valve replacement with a
20 composite score based solely on outcomes. We
21 have risk standardized mortalities but we also
22 have to look at the alternate to know the

23 stress-patient morbidity occurrence that is
24 very important to our patients and for us as
25 clinicians. We note the sternal infection,

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1 reoperation, stroke, renal failure and
2 prolonged ventilation, and this drives some of
3 the work in the STS crew.

4 Next, we have to get an idea of
5 whether patients' health status is improved
6 from their own perspective, or has not
7 improved, or potentially has deteriorated, and
8 there the time frame is obviously prolonged.
9 It starts with the establishment of baseline
10 measurements that serve as an index for the
11 individual patient to see to what degree they
12 improve or not, and it's particularly important
13 in the elderly or those with comorbid
14 conditions that could impact on the benefit
15 from the treatment.

16 So, the importance of measuring
17 patient health care status is outlined here by
18 my colleagues, and some of them are at

19 Colorado, like Dr. Rumsfeld. So we are talking
20 about living longer, living better. We are
21 talking about patient-reported health status,
22 which includes not just quality of life but the
23 symptom burden, the functional status, both
24 social and other validated patient health care
25 surveys that need to be disease-specific but

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1 sometimes need to be broadened to patients with
2 multiple forms of cardiovascular disease and
3 allow for quantification of these critical
4 patient-centered outcomes. And these patient
5 health care status surveys have been used to
6 successfully document the impact of treatments
7 and certainly we use them in long-term
8 follow-up in clinical registries like TVT that
9 I'm involved with. And it's also a baseline
10 marker for adverse outcomes and health care
11 costs.

12 So here if we look at this spectrum of
13 patient-reported health status, we start with

14 the disease and treatment, and assessing
15 symptoms, functional status, and health-related
16 quality of life. And we see, as shown below,
17 all the different things that impact on how a
18 patient may respond to a questionnaire and come
19 up with different answers, different variables.

20 So specifically within the TVT
21 registry when we were developing the basic data
22 elements that needed to be gathered, we decided
23 on the KCCQ as a health status measure that
24 integrates multiple aspects of symptoms,
25 functional status, and quality of life, into a

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1 single measure, and it has been documented to
2 be reliable, patient-centered, and easily
3 collected in routine clinical practice after
4 adequate education.

5 And this shows some of the impact that
6 we've been able to assess using the large
7 number of patients entered into the TVT
8 registry, which is approaching 100,000 patients
9 who've undergone FDA-approved commercially

10 available transcatheter therapy for valvular
11 heart disease, and what do we see here? We see
12 there are patients who fortunately have large
13 improvements in the KCCQ, we see those with
14 moderate improvement, greater than ten, which
15 seems to be an objective realistic goal, but
16 then there are patients who have no
17 improvement, no change, or decreased at 30
18 days. What does that mean and what can we do
19 about it?

20 Here we see transcatheter aortic valve
21 replacement according to baseline health
22 status, so it has prognostic value, not just
23 looking at deltas, but it helps us assess what
24 might come down the road, what are the chances
25 of patients benefitting from these therapies,

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1 something very very important as we go forward
2 trying to predict in whom is this treatment
3 going to be beneficial, and that helps inform
4 patients to make their decisions about whether

5 or not to undergo a treatment.

6 And the ability to develop conceptual
7 frameworks of describing tests as not
8 necessarily failure but lack of success when it
9 comes to various treatments is shown here, a
10 publication from Dr. Arnold looking at the
11 interplay of both KCC score but also patient
12 survival, and trying to identify in whom, is
13 there not either individual patient marks, in
14 whom is there a poor outcome, and can we
15 predict it, and a reasonable definition of a
16 poor outcome, what is that? And we have
17 certainly persistent low KCCQ as a reflection
18 of the patients' health status, and further
19 decrease in that score of course is not
20 something we like to see when we're trying to
21 help people.

22 We're entering an era where we want to
23 be able to predict outcomes and then assess
24 what happens in terms of testing the validity
25 of predictive tools, and that's where so much

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1 effort is going into risk model algorithms to
2 predict mortality, immediate treatment related
3 but also long term, and if we can do a better
4 job of predicting who responds and who does not
5 respond to a treatment, wouldn't that be
6 fantastic, to not only bring the therapy to the
7 people who respond, but not subject other
8 people to treatments that they may not respond
9 to, and the associated huge health care costs.

