CENTERS FOR MEDICARE AND MEDICAID SERVICES

Medicare Evidence Development & Coverage

Advisory Committee

July 22, 2015

Centers for Medicare and Medicaid Services

7500 Security Boulevard

Baltimore, Maryland

Panelists

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Matthew T. Menard, MD

CMS Liaison
Tamara Syrek Jensen, JD

Executive Secretary
Maria Ellis

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PANEL PROCEEDINGS

(The meeting was called to order at 8:10 a.m., Wednesday, July 22, 2015.)

MS. ELLIS: Good morning and welcome, 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 lower extremity peripheral artery disease.

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 an Internet or e-commerce

organization, that develops, manufactures, distributes and/or markets, consulting, evidence reviews or analysis, or other services related to lower extremity peripheral artery disease intervention. This includes direct financial interests, consulting fees and significant institutional support. If you have not already received a disclosure statement, they are available on the table outside of the auditorium.

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, voting members for today's meeting are Dr. Doug Campos-Outcalt,

Dr. John Jeffrey Carr, Dr. Aloysius Cuyjet, Dr. Richard Deyo, Dr. Peter Lawrence, Dr. Frank Lefevre, Dr. Sandra Lewis, Dr. Marcel Salive, Dr. Julie Ann Swain, and Dr. Diana Zuckerman. A quorum is present and no one has been recused because of conflicts of interest.

The entire panel, including non-members, will -- 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. This meeting is being webcast via CMS in addition to the transcriptionist. By your attendance, you are giving consent to the use and distribution of your name, likeliness and voice during the

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

In the spirit of the Federal Advisory Committee Act and the Government in the

Sunshine Act, we ask that the advisory committee members take heed that their conversations about the topic at hand take place in the open forum of the meeting. We are aware the members of the audience, including the media, are anxious to speak with the panel about these proceedings. However, CMS and the committee will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or at lunch.

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.

And now, I would like to turn the meeting over to Tamara Syrek Jensen.

MS. JENSEN: Thank you, Maria. I know we're running a bit late so I will keep my remarks very very brief. I wanted to thank everybody for attending.

This is a very important topic for the Medicare program and the Coverage and Analysis Group, and the reason for this meeting is really to see the state of the evidence today and then based on what we hear today, I think the Coverage and Analysis Group will go back and will take a look at it and make decisions on what we will do next policy-wise. So really, the focus of this is about the

evidence, that is key for us, so that is really what we want to focus on and that is what we want to hear about, because those, the basis of that evidence is what we will decide on what our next steps might be.

And currently, just to remind everybody, we do not have a national coverage determination open on this particular topic. I think that is why we are looking at this today, to determine if we do want to open up an NCD or

do something else with this topic.

Again, thank you everyone for coming today, it is a very crowded room, so I know everyone feels like they're literally on top of each other, but I think it will be a very good meeting. And again, thank you to the panel for traveling here as well. Dr. Peter Bach.

DR. BACH: Yes, I also -- we are running a bit behind. I am the timekeeper here, as well as the person who will try to keep the discussion focused. I thank you all for coming to this public process to move the discussion around the evidence for these interventions forward. Thank you all, again,

for coming, and I think we should probably start.

Jamie, before you start, I'll have the panel introduce themselves.

I am Peter Bach, I'm a physician and critical care doc at Sloan-Kettering. I'm the vice chair of this body and acting as chair today.

DR. CAMPOS-OUTCALT: I'm Doug Campos-Outcalt, medical director of Mercy Care, a state Medicaid health plan in Arizona.

DR. J.J. CARR: I am John Jeffrey Carr, at Vanderbilt University Department of Radiology in biomedical informatics and cardiovascular medicine. I have no significant disclosures, although my retirement account has numerous stocks and they could be Internet companies or something, but it's not significant.

DR. CUYJET: I'm Al Cuyjet, a cardiologist and intensivist and professor of clinical medicine at Stonybrook Medical Center, and medical director of Health Care Partners, IPA, and I have no disclosures.

DR. DEYO: I'm Richard Deyo, I'm a general internist working in the Department of Family Medicine at Oregon Health and Science University, and have no disclosures.

DR. LAWRENCE: I'm Peter Lawrence, I am the chief of vascular surgery at UCLA and direct the Gonda-Goldschmied Vascular Center, which is an interdisciplinary vascular center, and I have no disclosures.

DR. LEFEVRE: I'm Frank Lefevre. I am an internist. I am medical director for BlueCross BlueShield Association in Chicago,

and besides being paid by BlueCross I have no other disclosures.

DR. LEWIS: I'm Sandra Lewis, I am a cardiologist from Portland, Oregon. I have a clinical appointment at Oregon Health and Science University and practice at Northwest Cardiovascular Institute. I have no disclosures.

DR. SALIVE: I'm Marcel Salive, a physician from the National Institute on Aging, which is a part of NIH and the federal government, and I'm here representing myself.

I have no disclosures.

DR. SWAIN: Julie Swain, cardiovascular surgeon and director of Center for Medical Devices at Mount Sinai School of Medicine, New York. No conflicts.

DR. ZUCKERMAN: I'm Diana Zuckerman, president of the National Center For Health Research. Our center does not accept funding from pharmaceutical or device companies, but I personally have stock in Johnson & Johnson.

DR. KORMOS: Bob Kormos, I'm a cardiothoracic surgeon at the University of Pittsburgh Cardiovascular Institute. I'm the

Brack Hattler chair of cardiothoracic transplantation at the University of Pittsburgh. I have no disclosures.

DR. LYSTIG: I'm Ted Lystig, director of corporate biostatistics at Medtronic. I am the industry representative and I am an employee, shareholder, and hold options in Medtronic.

DR. HIRSCH: Good morning. I'm Alan Hirsch, I'm a vascular medicine specialist and clinical trialist at the University of

Minnesota. I work in our community health and cardiovascular epidemiology clinic. There are five relevant disclosures to our university for research from Astra Zeneca, Merck, Bayer, Pluristem, and Tactile Medical.

DR. BACH: Next we have Jamie Hermansen, from CMS, who is going to go over the topic and the voting questions.

MS. HERMANSEN: Hello. My name is Jamie Hermansen, and welcome to today's meeting of the Medicare Evidence Development and Coverage Advisory Committee. I'm a health insurance specialist here with the Centers for Medicare and Medicaid Services.

The purpose of today's meeting is to review the evidence of existing interventions related to lower extremity peripheral artery disease and address areas where evidence gaps may exist. The clinical outcomes of interest to the Medicare program include reduction in pain, avoidance of amputation, improvement in quality of life and functional capacity including walking distance, wound healing, avoidance of cardiovascular events such as

myocardial infarction, stroke, cardiovascular death and all-cause mortality, and avoidance of harm from interventions.

The MedCAC panels do not make coverage determinations, but CMS often benefits from their advice. By voting on specific questions and their discussions, MedCAC panel members advise CMS about how they may wish to use the existing evidence in the future. These voting questions include terms like asymptomatic, intermittent claudication, and critical limb ischemia, and these terms will be further explained in subsequent presentations.

For question one, for adults with asymptomatic lower extremity PAD, how confident

are you that there is sufficient evidence of an intervention that improves immediate/near-term health outcomes or long-term health outcomes?

Discussion topics for this question include: If intermediate confidence, meaning an average score of greater than or equal to 2.5, please identify the specific interventions and associated outcomes. Considering the heterogeneity of the Medicare population,

please discuss which subgroups of the Medicare population the evidence shows are likely to benefit or likely not to benefit from the intervention.

For question two, for adults with lower extremity intermittent claudication, how confident are you that there's sufficient evidence for an intervention that improves immediate/near-term health outcomes, or long-term health outcomes? And the discussion questions are the same as those for question one.

For question three, for adults with lower extremity critical limb ischemia, how confident are you that there is sufficient evidence for an intervention that improves

immediate/near-term health outcomes, or long-term health outcomes? And again, the discussion questions are the same as those for question one.

We are also asking the MedCAC panel to discuss the important evidence gaps that may not have been previously or sufficiently addressed, and finally, to discuss any apparent

treatment disparities and how they may affect the health outcomes of Medicare beneficiaries.

I thank you for your attention and will now turn the meeting back over to Dr. Bach.

DR. BACH: Thank you very much. I'm now going to ask Schuyler Jones, Dr. Schuyler Jones and Dr. Manesh Patel from Duke to come and address the technical assessments.

DR. PATEL: Good morning. Thank you, ladies and gentlemen, it's my honor to present some of the AHRQ evidence health care program, evidence on treatment strategies for patients with peripheral artery disease. I'm going to be speaking with Dr. Schuyler Jones on behalf of Dr. Vemulapalli about this program.

These are the relevant disclosures

displayed on this screen for both Dr. Jones and myself, Dr. Vemulapalli, the other coauthors on this document, which is PubMed searchable, and there will be some references that we will show you throughout the conversation. I have no conflicts of interest to disclose.

Of note, we did use a technical panel

in the TEC, sort of a technical panel of experts and peer reviewers, and they disclosed their relationships on the publication.

I'll start with things we may all know but we wanted to make sure we used similar language. I will walk through the background, Dr. Jones will go through the evidence review, and then we'll give you our conclusions.

So, peripheral artery disease, as many of you all know, is a chronic atherosclerotic narrowing or blockage of the arteries to the lower extremities, and its attendant consequences affect patients for both the limb and their cardiovascular outcomes.

You've already heard today something about the categories of how you might clinically think about patients with symptomatology of peripheral artery disease.

There are three groups that we will be exploring and presenting: 1) Asymptomatics; 2) intermittent claudication, which is defined as exercise-induced ischemic symptoms or leg pain while walking and/or weakness that is relieved by rest, we'll talk about how typical or

atypical their symptoms are in a moment. And then of course the mortality rate from stroke and MI is increased significantly for age-matched controls that have intermittent claudication; 3) And then critical limb ischemia, which you will hear a fair amount about, it's pain at rest eventually leading to gangrene and potentially amputation.

There are several disease classification systems for patients with peripheral artery disease. On this slide you see represented a few of those, there's the Fontaine stage, the Rutherford stage, and at the bottom a cutout from a recently published categorization by the Society of Vascular Surgery on patients with critical limb ischemia or wounds. And across the spectrum you can see that the staging systems give you information around patients that are asymptomatic, have

claudication, or critical limb ischemia. We will present that data when possible in the evidence review.

The first message, I think in background in many of the guidelines, is

focusing on the classical symptoms. This is the majority of patients with peripheral artery disease: this is one of many studies that show that only a third of the patients may have typical claudication, with greater than 50 percent that may have atypical limb symptoms but they are functionally limited, and then five to 10 percent of patients may have critical limb ischemia.

This is the ankle brachial index data from Jerry Fowkes and others that shows the fact that this test is fairly sensitive and when used with Framingham, is able to diagnose PAD and predict cardiovascular outcomes with the axis on the bottom showing you the patient's actual ankle brachial index, and then the hazard ratio for cardiovascular events across the Y axis, and you can see as the ischemic limitation increases, their cardiovascular events go up.

It's also notable that there are noncompressible vessels on the right side of the slide where patient's risk goes up again.

This is taken from Dr. Hirsch and

textbooks and others, the prevalence of PAD. The first message I think we're going to hear multiple times today is that PAD is a disease of the elderly, as you age the prevalence goes up. The other message that's important to recognize is that we fully don't understand the prevalence, as the disease is likely larger than what may be diagnosed amongst all the epidemiologic studies.

I'll speak for a moment about the risk factors. They include many of the things you see on the slide, but most specifically diabetes, tobacco use, renal insufficiency, and many of the other atherosclerotic risk factors we're aware of.