10 So we need objective functional
11 assessments, and the new metrics for success
12 are in front of us and shown here with this
13 individual undergoing a functional assessment
14 of not only how they report the success or
15 failure of how they're doing and using more
16 than the simple classification of the New York
17 Heart functional class, but looking at
18 six-minute walk tests, which can be done in the
19 majority of these patients, but some cannot due
20 to orthopedic and other issues that prevent
21 them from walking.

22 When we look at new therapies like
23 mitral valve clipping procedures and looking at
24 changes in the New York Heart classification,

25 baseline versus 30 days, we see significant

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1 improvements in their functional class
2 affecting the majority of patients but not all.

3 Certainly great emphasis has already
4 been placed on the freedom from
5 hospitalization, but also the loss of
6 independent living is as important as many
7 other parameters for our patients. The time
8 frame of assessment is important, it can be
9 done early on, but we really have to, again,
10 look in many of these therapies beyond the
11 immediate procedural results and look at
12 outcomes at one year. They are a reflection of
13 many things, not only the procedure, but the
14 quality of care subsequently.

15 And after transcatheter aortic valve
16 replacement in the TVT registry, we're able to
17 see what happens to these patients when they're
18 discharged, do they actually go home, do they
19 die, are they transferred to a rehab institute

20 or do they go to a nursing home? We need to
21 look at these parameters of what happens to
22 patients after therapy, that is an important
23 metric.

24 Certainly one of the benefits of the
25 stakeholder engagement and participation of CMS

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1 and FDA in the professional registries like the
2 TVT registry that's jointly sponsored by STS
3 and ACC is the ability to link patient records
4 with long-term CMS data and look at
5 rehospitalization rates as shown here. This
6 helps us further refine the benefit of therapy
7 and patient selection criteria, and identify
8 some unmet needs and how we might improve
9 things.

10 So in conclusion, the assessment of
11 outcomes must address these six major domains
12 that I've identified here. Survival is one.
13 The second is objective assessment of the
14 disease-specific anatomical-physiologic
15 variables that the treatment addresses. And

16 third, the presence or absence of treatment
17 complications. Fourth, the improved
18 patient-reported health status. Fifth,
19 objective functional assessment. And sixth,
20 freedom from hospitalization and loss of
21 independent living.

22 The timing of the assessment of the
23 different domains of outcomes should include
24 baseline assessment for comparison to post
25 treatment. Immediate to 30-day survival, but

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1 also objective assessment of the
2 disease-specific variables that the treatment
3 purportedly addresses, and the presence or
4 absence of treatment complications. At one
5 year, survival, improved health status,
6 objective functional assessment, and freedom
7 from hospitalization and loss of independent
8 living are key. Thank you.

9 DR. REDBERG: Thanks very much,
10 Dr. Carroll. Next we'll hear from Dr. William

11 Lawrence, who is associate director of clinical
12 effectiveness and decision science at the
13 Patient-Centered Outcomes Research Institute,
14 and Dr. Larry Allen, who is associate professor
15 of medicine and medical director of the
16 Advanced Heart failure at University of
17 Colorado Denver, a colleague of Dr. Carroll.

18 DR. LAWRENCE: Good morning, and on
19 behalf of both Dr. Allen and myself, I thank
20 you for having us this morning. So, first,
21 just disclosures for myself. I'm an employee
22 of PCORI and have no other conflicts.

23 So, this is a co-presented
24 presentation, and just a brief overview, I'm
25 actually going to give just a very brief

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1 introduction towards patient-centered outcomes,
2 and then Dr. Larry Allen will talk about his
3 work working with patients on LVAD
4 decision-making.

5 So first, just a couple words on
6 Patient-Centered Outcomes Research Institute.

7 I've got here our mission and goals. Really
8 the big thing I wanted to point out is that our
9 mission is to help people make informed health
10 care decisions by producing high integrity
11 evidence-based information that comes from
12 research guided by patients, caregivers and the
13 broader health care community, so my main point
14 today is to make sure that our stakeholders are
15 involved in the research from the start.

16 So, we fund patient-centered outcomes
17 research. This is a form of comparative
18 effectiveness research that, what we're really
19 interested in is that it considers the
20 patients' needs and preferences, and the
21 outcomes that are most important to them.
22 We're also interested in what works not only
23 for the whole population, but what works for
24 whom and under what circumstances. And then
25 finally, interested in helping patients and

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1 other health care stakeholders make better

2 informed decisions about health and health care
3 options.

4 So just a couple of things. We're
5 interested in the concept of
6 patient-centeredness, so we are actually
7 interested in basically answering the questions
8 or examining the outcomes that matter to
9 patients within the context of their own
10 preferences and that, our proposition is that
11 research questions and outcomes should reflect
12 what is important to patients and the
13 caregivers.

14 And the other thing is that we're
15 interested in patient and stakeholder
16 engagement, so stakeholders should be involved
17 from the start of the research and not just
18 basically the subject of the research. So with
19 that introduction, I'll turn it over to
20 Dr. Larry Allen from the University of
21 Colorado, to talk about his work with LVAD
22 patients.

23 DR. ALLEN: So, thanks, Bill, and
24 thanks to PCORI for inviting me, and thanks to
25 CMS for giving me the opportunity to hopefully

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1 contextualize this discussion about outcomes
2 from the patient perspective, and today I'd
3 like to use what we've done with left
4 ventricular assist devices, but I think it
5 applies to a variety of cardiac devices.

6 These are my disclosures. I do some
7 consulting for Novartis, Janssen and ZS Pharma
8 that's funded by the AHA and PCORI.

9 So, I think this is a good way to
10 think about how outcomes inform what we do. So
11 here you have a doctor who's saying hmm, when a
12 patient asks Doctor, I want to choose how I'm
13 treated, the doctor says hmm, you're not just
14 ill, you're deluded, but I actually think this
15 sets up the framework for how outcomes really
16 help us deliver good health care.

17 The first thing is that outcomes help
18 us decide what are medically reasonable options
19 for this patient. I don't know whether I can
20 recommend one or two or three options to a
21 patient, or say that's not an option, unless I

22 have good quality data that tells me whether
23 that's good for the patient or bad for the
24 patient, what the balance of that is. But
25 rarely do I come to a conclusion where I know

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1 exactly one thing is right for this one
2 patient, so we also need outcomes presented to
3 patients in ways that they can understand which
4 option among the ones that may be medically
5 reasonable is actually right for that
6 individual patient. So as we consider the
7 outcomes for measuring, we need to think about
8 not only what's good kind of from a standard or
9 societal perspective, but how do we help
10 individual different people sort through those
11 options in a way that they can then decide.

12 I think outcomes also help us decide
13 or approach the way that we present medical
14 options to patients. So sometimes we use
15 behavioral counseling, when scientific evidence
16 for benefit strongly outweighs harm. So in

17 smoking cessation or a beta blocker for heart
18 failure with reduced ejection fraction, and
19 then decision support designed to describe,
20 justify, recommend and engage is most
21 appropriate.

22 At the end of the day, even when we
23 think that smoking cessation is the right thing
24 to do and that's the one option in front of
25 this patient, patients still have to appreciate

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1 that that's right for them, and then feel
2 motivated to move forward. And so if we can't
3 present that the outcomes show the benefits
4 vastly outweigh the risks for that patient,
5 then it's hard for us to do behavioral
6 counseling. We've got to be able to have these
7 outcomes in a way that allows us to do that.

8 Increasingly, though, especially with
9 medical devices, I think we fall into the
10 second category, where shared decision-making
11 is most easily applied to preference sensitive
12 decisions, where both the clinician and the

13 patient agree that equipoise exists between
14 different options, and decision support helps
15 patients think through, forecast, and
16 deliberate those options.

17 So at the end of the day, we may not
18 have outcomes that tell us exactly what is the
19 right choice for this specific patient. What
20 we want to do is be able to help create a
21 discussion around whether a treatment that may
22 be good for one person may not be good for
23 another, and be able to have the data to do
24 that.

25 I also think that the concept of

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1 outcomes also applies to, do we have kind of
2 the data to be able to engage and then activate
3 and help patients deliberate and discuss what
4 are valued important decisions for themselves.
5 And we actually have measures for levels of
6 engagement, levels of activation, and those are
7 important.

8 So I'm going to talk about left
9 ventricular assist devices or artificial heart
10 technology, because I think it's a great case
11 study to illustrate with medical devices for
12 heart failure how the outcomes are so
13 important. So you know, 50 years ago,
14 artificial heart technology was pie in the sky,
15 and here we are today where left ventricular
16 assist devices are now done in over 4,000
17 patients a year in the United States, which has
18 outpaced transplantation, and even one of our
19 vice presidents has benefitted from this
20 technology.

21 This is a fast moving field, which
22 also challenges the data collection and
23 outcomes measurement. So, this is from the New
24 England Journal of Medicine in February of this
25 year, and you can see that there was one

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1 article on the new Heartmate 3 device which was
2 studied in the MOMENTUM trial, there's a second
3 article on the HVAD device studied in the

4 ENDURANCE trial. So this field, again, is
5 moving forward fast and we need good data.

6 The other reason mechanical
7 circulatory support, left ventricular assist
8 devices are such a great place to study
9 outcomes measurement is that there is almost
10 nowhere where there is such high risk, high
11 reward, right? This is where the benefits are
12 huge and the risks are huge, and so being able
13 to measure those and convey those in a way that
14 people can kind of weigh is critically
15 important to the therapy and the way that we
16 counsel people.