Throughout the evidence review you're going to hear us speak of sort of two consequences of PAD. As you've heard already, the first is functional capacity and quality of life. There will be also limb symptoms that we will try to speak to, and then there will be

consequences of PAD that are both patient-specific cardiovascular events and limb-specific, so everything from amputation, tissue

loss, to myocardial infarction, death, and stroke, and in fact the goals of treatment may be to affect both of these where the risk of those, what we'll say irreversible damage is high, and certainly symptomatic risk occurs.

The goals of therapy for PAD are, in all patients with PAD we've aimed to reduce cardiovascular morbidity and mortality. The evidence review will walk through some of the questions we asked with regards to that.

In patients with intermittent claudication, referred to as IC on this slide and in future slides, it's to improve their functional status and to reduce their morbidity and mortality from this disease.

And in patients with critical limb ischemia, it's to prevent amputation, restore mobility and the ability to ambulate, and then reduce their mortality.

Reducing cardiovascular mortality and morbidity has clearly been described previously, and strategies that can be included

include antiplatelet agents, angiotensin-converting enzymes, and other types of specific

modifying therapies, and then risk factor management, some of which we will not spend a long time in the evidence review on.

Two specific therapies for peripheral artery disease and functional capacity includes cilostazol, pentoxifylline. These are the proposed mechanisms, although, to be frank, the exact mechanisms are not clear for both agents. Cilostazol is said to prevent blood clots, maybe a potential antiplatelet effect, may affect the vasodilatory effect, it does have some noted side effects, and is contraindicated in patients with heart failure. Pentoxifylline prevents potentially some of the same mechanisms.

It should be noted in our evidence review that started more recently, most of the evidence was aimed at cilostazol rather than pentoxifylline, and Dr. Jones will cover that.

We will also review exercise training and functional capacity. Exercise therapy is aimed at improving endothelial function, reducing systemic inflammation and improving

the actuated muscle, manages the oxygenation

and maybe changes how the skeletal muscle uses blood flow.

We'll also spend some time looking at revascularization. The goals of revascularization, of course, are to restore blood flow, potentially improve wound healing and prevent amputation, and revascularization may be dependent on a variety of factors shown on this slide, many of which I think people will speak to.

The strategies that we specifically evaluated are surgery versus endovascular therapy. Although we know there are many opportunities with each of those, surgery has lower extremity bypass with many possible opportunities including endarterectomy. There's angioplasty with some drug-eluting balloons that are not shown on this slide and other therapies, stenting and atherectomy, multiple types of strategies, many used in combination, many used in hybrid procedures. We will review the evidence for what we have for those procedures.

The endpoints are the endpoints that

you've heard. We're going to look at cardiovascular endpoints, all-cause mortality, MI and stroke. Quality of life. We looked at limb-specific endpoints, based on our technical panel, of functional capacity, major amputation, amputation-free survival, wound healing, and then revascularization endpoints as you can see.

So, it's with that I'm going to have Dr. Jones review the evidence review, and then we'll come up with some conclusions for you.

DR. JONES: Thanks, Manesh. Thank you to the MedCAC panel for allowing us to present our data. This was a two-year process. This document is available on the AHRQ website. It's also, this data has been published in four manuscripts that are available online as well.

As we constructed the analytical framework that I show here in this slide, you can see on the left-hand upper slide that we used patient characteristics that Manesh talked about, asymptomatic, symptomatic patients with claudication, and symptomatic patients with critical limb ischemia.

We specifically looked at

interventions in the middle part of this slide. They consist of antiplatelet agents for all groups of patients, interventions for intermittent claudication including exercise training, medical therapy, endovascular intervention and surgical intervention. And then specifically for critical limb ischemia patients we looked at interventions including endovascular and surgical revascularization.

Like we've already said, the outcomes that we're using include cardiovascular events, amputation, quality of life, functional capacity, and then other limb-specific outcomes.

With each of these questions we looked at modifiers of effectiveness, so subgroups of patients including age, race, sex and others. We also looked at the safety of these interventions with each group.

With that analytical framework in mind, I'll go through the three key questions that we constructed and then tried to answer. The first key question, I'll refer back to these as key question one or KQ1, was:

In all patients with peripheral artery

disease, what is the comparative effectiveness of aspirin and other antiplatelet agents in reducing these outcomes? Similar to each of the other key questions, you can see that, does the effectiveness of these treatments vary, so are there modifiers of effectiveness for subgroups that are treated differently? And then C, what are the safety concerns with these interventions? So KQ1 or key question one is antiplatelet agents in all patients with peripheral artery disease.

Key question two revolved around intermittent claudication, so it specifically states, what is the comparative effectiveness of exercise training, medical therapy, endovascular intervention, which includes all types of endovascular intervention, and surgical intervention or surgical revascularization, on these outcomes? And does this treatment, does the effectiveness of this treatment vary according to subgroups? And then, what are the safety concerns of each?

Now to highlight this, we actually looked at specifically between treatment strategies rather than within treatment

strategies, and I'll show you some of that data on coming slides.

Key question three revolved around critical limb ischemia patients and specifically stated, what is the comparative effectiveness of endovascular intervention and surgical revascularization for these outcomes, how did these treatments vary according to subgroups, and then what were the safety concerns?

Those are our three key questions, the answers to which I'll present over the next few minutes.

We used the AHRQ methods guide to grade the strength of evidence for each comparison, and I'll describe each of those. High strength of evidence suggests that further research is very unlikely to change the confidence in the estimate. Moderate means that further research may change the confidence in the estimate. Low means that further research is likely to change the confidence. And then if there's insufficient evidence, that means that evidence either is unavailable, or

does not permit an estimation of the effect.

We performed this search in March, I'm sorry, in August of 2012. We specifically limited our questions to 1995 to the time the search was done in 2012. As you can see, almost 6,000 citations were identified, some of those were duplicate entries. We then reviewed almost 5,000 separate articles during our literature review. You can see, of those almost 5,000 abstracts, 11 qualified specifically for key question one on antiplatelet agents, 35 qualified for treatment specific to intermittent claudication patients, and then 37 qualified for treatments of patients with CLI.

We'll start with key question one, antiplatelet analyses. We were able to identify three specific comparisons, aspirin versus placebo or no antiplatelet agent, clopidogrel versus aspirin, and then clopidogrel plus aspirin dual antiplatelet therapy versus aspirin alone.

As I move through these slides, you'll see that I did include forest plots for

estimation of effect, I'll describe that and then give you the summary of these results as

we go.

In the aspirin versus placebo comparison, you can see that we looked at the composite vascular events at two or more years, so longer term outcomes. You can see based on that in asymptomatic patients the hazard ratios were actually right at one, suggesting that there's no difference in all-cause mortality, nonfatal MI, or composite vascular events in the patients who are asymptomatic, and the strength of evidence here was high.

For patients in the third study with intermittent claudication there were wide confidence intervals and, therefore, the strength of evidence for this was low.

There were no studies looking at functional outcomes, quality of life or safety concerns, and therefore it was graded as insufficient.

For the comparison of clopidogrel versus aspirin, the data was taken entirely from the subgroup of the CAPRIE study, the PAD

patients included in the CAPRIE study. You can see that there were 6,452 patients. In this, you can see that there was, that clopidogrel

was more effective for reducing nonfatal myocardial infarction, cardiovascular mortality and composite vascular endpoints, and we graded this with a strength of evidence of moderate.

There were not studies that looked at all-cause mortality, functional outcomes, quality of life or modifiers of effectiveness, and therefore we graded this as insufficient.

For the comparison of dual antiplatelet therapy or clopidogrel plus aspirin versus aspirin alone there were a total of four studies. As you can see, some of these were PAD subpopulations or subgroups from larger studies, some of them were mixed populations of claudication and CLI, and some of them were smaller studies of platelet inhibition. We found that there was no difference in all-cause mortality or composite cardiovascular endpoints, and graded this with a strength of evidence of moderate.

We did find that dual therapy, therapy

of clopidogrel plus aspirin, suggested that nonfatal myocardial infarctions were reduced with this therapy when compared to aspirin. We did not find a difference for nonfatal stroke

or cardiovascular mortality between these comparisons. And then we did find that minor bleeding was significantly higher with dual therapy versus aspirin alone, although with this there was only one study, which graded the strength of evidence as insufficient.

That concludes the description of the comparisons for key question one.

We'll move on to key question two which, I'll remind you, really is comparisons of these types of treatments for patients with intermittent claudication. As I said, we looked at between treatment strategy studies and I'll explain that a little bit more in the following minutes.

Because of the prior AHRQ review called Horizon, which studied same treatment strategy comparisons including angioplasty versus stenting, or stenting versus atherectomy, we did not repeat this comparison.

This study was published in 2008, and I will say that many of these comparisons have actually more data now than was present in 2008, but we did not recapitulate this study.

Our study really looked at between

treatment strategy comparisons, so specifically cilostazol versus placebo, exercise training versus usual care, endovascular intervention versus usual care, surgical revascularization versus usual care, and then compared to each other, and we did fixed effect models looking at these comparisons, and then we did a network meta-analysis trying to compare each of these comparisons against each other, and I will go over those results now.

We specifically looked for these patients with claudication at maximal walking distance or absolute claudication distance. When we looked at exercise training versus endovascular intervention, and in the combination of endovascular intervention with exercise, you can see that the hazard ratios are quite all over the place. When we look at supervised exercise and a combination of

endovascular revascularization and exercise, you can see that there were large improvements in maximum walking distance when compared to usual care. We graded this with the strength of evidence that's moderate.

With cilostazol and endovascular

revascularization there was a moderate improvement in maximal walking distance when compared to usual care. We've rated this with a strength of evidence as low.

When network meta-analysis was done to compare all of these things against each other, you can see that no individual treatment was found to have statistically significant effect when compared to the others.

For initial claudication distance or pain-free walking distance, another important endpoint for our claudication patients, you can see we used many of the same comparisons. We concluded that exercise training and endovascular revascularization were found to have moderate to large effects on initial claudication distance or pain-free walking distance. However, the strength of evidence

here is low.

Cilostazol was found to have no statistically significant effect on these outcomes. The strength of evidence here was also low.

When we performed network meta-analysis, there was no individual

treatment that was found to have a statistically significant effect when compared to the others, just like the prior outcome.

Quality of life is important for our claudication patients. You can see this is actually a network meta-analysis comparing each of the four listed comparators: cilostazol, exercise training, endovascular intervention, and surgical revascularization. With this you can see that each of them had moderate to large effects on quality of life when compared with usual care, although the strength of evidence was low and the heterogeneity was quite high.

When we did network meta-analysis comparing each to each other, there was no individual treatment that was found to be statistically significant for quality of life.

And we used the Short Form 36, I'll say, because the disease-specific quality of life measures did not have enough studies to actually compare.

We also looked in these claudication patients about the effect of these comparators on mortality, we did a network meta-analysis on this. You can see, and I'm going to repeat

myself here, there's no specific treatment that was found to have a significant effect on mortality, as expected, in patients with intermittent claudication when they were compared to each other.

All right. In addition to these outcomes that I've already described, you can see that there's inconclusive evidence for nonfatal MI, nonfatal stroke, amputation, modifiers of effectiveness, and safety, and we graded the strength of evidence as insufficient here.

In addition, there were zero studies looking at composite cardiovascular events, wound healing, pain, and safety in subgroups, and we graded it also as insufficient for these

intermittent claudication patients.

Now outside of the AHRQ review, this was a study that we performed using the same construct but without external funding, it was performed after the AHRQ review. You can see that we looked at over 6,000 articles, about 5,000, again, were screened at abstract stage, and 27 were included in this final report of supervised versus home exercise. So I'll

highlight again, this was outside of the construct because it was same treatment comparisons, supervised exercise, going to a place to get exercise, versus home exercise, and we did a systematic review and meta-analysis here, it was published in the American Heart Journal. The flow diagram, you can see, is very difficult to see here. I'll just say that I highlighted most of the important facts, and we did abstract data from 27 studies, and I'll show you the results here.