17 So let me give you some examples of
18 how we've tried to take the outcomes data from
19 the scientific community and digest it in a way
20 that patients can potentially comprehend the
21 gist, and then make a decision about. So, left
22 ventricular assist devices for people
23 essentially dying of heart failure can have
24 fairly significant survival advantages, so when
25 we did a systematic review of the data

1 available which, most of it only goes out to a
2 year, so we really can't even say what happens
3 at five years very well, but there's data out
4 there that without therapy, about 80 percent of
5 people will die and 20 percent will live, and
6 with the therapy, about 20 percent of people
7 will die and 80 percent will live. And the way
8 that this looks on a Kaplan-Meier curve, which
9 I think would be difficult for a patient to
10 understand, is that at a year we really move
11 people so that their survival more than
12 doubles, so the number needed to treat at one
13 year, that if we put in two LVADs, more than
14 one life is saved on average. That's pretty
15 impressive and that's pretty important to most
16 patients.

17 However, patients not only want to
18 live longer, they want to live better, and so
19 how do we convey that to patients as well?

20 Well, we also provide quality of life
21 information. We're going to have some
22 discussion today about what are the best

23 quality of life measures in terms of general
24 quality of life measures, disease-specific
25 quality of life measures, as well as functional

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1 outcomes and other things that should amount to
2 quality of life and independence. But what we
3 found when we went to patients is that
4 presenting a whole slew of scores with scales
5 that are not necessarily easily digestible is
6 actually very challenging.

7 And so we ended up with this figure
8 here, which essentially takes the KCCQ data
9 from the trials and shows that on average
10 patients move from a KCCQ score of 28 to a KCCQ
11 score of 70 among those who live. So, a couple
12 of key points about this. One is that I think
13 this is a very digestible way for people to
14 take in that information and it's on a scale
15 that I think makes sense, rather than 105 down
16 to zero, it's zero to 100, which I think is
17 important.

18 And then the last is, we spend a lot

19 of time trying to parse out very minor
20 differences between outcomes, and what we find
21 from most patients who are trying to take in
22 all this information is that it's actually the
23 big picture that's far more important than the
24 very minute details. And I think a lot of
25 times we split hairs over which quality of life

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1 measure we want to use, and if you actually
2 look at the data for all these diverse measures
3 that kind of map the quality of life domains or
4 health status domains, they actually kind of
5 all move in the same direction, and that's what
6 patients care about.

7 The other is that there are always
8 tradeoffs and there are always downsides and
9 always risks. And so we present on the top,
10 what are the average benefits, but people also
11 care about what are the individual bad things
12 that might be able to happen to me, and we need
13 to be able to convey that as well. So with

14 left ventricular assist devices, there are
15 plenty of bad things that can happen even
16 though the benefits are quite impressive on the
17 whole. So we talked about hospitalization,
18 because it is important to people, it maps the
19 independence, it maps the symptoms, and it also
20 maps the prognosis, and then it maps the costs,
21 not just for Medicare or for society, but it
22 also maps the out-of-pocket costs for patients.

23 Bleeding is a major problem for these
24 patients, and so understanding what are the
25 specific things that could happen and what are

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1 the frequency of those is important to
2 patients. Stroke is a big downside and a major
3 cause of death for patients who do get a left
4 ventricular assist device, and so talking about
5 this is important, and most people think
6 differently about stroke versus bleeding even
7 though they both may decrease quality of life
8 and even survival.

9 Talking about device-related

10 infections is also relevant, as well as what
11 might happen to these devices that could then
12 affect the patient. And then I think it's also
13 relevant to think about the fact that sometimes
14 therapies, they work on average but they don't
15 always work, and so one of the things patients
16 have told us is that they've gotten a left
17 ventricular assist device with the promise that
18 their heart failure would go away, and yet
19 about 18 percent of people continue to have
20 very significant heart failure due to right
21 ventricular dysfunction. So that's important
22 because of the disappointment and the
23 expectation management, and so measuring all of
24 these outcomes is important to people if
25 they're going to weigh all these tradeoffs, so

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1 I don't think there's one single measure that's
2 going to give us the answer or give patients
3 the answer.

4 The other thing that's really