The same outcome, functional outcomes that we talked about before, maximal walking distance and initial claudication distance are used, left panels for maximal walking distance,

right panels are initial claudication distance. Panel A, the top panel, is six-month outcome, and Panel B is 12-month outcome. You can see in many of these comparisons, supervised exercise is more effective at improving maximal walking distance and initial claudication distance than home exercise.

When we look at quality of life using the same setup here, so general quality of life using the Short Form 36 on the left side, and

then on the right side the walking impairment questionnaire using six-month and 12-month data at the top to bottom, you can see that there was no difference in quality of life between supervised exercise and home exercise in our findings.

Move on to key question three, and I'll remind you, this is critical limb ischemia patients comparing endovascular intervention and surgical intervention. We did find four articles that looked at endovascular intervention versus usual care. Many of these were mixed populations, it was difficult to tease anything out of, and the heterogeneity

was very high. Therefore, we'll focus on the direct comparisons on the bottom panel, endovascular and surgical revascularization. These are CLI-only patients, so not mixed populations, and you can see that there are 23 studies and almost 13,000 patients.

I'll highlight before I show you the results that one of these was a randomized control trial, the remainder of these were observational studies. Due to that, we did combine these into point estimates for

observational studies and randomized control studies, and then we gave you an overall point estimate at the bottom of the forest plot.

You can see at, all-cause mortality at two to three years here, there's no difference between endovascular and surgical revascularization. You can see that amputation-free survival at two to three years is also very similar at, with these findings. So to show you more data, at one year there was no difference in primary patency. We rated this with a strength of evidence of moderate.

We did show a trend that endovascular

revascularization may reduce all-cause mortality at less than six months, and improve secondary patency at one year. After one year there was no difference, though, in all-cause mortality, amputation, at all time points, and then amputation-free survival at greater than a year. However, the strength of evidence here was low based on the number of studies and the quality of the studies.

There was inconclusive evidence on nonfatal MI, wound healing, primary patency of two years or greater, length of stay, and then

modifiers of effectiveness and safety.

When we were asked to present in March, we were asked to update this literature review. We did that starting in March, and so our updated search terms were from August 2012 until March 2015. 1,700 citations were included after we did the literature search and we performed abstract review on each of these. 61 abstracts were included for full text review, and I do want to say that there were 25 individual full text articles that were reviewed for qualitative review but we did not

repeat our meta-analysis and systematic review. I'll show you some of the studies that were thought to fit into the constructs of our review, but again, we did not perform quantitative meta-analysis with these updated studies.

There are a total of seven studies for KQ1, so again, the antiplatelet study of all patients with PAD. Only four of these are good studies. You can see Dr. Bonaca did a subgroup analysis looking at Vorapaxar, Dr. Patel behind me did a subgroup analysis of Ticagrelor versus clopidogrel in the PAD subgroup, and then there

were two studies below that of slightly lower numbers, but again, four good quality studies to add to the evidence review for antiplatelet agents.

When we look at key question two, so the intermittent claudication study for comparators, only one good quality study out of 13 that were included, we would have called good quality, and that was the 18-month update, 79 patients from the CLEVER study, looking at aortoiliac stenosis, exercise and endovascular

revascularization versus optimal medical therapy.

For key question three, critical limb ischemia, for the updated search there are eight studies. None of them were rated as good studies or good quality studies. Three of those eight had a mixed population of intermittent claudication and CLI and, therefore, the heterogeneity was quite high.

So from all of this, we concluded that there was a limited impact of the updated evidence for either KQ2 or KQ3.

All right. I'll conclude here by going through the key questions with our

findings.

You can see for the aspirin versus placebo comparison, there was no benefit for preventing vascular events in asymptomatic PAD patients, with a strength of evidence that's high.

Aspirin was favored for reducing nonfatal MI and combined vascular events in intermittent claudication patients, although the strength of evidence was low.

For clopidogrel monotherapy versus aspirin monotherapy, clopidogrel was favored for reducing adverse cardiovascular outcomes in PAD subgroups from CAPRIE, and we rated that strength of evidence as moderate.

And then with dual antiplatelet therapy versus aspirin monotherapy, you can see that there was no difference in reducing stroke, cardiovascular mortality, or other outcomes in PAD subgroups, intermittent claudication or CLI patients, and we rated that strength of evidence as moderate.

We did find that dual therapy was favored for reducing nonfatal MI at the cost of minor bleeding in this population.

I'll give you the conclusions for KQ2 and KQ3 next. You can see in orange here, exercise or endovascular revascularization versus usual care favored exercise training for improved walking distance with a large effect, strength of evidence here was moderate. It favored endovascular revascularization for improving walking distance, and that effect was moderate and the strength of evidence was low.

I apologize, there's a mistake here in the green panel. This should be endovascular intervention versus usual care, and you can see that endovascular intervention was favored for functional improvement but not quality of life. This was a moderate effect and the strength of evidence was high.

And then when you look at the combination of endovascular intervention plus exercise versus exercise alone or endovascular intervention alone in claudicants, that the combination of endovascular intervention and exercise improved maximal walking distance, with a large effect, and strength of evidence was moderate.

For KQ3, critical limb ischemia

patients, you can see that we did not find a difference in effectiveness between endovascular intervention and surgical intervention in this population. We also did not find a difference in all-cause death at greater than a year, amputation at all time points, and amputation-free survival at greater than a year, although this strength of evidence

was low and the heterogeneity was high.

So as I conclude here, I'll tell you about the limitations of our evidence base that we looked at. I'll tell you that there were few published large scale randomized control trials comparing antiplatelets in PAD patients. There were few direct comparison strategies in general in patients with claudication. Same treatment strategies were excluded in our analysis because they had been studied previously and published by AHRQ. No studies comparing a majority of treatment strategies occurred in patients with atypical leg pain. And then we were unable to stratify analyses by disease severity, risk or symptoms because the available evidence didn't support it.

So the challenges that exist, before I

let Manesh come back and conclude, are that there are population differences that are often poorly described, endpoint differences that haven't been similar across studies. Some of our biggest challenges was actually finding length of followup that were similar so that we could compare them. Obviously

revascularization has evolved over the last ten to 20 years and that's poorly captured in these studies. And then there was little to no evidence to suggest which treatment was better in terms of a crossover from one therapy to the next.

I'll let Manesh conclude here with the last five slides.

DR. PATEL: Thanks, Schuyler. I think we're just going to, to be on time, walk through a few more updates on, since the evidence review, what are the population data that we're aware of? Some of these data are taken from large administrative data sets that might be informative to the group.

The first is this one published by Schuyler and others here on Temporal Trends and Geographic Variation of Lower-Extremity

Amputation in Patients with PAD, this is from 2000 to 2008. Subsequent publications in the Journal of Vascular Surgery and others have shown us that in fact as you look at the top panel, thankfully amputations are going down across the United States, but it seems that

there's still a large variation, as you can see on the map of the United States.

Also, you can see there's some trends in the settings for vascular interventions from both inpatient setting to the outpatient setting, and of course there are multiple specialties represented here performing the procedures.

I will also say that many in the room worked with the FDA and many stakeholders to generate a consensus definition for patients with peripheral arterial disease, a document called PARC. The hope is that future studies will use similar definitions for outcomes and safety events, and so that will help in the future.

When we end here by talking about what studies are coming, this is a publication in 2014 in Circulation where we reviewed on ct.gov

for all the ongoing studies and concluded that there was a low number compared to the other cardiovascular disease states, and it was also concerning in that there was geographic limitations where patients were being recruited

from in the United States for PAD.

We did update this search for this meeting, we tried to look at ct.gov for all studies of patients greater than 500 patients in randomized comparisons. So it's a bit selective, but we looked for randomized trials, there are large registries and other ongoing studies, but in the randomized comparison space we basically found two that I think people will speak to some here.

The first is an ongoing large randomized trial looking at ticagrelor versus clopidogrel in patients with peripheral artery disease with an expected enrollment there of 13,500 and a report out date potentially next year, and then I think we are going to hear from BEST-CLI and others about an open label randomized trial of endovascular versus surgical revascularization in patients with critical limb ischemia.

With that I want to thank the AHRQ for funding the evaluation and thank you all for your patience as we went through the data.

DR. BACH: Thank you very much.

(Applause.)

Thank you for that detailed review, and thank you also for finishing ahead of time.

So, I would like to welcome Dr. Jack Cronenwett, medical director of the Society for Vascular Surgery Patient Safety Organization, and professor of surgery at Dartmouth.

DR. CRONENWETT: Good morning. I think we have your slides, Matt. Should we switch order or can we switch slides?

DR. BACH: We'll go ahead and switch order. Oh, we may be ahead technologically. You might tell a few jokes while we wait.

DR. CRONENWETT: Well, I'll start. So, I'm here as the medical director of the Vascular Quality Initiative, and as you just heard, in many cases the evidence that we're basing all these decisions, treatment decisions on is moderate and sometimes even low, and what I'm going to tell you about this morning is the potential use of clinical registries to develop

the type of evidence that we need in real world practice to help us in the future to be better able to make these decisions. I have no

disclosures, and now I need my slides.

DR. BACH: We're working on it.

DR. CRONENWETT: So, the Vascular Quality Initiative was launched by the Society for Vascular Surgery in 2011 -- here it is -- but it really is multispecialty, and it was launched as a quality initiative to improve quality, safety and effectiveness, and reduce costs of our vascular care, and it incorporates a national registry that's housed in a patient safety organization, so it's somewhat unique in that regard. It's unique because it uses 18 regional groups around the U.S. that take responsibility for practice change in their region, and it has a realtime web-based reporting system and data collection system.

And although hospitals or physician groups pay for the privilege of submitting data, the growth has continued as they recognize the value, and you can see it's quite widely distributed around the United States.

The value of a patient safety

organization for collecting these types of data is quite significant. It first allows the data

to be collected for quality improvement without informed consent. It protects the work product, which means any comparative data, from discovery, which encourages honest reporting. It precludes comparative data to be used for disciplinary purposes or for marketing. But it does allow us to publish, if you will, non-identifiable data for research purposes. So it really is an ideal vehicle, we believe, and it is, in the past it focused only on procedural topics, so we look at the procedure data and the subsequent outcomes, but we're actually in the peripheral artery disease arena now working on a medical management module that we're going to implement in early 2016, and so it has a lot of bearing on what we're talking about today.

The advantages of this are somewhat obvious, but it allows us to collect data on all the patients, not just those who gave informed consent, so it should be non-biased. It certainly has much more detailed information than is available from administrative claims,

and we collect many variables about the

preoperative status of the patient that could influence their outcome, the treatment details that likely influence outcome, and then of course the outcomes. We're able to collect one-year followup in over 70 percent of the patients when they return to the practitioner's office, and in the last year we've been able to match the data with Medicare claims to really look at even longer downstream intervention and outcome events.

And we're able to then report to the practitioners realtime data such as these that I just selected for freedom from amputation after PVI for critical limb ischemia. Where it's shown in blue the national results, and red the center results, are the same type of data for lower extremity bypass. And these are realtime, it can be pulled up at any point by the hospital or physician to compare themselves with others.

And since we've started this, we've collected over 200,000 procedures, now collecting about 7,500 per month, and if we focus on the PAD space, you can see that we

have over a hundred thousand procedures in the registry that are applicable to the type of, answering the type of questions that we're asking today.

So, a few highlights. We have a large number of patients, obviously, with some long-term followup, and I'll give you a few examples of what we've been able to do with this type of information.

Looking at the question of medications and how useful they are in the real world in these patients, we decided to look at the value of antiplatelet agents combined with statins if they were simply prescribed to the patient when they were discharged from the institution after receiving one of these treatments for peripheral disease, and then we looked at the outcome.

Well, the first thing we saw was there was huge variation across the centers in the rate that these medications were prescribed for these peripheral arterial procedures highlighted here in red, so there's huge variation, but what we found, amazingly, was that if these medications were prescribed, and

we looked at the long-term survival of the patient, there was a 27 percent absolute improvement in five-year survival, and that's almost impossible to achieve, compared with patients who received neither of these medications at the time of discharge.

And we also found that the longer a center was participating in VQI, the more followup and feedback reported, the more encouragement they obtained, their rate of use, on average, went from 58 to 70 percent over those number of years.

So if we have big data like this, we can also use it to answer other clinical questions that we can't necessarily answer based on an individual's practice, and so we looked at a common problem after surgical bypass, which is infection at the surgical incision. That's a high cause of morbidity, and we could even see across the VQI centers that it ranges as high as 30 percent, and there's quite a bit of variation compared to the expected predictive value.

And when we looked at modifiable risk factors, we found that if you shorten your

operation or reduce your blood transfusion rate it would reduce infection, but we also found if you simply change the skin prep and use chlorhexidine instead of iodine, it would reduce the infection rate by half. And so we then sent this information out to centers, individual centers, and showed them specifically how in their center what their opportunity profile for improvement was.

So this center had an opportunity to improve their chlorhexidine usage rate, they had a 9.4 percent infection rate. And then the question was, if we gave them this feedback, would they change their practice, or how rapidly would they change their practice, and we believe that if they had confidence in the data, they might change more rapidly than conventional wisdom says, the literature doesn't influence us that much.

So we sent these reports out and within two months the rate of chlorhexidine usage changed from 79 percent to 93 percent, and in those centers where they changed their chlorhexidine usage and had a significant increase, they had a concomitant marked

reduction in their surgical site infection rate.

So we're now able to push out reports electronically to members, hospitals and individual physicians to give them very detailed information such as the data shown here, that show them all the factors that influence length of stay after a certain procedure and what their opportunity is for their hospital, what they can change compared to others to reduce that length of stay.

So as I mentioned, one of the things we have to ensure in a registry is that it's a comprehensive registry, it's not just a registry, a voluntary registry, and we ensure that by auditing the procedures each year against hospital claims to be sure that every procedure was submitted. If it's not submitted, they have to go back and submit it. We captured 99 percent of procedures that were done.

We then use statistically based audits where we identify potential underreporting and audit those procedures at those hospitals to

make sure that they're accurate. We have a lot

of opportunity to do comparative effectiveness analysis because we look at open surgical procedures versus all the endovascular procedures, and as I mentioned, starting next year we're going to be looking at some of the medical management that you're going to hear about today.

And then finally, this is real world practice, it's not just academic centers and it's not just surgeons. So here's a distribution of the hospital types, it's perfectly divided between academic and affiliated and community hospitals, and if you look at the types of physicians who are participating among all the 2,500 procedures, there are the dominance of surgeons, but if you look at the procedures, the peripheral intervention procedures where other specialists participate, that's half surgeons and half non-surgeons, and it's equally divided in half between cardiologists and radiologists, so it's a very nice distribution of real world practice.

So, what have we learned that is really applicable to what we're talking about

today? You've heard that the evidence levels are low and you would think, therefore, that that would lead to tremendous variation in how we interpret the data, and that's absolutely true. So if we look at how do we select patients and which type of intervention do we select if we decide to treat them, if we look at how we're treating PAD, when we're treating it, you heard about the ABI and the severity of disease. We know that in patients with claudication the intervention is much more subjective based on the patient, the disability that it's causing in different patients.

So we decided to look at how much the ABI varies in patients who were selected for treatment across these centers, because if we all agreed, we would all be operating or intervening at the same ABI. Well, it doesn't work out that way. So you can see here that the blue line is the ABI of patients who were treated for claudication with peripheral

intervention, and the red line is the ones who were treated with bypass. So the bypass patients had worse ABI and worse circulation,

if you will, but there were huge variations.

So if you look at the far right in this slide, those were centers that had a very low threshold, they treated patients with relatively high ABI, and at the bottom you see patients that had very poor circulation. So there's little agreement, which is not surprising based on the evidence, but there's an opportunity to learn from this.

And then, how do we decide which treatments we apply? We heard from Schuyler that there's not much difference in terms of evidence between endovascular or surgical intervention, and so you might expect there would be variation. Well, there is. If we look at the treatment of claudicants overall in VQI, 26 percent were treated with bypass but most were treated with PVI, but it varied from zero percent treated with bypass to 76 percent, so there was a lot of variation.

If we look at critical limb ischemia

there's even more variation, it's a hundred percent variation. Some centers had zero percent treated with bypass, others had a hundred percent of the same type of patients

treated with bypass, obviously influenced by many factors.

So we're using VQI to generate evidence now. We have over 50 national and a hundred regional projects that are focused on quality improvement but that generate evidence for use by all. Over 60 publications in the last three years and I've just listed a few of the topics on the slide, but they range across the board, but we're certainly beginning to look in a very focused way at outcomes around these different interventions to try to understand which patients benefit from which procedures, which is something that's really hard to understand from a meta-analysis in the literature but quite easy to understand if you have a hundred thousand patients with detailed clinical data.

So I think in conclusion, what I would say is that registries can provide very

valuable real world evidence about when is treatment appropriate, and by appropriate treatment we mean the correct indication, so patient selection, the correct treatment, the procedure selection, and the correct outcome,

both early, late and patient-reported. So I think that registries, comprehensive registries that have the appropriate safeguards to be sure that the data are accurate can inform Medicare coverage decisions based on appropriateness assessment.

And so I'll just close by saying that what CMS and other payers can do to promote this type of evaluation is, first, to encourage participation, and how can that be done? Well, first we ought to differentiate registries. We need to have some type of mechanism to certify registries who are doing it right, are collecting the type of information that we can rely on. And second, we need to do something to incent participation, and I believe that it would be appropriate to increase payments for providers and centers that participate in qualified registries and to reduce payments for

those who don't.

And second, we need to encourage proper outcome assessment, and so if we -- we need to provide certified registries with better access to claims data, both Medicare and ideally private payer claims. We need to

incent providers somehow for entering the detailed information that we need that's not available in the claims, and I believe we need to provide more grant support to these type of registries so that we can all implement patient-reported outcomes. Thank you.

(Applause.)

DR. BACH: Thank you very much, Dr. Cronenwett.

I would like to welcome Dr. Matthew Menard, the codirector of endovascular surgery and program director of vascular surgery fellowship in the Division of Vascular and Endovascular Surgery at Brigham and Women's Hospital.

DR. MENARD: Good morning, and thank you very much. I really appreciate the effort to speak on the trial and what we have been

trying to do with the BEST-CLI trial to CMS and to this audience.

These are my disclosures. The trial is an NHLBI funded trial.

I'm speaking today on behalf of a number of people that have devoted an enormous amount of work to the effort to date. My

fellow clinical coordinating center principal investigators are Alik Farber, who's the chief of vascular surgery at Boston Medical Center; I'm a vascular surgeon at Brigham and Women's Hospital; Ken Rosenfield here today, he'll be speaking a little bit later, he is an interventional cardiologist at Massachusetts General Hospital; Meaghan Dunn is our national trial coordinator. We partnered with New England Research Institutes, Sandra Siami and Susan Assmann are co-PIs of that effort. We had some incredibly talented cost effectiveness folks from Brigham and Women's, Jerry Avorn and Niteesh Choudhry. And we've had tremendous support from NHLBI, Diane Reid and George Sopko, our advisors.

So really, you couldn't get a better

lead-in to our trial than Schuyler and Manesh, coupled with Jack, to really lay the groundwork for why we decided to do this and why we think it's an important trial and what we're hoping to achieve with it, so I'm not going to spend too much time on the background of what's been done to date other than a few slides. I'm going to try to give you a flavor of what the

trial is about, the architecture of the trial, and the progress to date.

But clearly critical limb ischemia, as everyone in the room knows, is associated with tremendous morbidity and mortality, it's increasing worldwide, it's showing no signs of letting up, and untreated, again, it can create many problems.

So there's a big spectrum within critical limb ischemia, from folks with rest pain whose peripheral exam would not be too distinguishable from normal patients, to those folks with varying ulcers. This is a painful ischemic ulceration, this is some dry gangrene, this is a diabetic mal-perforant ulcer in someone probably with neuropathy and associated

peripheral arterial disease, and this is probably the most feared, a patient we see with a very challenging heel ulcer who needs extremely good perfusion to salvage the limb.

We all know about the explosion of endovascular therapy over the last number of years, and the changing demographics in terms of who's treating CLI. The slide you just saw

is quite prevalent. The group from Dartmouth, and Phil Goodney's efforts have recently updated that slide and the trends are showing no signs of changing. The top slide is angiography, the increasing slope is, again, endovascular intervention, and surgery is on the bottom.

The Reach Registry tells us that we actually spend more money on peripheral arterial disease than we do on critical limb ischemia in the United States and really, in 2015, we have a number of options to treat challenging CLI patients. We have medical therapy that's not particularly effective, as you just saw. We do an increasing number of

hybrid procedures. We have primary amputation and that's appropriate at times, but really and frequently it's a choice between surgical therapy and endovascular therapy, and that's the backbone of the trial, trying to answer this question, which is best.

When you look across the landscape of vascular disease, we have a number of high quality Level I studies to guide us in the realm of carotid disease, carotid stenting

versus carotid endarterectomy, aneurysmal disease, but when one looks at CLI, there's really a single study that attempted to answer the questions that we're attempting to answer and that's the BASIL trial.

The data, as again, Manesh and Schuyler very expertly reviewed, is extremely limited. There is a large void in helping us to decide what to do for a given patient in front of us. The trials are largely retrospective, they're very poorly controlled, the gold standard endpoint of amputation-free survival falls short in terms of really assessing the relevant outcome to the therapy

that's provided. Target lesion and target vessel revascularization are appropriate for the coronary anatomy world but not particularly well suited to critical limb ischemia. Sponsor bias and operator bias are prevalent in the studies to date. Again, as you saw, there are many studies that have mixed claudicants and CLI, and the followup has really been suboptimal to date.

The BASIL trial was a very valiant effort that definitely provided us with

information that we use. What it did show was no significant difference in amputation-free survival at five years, with a trend to benefit for surgery in those who survived more than two years. One of the limitations of the BASIL trial, certainly it was underpowered. Probably the biggest limitation in the eyes of those of us who treat CLI is that endovascular therapy was limited to angioplasty alone. This study was carried out over ten years ago in England. The practice patterns in Britain are extremely different than they are in the United States and Canada. There was a lack of lesion

standardization, it was difficult to determine who exactly was in the BASIL trial, and again, the endpoint of amputation-free survival was limited.

This is an article written 24 years ago by Sean Tunis, who used to be the head of CMS, it's published widely on cost effectiveness research. This trial, or this article could have come out this year in terms of what little has changed. He looked at angioplasty versus bypass versus amputation. The concept was if angioplasty took off,

surgery would decrease, amputation would decrease. That's exactly what's happened, recent studies have mirrored this concept. Unfortunately, costs have not come down as was predicted in this paper; in fact, it's the exact opposite.

So in trying to take on the concept of a clinical trial, the study, the question at hand, it really gets to what is the equipoise, and equipoise is comprised of two important components. The first is our individual equipoise, what I as a vascular surgeon bring

to each individual patient in front of me, what are the question marks in my mind and those, the complete opposite, which is my view of when I'm not confused, what my strongly held bias is. And that's compared to the strongly held bias of a completely different group of care providers, it could be within the same specialty or it could be across specialties.

So I've just got a couple of slides to highlight what the equipoise challenge is. I can tell you that my belief having undertaken this endeavor for about eight years now is that the degree of equipoise across the country is

extremely high, it's probably the biggest reason why we've had enormous support for the trial, a big thanks to the many people in the audience who are partaking in the trial and doing the hard work of enrolling patients at their given sites.

But this is a challenging patient with a plantar heel ulcer, she needs as much blood as she can possibly get to her foot, she's got an excellent vein, excellent inflow as you can see from this angiogram, a typical diabetic

pattern where she has tibial disease, and you might wonder why I'm providing this slide to talk about equipoise. The vast majority of providers would provide endovascular therapy to this particular patient, in fact that's what I did, and got a good angiographic result, but I can tell you that I have very little understanding of how long this result is going to last, it might last three days, three months, three years, it may or may not bring her the foot pulse she needs to salvage the foot in a very challenging clinical situation.

More typically when one talks about equipoise when looking at patients such as

this, the challenging long segment superficial femoral artery and popliteal disease, throw in some multilevel tibial disease as well, and the question in terms of what the right thing to do becomes even harder to answer.

Again, a typical patient with classic right toe ulceration, this is a very typical angiographic appearance in someone with critical limb ischemia and long-stem disease. Kenny as a cardiologist and I as a vascular

surgeon frequently debate patients just like this, he'll think absolutely this is a chip shot, the patient should be done endovascular. I have a little bit of a surgical bias and say I would absolutely treat this with surgical therapy. As we traverse the country and poll audiences, I can tell you that the degree of equipoise in patients exactly like this is extremely high, and again, supports the need for the trial, the enthusiasm for the trial, and the questions exactly that we're trying to answer.

Jack showed you this slide. You couldn't get a better example of the equipoise that I've been talking about across the United

States and Canada. And so with that background in mind, I'm just going to highlight the components of the trial and how we tried extremely hard to look at all the efforts to date, look at the BASIL trial, and try to design a trial that would be feasible and would get to the exact information that we wanted to answer.

The objective was to compare treatment

efficacy, functional outcomes and cost in patients who are undergoing best open surgical or best endovascular revascularization. The trial is a prospective randomized multicenter open label superiority trial. 2,100 patients at 120 clinical sites in the United States and Canada. Each patient will have at least two years of followup. The trial was generously funded by the NHLBI for nearly $25 million.

It is really two trials in one. The first cohort is so-called best case surgical scenario, with patients who have adequate single segment saphenous vein, and they will be randomized open versus endo. The second smaller cohort is everyone else, so-called disadvantaged conduit, and they again will be

randomized separately and powered separately for open surgical versus endovascular treatment.

We have the ability to look a little bit more closely at several variables. We thought clinical presentation or the questions of ischemic rest pain versus tissue loss, and the anatomic question of presence or absence of

significant tibial disease was worthy of further investigation in patients that we stratified for these variables.

A key component is that the trial is pragmatic. Unlike BASIL, unlike the CORAL trial, unlike many other trials that specify a specific platform that a given investigator may or may not approve of or like, we left the definition of best treatment to each individual investigator, so everyone participating in the trial can treat patients with critical limb ischemia exactly how they see fit and how they're typically doing it.

We do have an investigational device exemption. This has thrown some people off. We are not in any way examining new or experimental therapies, we are merely allowing

every participant to do what we do on a daily basis, and that is to use FDA-approved devices in an off-label fashion and continue to get paid for it. All surgical bypass techniques and conduits are allowed.

We do have a committee that assesses new technology as it comes on line. They

recently met and approved both drug-eluting balloons that were recently approved by the FDA.

A lot of thought and discussion about what the appropriate endpoint is. The Society of Vascular Surgery convened a committee that looked at the trial endpoints, the OPG committee, and they came up with a number of novel endpoints thought to be better suited to clinical trials. We borrowed heavily from that committee's results. A major adverse limb-event-free survival was the endpoint that we thought was most appropriate for our trial.

MALE is defined as above ankle amputation, a major reintervention, which includes a new bypass graft, a jump or interposition graft revision, or a thrombectomy or thrombolysis. What it does not include is

minor reinterventions, and there was some enthusiasm that this, reintervention and amputation-free survival would have been the more appropriate endpoint, but we thought that would unfairly bias the trial against endovascular therapy, so we ended up keeping

the original endpoint, but we are well powered to this endpoint that includes both major and minor reinterventions. We are well powered for the gold standard of amputation-free survival and MALE perioperative death.

We are taking a novel look at endpoints that many of us think are very valuable and have been long missing from other efforts, and this is freedom from hemodynamic failure, freedom from clinical failure, and analogous to the cancer world, freedom from critical limb ischemia.

Again, we are going to be well focused on reinterventions, number of reinterventions per limb salvaged, freedom from secondary interventions major and minor, and additional endpoints you see here.

The typical safety endpoints you would expect and hope for, MACE, non-serious adverse

events and perioperative complications.

And just a word on the cost effectiveness and comparative effectiveness efforts of the trial. So, a typical trial that you might see involves an intervention and a

control arm. In our case there's no control arm, it's surgical therapy versus endovascular therapy. A typical trial will look at the outcomes until the trial completion. A typical comparative effectiveness or cost effectiveness trial will throw in the green dollar signs and will look at the accumulating cost of the trial over the course of the trial completion. We are going to attempt to do one step further and use Markoff modeling based on the results of the core trial to then project the outcomes and the costs over the course of the lifetime of each patient in the trial. So that's a very important component that has not previously been done.

Again, the cost effectiveness component will include all the financial costs of care, hospital care, outpatient care, rehabilitation. It will include a robust functional status, again, as an additional

measure. We will look at all treatment-associated costs both in and outpatient, and use the quality system, again through Markoff modeling, to really get a solid handle on the

economic and functional outcome of each intervention. The VascuQol and the EuroQol and the SF-12 are the backbone of the functional endpoints.

Switching gears a little bit, another key component of the trial is our efforts to be collaborative. We have an absolute mandate from NHLBI that they were not interested in funding a trial that was one specialty alone. We've worked hard to include everyone across the country and across Canada that treats CLI, and currently as represented by folks in this room, that includes interventional cardiologists, radiologists, vascular surgeons and vascular medicine specialists. The trial is widely distributed amongst these subspecialties, there's more vascular surgeons as one might expect, but a very appropriate constitution of cardiologists and radiologists. Almost 80 percent of our sites have some representation from multispecialties

participating in the trial.

As Jack alluded to and Manesh alluded to, we feel it was important to have a wide

geographic distribution. We have a good mix of private practice participants and academic centers as well, and for these reasons and other reasons, we've been very fortunate to have the support of multiple societies, the Society of Vascular Surgery in particular, VIVA, Society of Vascular Medicine, SIR, SCAI, and the FDA have all been incredibly supportive and have helped us throughout our efforts.

I put together this trial at a naive time and I thought I'd pick up data, our updated data. We have currently almost all of the 120 sites planned activated days and we've pressed at 200 subjects enrolled and we have a challenging enrollment, a challenge ahead of us but not unexpected. And it's somewhat remarkable, the parallel progress and the timing of the BEST trial along with the BASIL-2 and BASIL-3. We started almost simultaneously, we have very similar enrollment curves, and really the opportunity to combine the BEST-CLI data set with the BASIL-2 and BASIL-3 data set

and really make an impact on the knowledge gap, is unprecedented.

So in summary, what do we hope to achieve with the BEST-CLI trial? Certainly we want to assess the role of infrainguinal bypass with optimal conduit. We obviously want to assess in a parallel fashion the outcome and the role of endovascular therapy across all aspects of each patient. The bypass when optimal conduit is available compared to endovascular therapy and when it's not available. Associated quality of life and cost effectiveness. The many variables that Manesh and Schuyler highlighted that are of interest to each and every one of us as we struggle with individual patients. Dr. Mills is going to highlight his efforts to develop a much more robust and much needed new system of classification; we are utilizing the WIFI classification and hope to validate it within the confines of the BEST trial.

Again, we're going to take a close look at hemodynamics, everything in synergy with BASIL-2 and BASIL-3, and what we're hoping to do is really define an evidence-based

standard of care. The trial really has been

collaborative. We've been extremely fortunate and pleased to see the degree to which individual sites have risen to the challenge of collaborating. We have a CLI team construct, each patient in the trial has a requirement to be reviewed by two members of the team, they don't necessarily have to be within specialties or across specialties, but again, the end result of this collaboration can only help the trial, it can only help everyone, and is an important component of the trial.

So I'll stop there, and once again thank CMS for the opportunity to present today. I thank everyone across the country that's been hard at work enrolling patients.

(Applause.)

DR. BACH: Thank you very much. So, thank you to Dr. Menard and all of the morning speakers, thank you for staying on time and actually helping us catch up. We're going to follow the agenda but we're obviously earlier in the day than we expected to be. I have it now as 9:37. Please come back in ten minutes, we're going to start again at 9:47 with the

scheduled public comments. Hopefully this will give us some room for discussion in the afternoon. Thank you again.

(Morning break.)

DR. BACH: Thank you all for coming back. We're going to start the scheduled comments from the public. Each speaker, hence the genesis of Dr. Gibbons' joke, each speaker has only four minutes, so you have 32 seconds left.

DR. GIBBONS: Then I will conclude my remarks.

DR. BACH: Okay. I would like to introduce Dr. Gary Gibbons, the medical director at South Shore Hospital Center for Wound Healing and professor of surgery at Boston University School of Medicine. He is representing the Association for the Advancement of Wound Care. Thank you very much for coming.

DR. GIBBONS: Thank you, thank you all, and I would like to commend the previous presentations this morning and only to capitalize on that a little bit, because I'm going to talk about the wound care that is

associated with many of these problems. I'm a vascular surgeon by trade. I was blessed by growing up in the Deaconess Joslin where Dr. Joslin himself and Dr. Wheelock and others set a patient-centered standard of care, multidisciplinary, interdisciplinary approach to wound care.

I'm speaking on behalf of the Association for the Advancement of Wound Care and we, I think we all agree, we heard it this morning, peripheral arterial disease is present, but what we're seeing now as the baby boomers are getting older, a lot more comorbid conditions, so it's not pure peripheral arterial disease, we're seeing peripheral vascular disease, lymphedema, edema, venous disease, dialysis, combinations affecting these people's lives.

And wounds, there are eight million people living with wounds to the lower extremities. These wounds are very costly in terms of quality of life and resource utilization.

We would like to agree that we need consistent identification of peripheral

arterial disease. Like the specialties treating vascular disease, there are a number of specialties involved in wound care, and we too have wide variation in practice, wide variations in outcomes, so we need to come together as one voice, following one set of guidelines. We're currently looking at WIFI, and again, you can't have some specialty here following one set, like Wagner, another following Rutherford. I think this is an opportunity in working together that we can all follow one set of guidelines to really look at the effect of ischemia as well as infection, and the microenvironment of the wound and what it does.

PAD is common, but for the diabetic it is an inflammatory vascular disease and one size does not fit all diabetics. A PAD in one diabetic patient may not mean the same thing in another diabetic patient, especially those who have a limb-threatening wound or compromised peripheral vascular disease.

Wounds in patients with PAD are seen by multiple specialists, all listed, you're going to hear many of these people today. What

we have found, though, is not all specialties have expertise in wound management, so what we're seeing is inconsistent application of evidence-based treatments like offload, wound management, debridement, compression, and that's an important part of all of the endeavors to get these patients to healing.

So again, the most important thing, we believe that we need to have somebody on the team in a multi-interdisciplinary approach who has involvement with wound care who can understand that micro-wound environment in the initial phase of evaluation carried into the post phase, and then important for prevention of recurrence. So wound specialists, they need to be involved in creating and following common based algorithms. We have evidence out there about offloading, compression, and some of the other treatment modalities that are available, but we have wide variation in practice.

We've seen evidence of poor debridement in almost 35 percent of cases. Poor compression, less than 60 percent. Offloading, it's documented, only two percent

25 of this country offloads plantar diabetic foot

1 ulcers, yet they won't heal unless they are
2 offloaded.
3 So in question four, we need one set
4 of guidelines for the prevention, treatment,
5 education and research of patients with wounds
6 associated with peripheral arterial disease,
7 and we need to bring people together to
8 establish these guidelines in working this out.
9 DR. BACH: Please try and wrap up,
10 Dr. Gibbons.
11 DR. GIBBONS: Yeah. Randomized
12 control trials, they don't have really the real
13 world, they eliminate a lot of patients with
14 ischemia. There are many guidelines out there,
15 a lot of gaps in practice, and again, what
16 about the patients who aren't candidates for
17 vascular reconstruction? So what we're saying
18 is that we need to pay attention to the wounds,
19 we want to have MedCAC consider the complexity
20 of these patients, multiple comorbidities. We
21 need to have beneficiary access to a team of
22 services, not just one specific specialty
23 group. You can have the greatest

revascularization --

DR. BACH: Dr. Gibbons, I'm sorry.

Thank you very much.

DR. GIBBONS: Okay, thank you.

DR. BACH: Thank you for your time. Please don't put me in the uncomfortable position of having to cut you off, please stay on time.

I would like to introduce Jeffrey Carr, who's a board member of the Cardiovascular Coalition, immediate past president, and with the Outpatient Endovascular and Interventional Society. Dr. Carr.

DR. J. CARR: Thank you. I am Jeff Carr, I'm a past president of the OEIS, or Outpatient Endovascular and Interventional Society, and I am representing the Cardiovascular Coalition today as a board member.

These are my disclosures. I received no compensation for my time and travel for this meeting today.

The Cardiovascular coalition is comprised of service organizations, industry

groups and multiple physician groups, including the OEIS, which is a multidisciplinary society of vascular surgeons, cardiologists and

radiologists that formed together to set standards of care for office space interventional suites. The Cardiovascular Coalition represents 149 freestanding cardiovascular centers in 26 states. It was established to provide policy-makers with greater understanding of the value of these freestanding centers, and one of the key focuses of the Cardiovascular Coalition is the utilization of appropriate vascular procedures to prevent nontraumatic amputations in patients.

But we know that amputations are still vastly underutilizing arterial testing prior to amputation, with a pre-amputation ABI testing rate of 47 percent and lower extremity arteriograms only being performed in less than 40 percent of patients prior to an amputation. Well, the Avalere Health Group recently conducted a study looking at 43,000 Medicare patients who received a major nontraumatic

amputation in 2012, and they found that by encouraging revascularization over amputation, we could potentially reduce Medicare direct spending costs by up to $2 billion over ten

years.

Although medical therapy advances have reduced cardiovascular major events in the cardiac and peripheral vascular patients, these agents have not been demonstrated to improve quality of life and critical limb ischemia outcomes. Alternatively, advances and innovations in devices in endovascular therapy have allowed providers to treat an ever expanding population of patients who were previously only treated with medical therapy and relegated to conservative management.

Well, the AHRQ 2013 study, as we have seen, predominantly analyzed balloon angioplasty and bare metal stents as their primary endovascular revascularization strategies. But since 1998 we have seen a growth of multiple devices, numerous atherectomy devices, drug-eluting stents and drug-coated balloons have gained significant

adoption over the past ten years.

What's been challenging is to compare these different and new devices with studies, because up until recently there have been no established definitions or consensus guidelines

for clinical trial endpoints. So the PARC, as we heard, recently convened, and just published this year definitions that we hope will add consistency for future PAD trial outcomes.

Since the AHRQ study, we know that there are several trials that have been published which offer a wide spectrum of analysis for all the interventional modalities, including supervised exercise training versus endovascular, directional laser, orbital atherectomy, drug-eluting stents and drug-coated balloons, and there are several current and pending trials which we are excited about that will add much more weight to the evidence for the questions that MedCAC is considering today, including observational studies with direct comparative analysis, we've heard about the BEST trial, and also real world analyses of very complex patients and lesion

subsets.

So in conclusion, intermittent claudication and critical limb ischemia patients will benefit from a comprehensive approach of lifestyle modification and revascularization. Interventions that

ultimately result in limb preservation offer the best possible clinical outcomes. We feel that vascular diagnostics are still underutilized in CLI patients despite the proven benefits of revascularization. And by increasing vascular procedures associated with lower amputation rates, it will reduce health care spending. By standardizing outcome definitions with future data, you will be able to increase knowledge for our evidence-based decision-making. Thank you.

DR. BACH: Thank you very much, Dr. Carr. I'd like to introduce Dr. Paul van Bemmelen, a professor of vascular surgery at Temple University.

DR. VAN BEMMELEN: Thank you very much. Good morning. I'll start with the disclosure that I patented the first arterial

compression device. These are all the pneumatic devices that are currently on the market for PAD. The device puts out a pressure of more than a hundred millimeters of mercury in a short amount of time. This completely empties the veins in the foot and leg and thereby lowers the venous pressure. Without

changing the low pressure in the arteries, this increases the difference in pressure between arteries and veins, and increases the flow through the tissue.

The increase in flow velocity can be seen immediately upon a single compression, shown here in the popliteal artery. Repeating this three hours a day over a three-month period at home results in a visible increase in the collateral arteries that develop around the blockages. These collaterals can be a hundred times larger than the capillaries created with angiogenesis and can carry a hundred million times the amount of blood per minute than a capillary.

For intermittent claudication, four different prospective studies have looked at

arterial compression. Collectively, 82 patients were compared to 53 controls who received standard exercise and aspirin. The absolute walking distance in all four studies increased by nearly 100 to 200 percent. Compare this to the multicenter cilostazol trial with only a 29 percent increase in absolute walking distance, or the 11 percent

increase in the patients who were able, and that's not everybody, to complete a supervised exercise program. So compression is underutilized in patients who do not respond to cilostazol.

Next is CLI. This is an example of a Rutherford 5 patient before and after compression treatment.

The largest clinical experience has been obtained in Ireland without any support from the industry. 171 patients were treated and closely followed. Almost half these patients were high anesthesia risks. This survival curve demonstrates that nonreconstructible PAD has a worse prognosis than most cancers, with only nine survivors of

the 171 after four years. Because of this high mortality, the 94 percent limb salvage rate was attainable with compression, major cost savings were found, better quality of life, and no harms from this intervention.

Another study done in Canada showed similar results and there was a blinded control group randomized to placebo device. Two-thirds of the placebo-treated patients lost their leg

within two years. So for nonreconstructible PAD, arterial compression should be made more easily available and not restricted.

The future question will be a better definition of nonreconstructible, and perhaps some guidelines for the tibial angioplasty. Here we see two comparable heel ulcers. After successful tibial angioplasty the one on the bottom still took nine months to heal. The patient on top died two weeks after the picture was taken from a heart attack. So ask yourself, is it wise to spend 20 times more up front on a patient if the survival is so limited.

Thank you for your attention.

DR. BACH: Thank you very much, Dr. van Bemmelen. I would now like to introduce Dr. Margaret Doucette, who is the chief of physical medicine and rehabilitation at the Boise VA Medical Center.

DR. DOUCETTE: Good morning. I serve in the VA as director for the high risk foot program, the prevention of amputation and amputee care. And I would like to clarify that I have no disclosures. I also need to clarify

that I do not formally represent the VA here today in my opinions. I do represent some of the benefits of serving in the VA, hard to believe as it may be that there are some.

And what we have been able to do in our population of patients is utilize the arterial pump, and what's different in the VA is we are allowed to use this based on our clinical decision-making, not based on any reimbursement process. We have close to 50 patients now that we're tracking and we're building a robust database. We utilize the WIFI classification system. We have clear processes for vascular evaluation and

endpoints.

What I'd like to present today are a couple of cases that reflect the trends we're seeing in wound healing, prevention of amputation, and reduction in pain and increased ambulation.

The first case is a 71-year-old veteran who was referred for an ischemic right great toe. He was deemed inoperable. He had severe neuropathy from active alcoholism, smoked incessantly and had significant pain for

which he was using opioids. We attempted to use the pump prior to going to amputation; however, his follow-through was quite poor and in October of 2014 he underwent a right below the knee amputation. He was admitted to our nursing home rehab unit for wound healing and gait training and was a prosthetic candidate. Unfortunately, he was quite inconsistent with his use of the pump and at the time of discharge his gait was limited to 40 to 50 feet due to claudication.

Subsequent to his discharge home, however, when he was quite angry and bitter

upon discharge, he did start using the pump more consistently, and we saw a very dramatic increase in his gait and his ambulation distance. At the time I saw him two weeks ago he was ambulating unrestricted. In fact, the only restriction was the therapist's time available to clock his distances. He maintains successful sobriety in part because he states that the pain is so much reduced and he has no need for the alcohol to deal with his pain management.

The second case is a 65-year-old

gentleman with diabetes known to us through a venous ulcer. He subsequently presented with severe vasculitis from a drug reaction. He had progression of ulceration on his feet due in part to his neuropathy, and mechanical irritation from footwear. He was very noncompliant, filed multiple outpatient visits. He had several admissions for infection, and in his admission in March he was targeted to have amputation either at the TMA or BK level.

He discharged himself and did start using the pump, and in his own words became

religious in using the pump, and in May and June presented with significant improvement in healing, such that at his visit two weeks ago he was completely intact and ambulating without restriction.

The last case is a gentleman who was morbidly obese, underwent a left above-knee amputation for nonreconstructible disease. He had concurrent disease and pain on the other side. At the time of amputation we started him on the pump, and now almost two years later he has maintained an intact limb. He's had multiple superficial injuries from running his

wheelchair into various objects and people but has gone on to heal, and has maintained an intact limb.

In summary, I'd like to advocate for having the pump available to those individuals who are not surgical candidates for either the extent of their disease, comorbidities, or self-care deficits. We found it to be cost effective and clinically effective. Thank you for your time.

DR. BACH: Thank you very much,

Dr. Doucette. I'd now like to invite Dr. Michael Dake, from the Department of Cardiothoracic Surgery at Stanford University School of Medicine, who is here representing Cook Medical.

DR. DAKE: Thank you, Mr. Chairman, good morning. I'm an interventional radiologist and on behalf of Cook Medical I would like to present its statement to the panel this morning. These are my disclosures.

MedCAC convened today to answer the following questions: For adults with asymptomatic lower extremity PAD, lower extremity intermittent claudication and lower

extremity critical limb ischemia, how confident are you that there's sufficient evidence for an intervention that improves immediate and near-term health outcomes and long-term health outcomes?

As global principal investigator of the randomized Zilver PTX Drug-eluting trial, I would like to say that the clinical studies with this device should provide confidence in this technology's ability to improve outcomes

for patients with intermittent claudication and critical limb ischemia.

The Zilver PTX drug-eluting peripheral stent was developed to address limitations of existing therapy. It has been tested in a clinical program that includes studies along the disease progression continuum in terms of clinical manifestations and anatomic involvement. Starting with the randomized clinical trial and moving on to the single arm study and the Japan postmarket surveillance study, the device has been evaluated in increasingly complex patients and lesions.

The Zilver PTX randomized clinical trial allowed for randomization of the DES

therapy versus angioplasty and provisional bare metal stent placement. With a mean age of 68 years, the majority of patients enrolled in the randomized clinical trial were Medicare beneficiaries.

At five years Zilver PTX demonstrates a 48 percent reduction in reintervention compared with standard, endovascular standard of care comprised of optimal PTA or provisional

bare metal stenting after failed PTA. Likewise, the patency rates at five years were also statistically significantly different. At five years, Zilver PTX has a superior clinical benefit in terms of rate of freedom from persistent or worsening claudication, rest pain, ulcer or tissue loss, and this clinical benefit was statistically significantly different when compared to endovascular standard of care. These metrics of freedom from TLR, patency and clinical benefit were also statistically significantly better than, for provisional Zilver PTX versus provisional bare metal stenting.

Now beyond the randomized clinical trial, looking at the single arm study and the

Japan postmarket study, we can see that although the single arm study and Japan PMS did not involve Medicare enrollees, these studies represent a broad real world patient population with a large majority of patients greater than 65 years of age.

The increasing complexity of disease across these three studies is manifest by

higher frequency of renal failure and renal disease, total occlusions, in-stent restenosis and CLI, as we go across from left to right. Also note, the lesion length increases from 6.6 centimeters up through ten and 14.7 centimeters.

Now, despite these differences across those three trials, the overall freedom from TLR is similar in both premarket studies compared to the randomized clinical trial. Likewise, the overall primary patency by duplex ultrasound is similar in the Japan PMS compared to both premarket studies.

In conclusion, Zilver PTX is the single most rigorously studied device for treatment of PAD of the SFA, seven completed or ongoing clinical studies for regulatory

submissions with greater than 2,400 patients. The five-year data for Zilver PTX demonstrates superior clinical benefit and greater than a 40 percent reduction in reintervention and restenosis versus both endovascular standard of care and bare metal stenting through five years. Consistently positive clinical results

in the U.S. Medicare population and similar populations around the world, both in claudicants and CLI, resulted in the CMS granting substantial clinical improvement and conferring the new tech DRG add-on status for Zilver PTX. Thank you very much.

DR. BACH: Thank you very much. I would now like to introduce Dr. Ronald Fairman, who's the Clyde F. Barker - William Maul Measey professor of surgery and chief of Division of Vascular Surgery and Endovascular Therapy at the Hospital of the University of Pennsylvania. Thank you.

DR. FAIRMAN: Good morning. I'm here representing the Society of Vascular Surgery as now president-elect. I have no disclosures. In addition to the SVS I'm also representing about 1,300 vascular surgeons who belong to the

Society for Clinical Vascular Surgery, and I'll give you a little overview.

The SVS represents more than 5,000 practicing vascular surgeons across the United States. We are the nation's oldest professional medical society with a core

mission dedicated to the comprehensive management and total care of patients with noncardiac vascular diseases. By virtue of our ACGME training requirements and the comprehensive nature of our practice, we are uniquely qualified to comment on the scientific evidence of existing interventions that aim to improve health outcomes in the Medicare population and address areas where evidence base gaps exist related to lower extremity peripheral arterial disease.

Specifically, we as vascular surgeons utilize all available modalities, medical, exercise training and interventional, both endovascular and open surgical, and provide importantly longitudinal followup of our patients with lower extremity peripheral arterial disease. If you visit my office, you will feel that it is very much akin to a

primary care practitioner.

Jack alluded to this and gave a very nice talk earlier, but the SVS founded the VQI in 2011 as a registry to collect data about the safety, quality, efficacy and cost of vascular

care. The data is analyzed and shared among regional groups to improve vascular health care. We established a patient safety organization with the federal Agency for Healthcare Research and Quality, and participation requires a 100 percent capture of all procedures and one year of follow-up reporting in addition to perioperative reporting, a very different registry from some that you're familiar with such as NISWIP. Outcome data is used for benchmarking that will lead to cost reduction, quality improvement, new practice guidelines and device performance.

You've seen this slide before, which demonstrates the exponential growth of the VQI. Jack alluded and nicely pointed out to the fact that at least 50 percent of the participating physicians are not vascular surgeons. This demonstrates the growth of regional quality groups across the United States.

And again, you saw this slide previously, and if you look at Medicare published data, for better or worse, vascular surgeons are the dominant providers of lower

extremity interventions when you combine both open and endovascular procedures.

You're going to next hear from two members of our society who have been responsible for two practice guidelines, one the WIFI classification which will be presented by Joe Mills, and next the management for asymptomatic disease and claudication presented by Mike Conte. Thanks for the opportunity to speak.

DR. BACH: Thank you very much, and we invite Dr. Michael Conte to speak. He's a professor and chief of the Division of Vascular and Endovascular Surgery at the University of California, San Francisco.

DR. CONTE: Thanks, and good morning. I'm a practicing vascular surgeon and have served as the chair of the lower extremity guidelines committee for SVS, and also recent chair of the AHA PBD council. These are my disclosures.

In 2015 the SVS published a practice guideline that addressed the issues of asymptomatic PAD and intermittent claudication,

two of the key questions today. To do this, we commissioned independent evidence-based reviews of the data, and had a consensus guideline development process with the publication that came out this year in the Journal of Vascular Surgery.

Related specifically to asymptomatic PAD, as earlier presented, this is a highly prevalent condition in the Medicare population due to standard prevalent risk factors. We know it portends a high risk for mortality and major cardiovascular events. To date the evidence does not really strongly support broad evidence-based population screening and more research is needed in terms of the benefits of targeted screening. Basic interventions such as smoking cessation, patient education and lifestyle modifications are felt to be Grade I recommendations by our group.

Unfortunately, the evidence supporting medical intervention specific to the asymptomatic population, as presented earlier,

is somewhat weak. The current guidelines, for example on statin use, do not address

asymptomatic patients or the use of the ABI. We need more research specific to interventions targeting this population as far as their disease progression.

Very importantly, we strongly recommend against the use of invasive treatments for asymptomatic PAD regardless of hemodynamic measurements or imaging findings that demonstrate disease. This was felt to be a very strong recommendation. There may be some unique exceptions, including the treatment of popliteal aneurysms which may not be considered here, repeated interventions to maintain bypass graft patency, and the benefit of repeated interventions to maintain endovascular interventions is really not well known and more evidence and research is needed here.

In terms of intermittent claudication, it's the most common symptom relating to peripheral artery disease in the Medicare population, it portends a higher risk of cardiovascular events and significant

disability, but we know there's a very low risk

of major amputation. Smoking cessation, risk factor modification and medical therapies are standard of care.

Specific to the limb, pharmacotherapy, exercise therapy and revascularization do yield improvements compared to standard of care.

Medical therapies, as I mentioned, for atherosclerosis are standard of care, but specific to the treatment of the disability we did recommend with a relatively weak level of evidence the use of cilostazol and potentially the ACE inhibitor ramipril. Further studies are needed here and the overall degree of evidence is relatively modest, as recently shown by earlier speakers.

Importantly, supervised exercise does have very strong evidence to support its use in improving functional outcomes in claudication, and even home-based exercise now has growing evidence to support potential efficacy, and we recommend this as a first line of treatment for most patients. The limitations currently are lack of reimbursement and also, the data also lacks in terms of long-term sustainability of

the intervention on patients.

As far as revascularization, we understand and we recognize the limitations of the current data that are available. In current practice revascularization for claudication must be a carefully considered individualized decision based on numerous factors such as the severity of disease and the anticipated risk versus benefit. Key factors that are predictable include comorbid conditions and the anatomic pattern of disease that we know determine the subsequent efficacy.

Importantly, our group has decided that it was time to submit a minimal threshold of efficacy for this disabling disease which is non-limb-threatening. We believe that on average, patients should expect at least two years of clinical benefit for an invasive therapy for claudication, and that should be tailored to the anatomic circumstance where those expectations exist. And also, the level of evidence that supports this presently is low, clearly more research is needed to support this kind of evidence and we need longer-term data than the regulatory studies currently

afford us. Thank you very much.

DR. BACH: Thank you very much.

Dr. Joseph Mills, the chief, Division of Vascular and Endovascular Surgery, the director of the vascular fellowship and residency programs, also professor of surgery in the Department of Surgery at the University of Arizona. Thank you.

DR. MILLS: Thank you. I've been involved in the SVS practice guidelines on lower extremity disease, diabetes, and internationally. I have since relocated to the Baylor College of Medicine. These are my disclosures.

I think, if I could emphasize one thing, the reason you're going to have to vote you don't know the answer to these questions today, especially for critical limb ischemia, is that that term was developed over 40 years ago when our patients were different, they were smokers, the primary problem was ischemia and they weren't diabetic. Now we have this wide spectrum of disease, and if you look at these slides, these are patients I've treated over the last 30 years. They're all Rutherford

category 5 except possibly the one on the right, and you can see that the treatment for this is going to vary a lot, there's not going to be one answer.

The reason things have changed is the global epidemic of diabetes, which is one of the noncommunicable diseases. There's now almost 30 million diabetics in this country, there's almost 380 million diabetics in the world, and the most common reason a diabetic comes to the hospital is for a wound, possibly infected, which results in an amputation once every 17 seconds in the world. Diabetics are high cost, it's about 20 percent of the cost related to the foot from diabetic foot admissions, and each episode costs somewhere between $40 and $94,000 for inpatient diabetic foot admissions.

So, the reason we came up with this system is we think that the term CLI doesn't apply to most of our patients and that we needed a different classification system. And if we don't define the patients differently up front, much like cancer with T&M, we'll never know what the outcomes are.

So, why do I say that? This is the original paper, over 40 years old, of definition of critical limb ischemia. It was a consensus one-page paper, and what everybody forgets is that diabetics were excluded from this. If you have diabetes you also have neuropathy, you have a wide spectrum of wounds, there is no single cutoff that predicts healing, and they're often complicated by infections. If you have PAD plus infection, this is from the EURODIALE study, it triples the amputation risk, and yet infection is not even mentioned in Rutherford or Fontaine.

So, we think ischemia is a spectrum and how much revascularization, or even if revascularization is required depends on other things than just ischemia, and so we came up with WIFI which briefly, and I won't go through the whole thing here, but it's based on categorizing wounds, ischemia and foot infection from zero, none, to mild, moderate and severe, and based on those classifications you can place the patient into four categories of limb risk. And this turns out to be true,

25 now, by four validated single center trials

1 done in almost 1,800 patients, showing that
2 this does predict risk of amputation regardless
3 of therapy, whether it's endovascular, open, or
4 medical therapy.
5 Now to answer some of the specific
6 questions you have to vote on, is
7 revascularization for limb salvage effective?
8 I think the answer is a qualified yes, based on
9 historical controls such as the Circulase
10 trial, and large studies from Europe where
11 untreated patients with severe limb ischemia
12 had 15 to 34 percent amputation rates in six to
13 12 months without revascularization.
14 Now, an interesting thing that's been
15 alluded to earlier is amputation is regional,
16 there are certain hotbeds, and if you look at
17 this data from Goodney, the more vascular
18 attention that's given to the problem, the
19 fewer amputations, so if there's more
20 angiograms, endovascular therapy and bypasses,
21 the amputation risk drops, so we recommend that
22 referral to vascular specialists for such
23 patients be encouraged.

Secondly, lack of recognition of ischemia is a common problem. We recommend

that all patients with nontraumatic foot wounds, especially diabetics with or without infection, get blood flow measured.

We think that we should encourage the development of teams. There are multiple studies that show teamwork, which frequently consists of podiatry plus a vascular specialist reduces amputations, and to that end the SVS and APMA combined to develop a collaborative effort, and we recommend that this be encouraged.

There is only one trial for this problem despite how common it is, and it did show if patients live longer than two years, they had lower mortality and better limb salvage if they had bypass first.

Our final --

DR. BACH: Dr. Mills, you're out of time, so if you don't mind, just wrap up.

DR. MILLS: Our final recommendation is these studies be encouraged because we don't have any data.

And finally, I have some slides for disparity, which you can view on your own. Thank you.

DR. BACH: Thank you very much. I would like to introduce Dr. Oscar Alvarez, who's the director of the Center for Curative and Palliative Wound Care at Calvary Hospital in the Bronx.

DR. ALVAREZ: Good morning. Calvary Hospital is the only acute care hospital totally dedicated to the management of palliative care patients. In this morning's presentation I'd like to give you our humble attempt in a clinical trial looking at high pressure intermittent pneumatic compression for the treatment and palliation of patients without an operative option.

My disclosures, I am a Yankee fan, being here in Oriole country, and none others other than the funding for the study, which I'll mention later.

There are several HPIPC devices available and they vary tremendously in cost. Compression has been used to treat PAD and CLI

since 1917 and there's quite a bit of evidence, albeit not always graded to the standards of today's standards, but quite a bit of evidence in fact does exist. There are also systematic

reviews available also.

In our study we screened 64 patients, we randomized 34, and it took us almost five years to actually do this trial, so this gives you an idea how difficult they are to do. And there were 18 in the treatment group and 16 in the exercise group, which was not supervised, and the major evaluations involved different wound healing, pain, and mostly patient-reported outcomes.

Here's an example of the pump. As Dr. van Bemmelen pointed out before this talk, they are rapid high pressure compression provided at intermittent times. We used the Baker-Wong FACES scale and the VAS scale for evaluating pain, and we used a Short Form 36 to evaluate quality of life, both the physical component and mental component.

The statistics are here. The mean peak walking times for HPIPC and control were

both increased, a little greater for the HPIPC, especially at the 16-week time point. It took 16 weeks but if you look at the mean change from baseline in peak walking times at four, eight and 16 weeks, that 16-week group showed

statistical significance.

The r-ABIs did not significantly change. However, the temperature change between the foot and chest ratio did increase, showing a sign for vascularization.

The perceived improvement from the health survey questionnaire shown here showed that there were statistical significances in both the physical function and bodily pain, comparing both the HPIPC group and the exercise control.

The percent reduction in wound care, only 20 percent completely healed, which is seven out of the 34, but in fact they all improved. Here's an example of improvement but not healing. You can manage a wound like the panel on the right very easily, these are not difficult wounds when they start to heal.

Leg pain at baseline and after

treatment was statistically significant when we used the Baker-Wong scale in favor of the HPIPC, and the mechanism of action was also elucidated earlier on.

So, I acknowledge the New York Department of Health for funding the study at

$25,000 a year for four years. The arterial pneumatic compression devices were provided at no cost from BioCompression, and the Bronx YMCA provided free temporary memberships for our patients to do the exercises. Thank you for your attention.

DR. BACH: Thank you very much, Dr. Alvarez. I would like to introduce Dr. Gary Ansel, executive board member of VIVA Physicians.

DR. ANSEL: Thank you very much, I appreciate the opportunity to participate today. My slides -- there you go.

DR. BACH: We also can't hear you, despite the fact that you're insecure.

(Laughter.)

DR. ANSEL: Just as long as I don't get strip-searched, I'm good.

So, I'm glad to present to the MedCAC panel. Don't take that time from me. My travel and lodging was supported by a not-for-profit, VIVA Physicians Group, which is a multispecialty group based on research and education for vascular disease. These are my financial statements. I'm the system medical

chief for vascular at a large health care system that's a multilevel hospital, multiple different specialties, primarily a non-RVU quality-based performance model for reimbursement. I'll be addressing the critical limb questions.

The take-home points and some things that, I left a nice big slide set for you to review, so I'm not going to reiterate all the things you've heard about the prevalence of peripheral artery disease, how this is a brittle population, how they have a very poor early and late prognosis. I really want to get to the fact that this is a diabetic population that's expanding. You've already heard this leaves out a number of patients from the Rutherford class, and as I want to point out,

these are infrapopliteal lesions, these are long total occlusions.

But even that is not what it's really about, and even Best trial doesn't take into account the fact that many of these patients do not have patent plantar arches. The reason that's important is if you don't provide perfusion to the area that is not getting blood

flow, the chance of healing goes down. This should not be an endo versus surgery requirement, this is actually customizing the care for the patient to make sure that we get the best chance for healing.

Angiosome, which is perfusing the area that has limb ischemia or wound, is the model that we should be using to make sure we're supplying the blood that needs to be there for healing. You can see if you don't do that, your chances of healing go dramatically down, and this is the diabetic population.

This is just a picture of a bunch of the patients that have diabetes that don't have intact plantar arches, and why we have to be very aggressive. Whether it's a heel ulcer or

toe ulcer is very different on how we should be approaching these patients. I'm going to give you an example of that.

This patient has pretty good flow to the anterior tibial artery, but really needs reconstruction in the foot to be able to get flow to that heel ulcer and the toe ulcer.

With advanced therapy that's only available at several hospitals in the United

States and around the world, but pioneered in Italy, you can see that with this new technology we have been able to get through these total occlusions and really supply this with long balloon angioplasty and come up with reperfusion for these limbs where the area is being constructed. This is not just diabetics but is also in the dialysis patient population.

And in summary, I want you to know that there's not just one technology that's best. Even in endovascular you're going to see that this patient population needs to be treated when they're ambulatory, we want to make sure that they get the best device for that wound, and that may be different for the

lesion that may need surgery, but we have to customize this for the patient.

Yes, there is data. If you look at Italy, that has the lowest amputation rate in the world. You can see almost a thousand patients with a five-year repeat intervention rate of 12.7 percent, very high limb salvage, whether it be excimer laser or whether it's the more recent balloon angioplasty, very low one-year retreatment rates and very high limb

salvage rates.

You have already heard, and you will hear about the BASIL trial, and again, we're seeing longer-term data for both surgery and endovascular, it's about customizing for the patient.

So with that I'll go to my final slide just to summarize and keep us on time, but I'm giving you a slide set that you can go through to get all the different trials. One of the things is that as we've seen endovascular increase and vascular surgery decrease, we have seen a lowering of the amputation rate, and that's important.

And I'll get to the take-home messages. Modern management of CLI is a balance between arterial conduit and limb preservation and the patient's functional outcomes. Technology and techniques will continue to evolve and allow us to improve on current treatment options, both endovascular and surgery. Future trial data sets will hopefully help define the best treatment guidelines for specific patient populations, not an us versus them mentality. Thank you

very much.

DR. BACH: Thank you very much. I'd now like to introduce Dr. Kenneth Rosenfield, who's the president-elect for the Society for Cardiovascular Angiography and Interventions.

DR. ROSENFIELD: My name is Ken Rosenfield, I'm president-elect, as you said, of the Society for Cardiovascular Angiography and Interventions, or SCAI. I'm an interventional cardiologist and a vascular medicine physician, and section head for vascular medicine at Mass General Hospital. I cofounded the NCR carotid and peripheral

vascular intervention registries and have led many PAD trials with Dr. Menard, who spoke earlier, and Dr. Farr. I'm the co-PI of the BEST-CLI trial which emphasizes, again, the multidisciplinary team approach to CLI, and I was the PI of the LEVANT 2 drug-coated balloon trial just recently reported in the New England Journal, which sets really a new standard for rigor in PAD device trials. These are my potential conflicts.

For today's panel meeting I have the, as president-elect of SCAI, I have the special

privilege to introduce a coalition of seven professional organizations that came together to advocate for patients by providing a cohesive series of presentations which will follow, to address the MedCAC questions. This unique coalition includes the ACC, American College of Radiology, American Heart Association, SCAI, Society for Interventional Radiology, Society for Vascular Medicine, and VIVA Physicians. Collectively, this multidisciplinary group represents nearly 150,000 members dedicated to high quality

value-driven patient-centric vascular care.

Feel free to review my slides, which provide a general backdrop for PAD, but I will not go into them in detail here. What I will say is the next eight speakers will speak to these issues, and they are members of this coalition. They include Dr. Beckman, who's going to talk about underdiagnosis and undertreatment of patients with PAD; Drs. Jerry Bartholomew and Rob Lookstein talking about asymptomatic patients with PAD; Drs. Jaff and Aronow addressing intermittent claudication; Dr. Shishehbor, who will address critical limb

ischemia; and Dr. Misra, who will talk about evidence gaps in treatment decision-making; and the final talk will be by Dr. Jim Froehlich, who will talk about the treatment disparities.

The essence of what this group believes is as follows: We are all passionate about improving the lives of our patients, their longevity, their quality of life, their ability to walk, to function, and preserve limbs, and we believe current treatments are already making a difference for our patients

with PAD, as you've heard today, but we can do better.

Treatment can be redefined and improved, and there are four particular shared tenets that tie us together. The first is that peripheral artery disease is a complex one; treating it requires an interdisciplinary team approach in order to provide optimal care and achieve the best outcomes for all patients.

Secondly, the foundation for care of patients with PAD from undiagnosed, to asymptomatic, to typical and atypically symptomatic, to CLI, rests on provider expertise and quality of care, and since

quality of care is paramount to ensuring good outcomes, it must be measured.

Thirdly, we all acknowledge that there are large treatment gaps in our evidence base and we are committed to closing them as a team. Rapid advances and increasing therapy alternatives, particularly less invasive endovascular options, have created a moving target. An additional challenge is establishing what really truly constitutes a

meaningful outcome for patients. Registries can be effective, as you heard, in adding to the evidence base, and they should also be used to track outcomes and to improve the quality of care. To be effective in this space, though, registries must allow for universal participation and not be restrictive. CMS should partner with all of the organizations speaking at today's MedCAC panel meeting to determine necessary and sufficient elements to be included in a registry.

And finally, choice is important to our patients. Medicare beneficiaries should be entitled to have access to therapies that offer the prospect to improve quality of life,

ability to walk, and maintain independence. Recommendations coming out of this important panel meeting should preserve the ability for patients to make individualized choices based on open discussion of benefits and risks with their team of providers.

So on behalf of this multidisciplinary collaboration and the efforts we extend to the patients we serve, we greatly appreciate the

opportunity to speak on these important issues. Thank you.

DR. BACH: Thank you very much, Dr. Rosenfield. I would now like to introduce Dr. Josh Beckman, who will be speaking on behalf of the American Heart Association.

DR. BECKMAN: Good morning, and thank you very much for having me. My name is Josh Beckman, I'm the current chair of the PVD Council for the American Heart Association. Here are my disclosures. Neither the AHA nor I received funding to participate in today's meeting.

The AHA is an organization of more than 22 million volunteers dedicated to reducing cardiovascular morbidity and mortality

through scientific-based remedies.

Today we're going to be discussing patients with PAD. This meeting is basically focused on what happens after we diagnose them. We need to consider how patients with PAD are first identified, especially in the asymptomatic and atypically asymptomatic patients, and the problem is there's a dramatic

underdiagnosis. We know who has PAD. In the fourth line down you can see a screening study of people over the age of 65; one in five men and one in six women have PAD. This is a huge population for CMS.

We know that most people are not recognized. Rina Pandi published using the NHANES database. You can see here that of the 7,500 patients over the age of 40, 647 of them had PAD. Only 196 were diagnosed with recognized PAD, whereas 451 weren't. This corresponds to nearly five million Americans who have undiagnosed PAD, five million Americans.

We know that this is a problem because from the same paper, when you're not treated appropriately, you die more quickly. Notice

here that the patients who received two or more preventive therapies of aspirin, an ACE inhibitor and a statin, had a 65 percent reduction in mortality, whereas everybody else basically died like smelts.

PAD is treated less well than atherosclerosis and other vascular beds. PAD

is the disparity. There are millions of patients who are underdiagnosed or untreated. Inadequate treatments increase mortality, and recently improved medications may reduce the need for revascularization.

The ABI needs to be covered by CMS because it is a diagnostic test and meets the CMS definition for diagnostic test. A diagnostic test from the Medicare Benefits Policy Manual is a test that aids in the assessment of a medical condition or the identification of a disease, and it is also given to determine the nature and severity. That is the ABI. It is not a screening test, that is a historical accident.

CMS defines a preventative service as one that can prevent you from getting the disease, or diagnose it really early on. By

the time you have peripheral artery disease you have a tremendous amount of atherosclerosis and a highly increased risk of death and cardiovascular morbidity and mortality. We strongly recommend that all patients in the Medicare population should have at least a

one-time screening ankle-brachial index covered by CMS. We know that the patients, one out of five men and one out of six women has PAD in the Medicare population, we know we are missing five million people with the disease, and we know we can make their lives better and longer.

We also know that PAD is undertreated. Once diagnosed, patients do not get the same level of treatment as atherosclerosis and other vascular beds. They do not get access to supervised rehabilitation like all other atherosclerotic patients do. You can see that they feel just as bad as patients with Stage III New York Heart Association heart failure, and we know that when you put them on an exercise treadmill and you supervise them, they walk longer. This is the CLEVER trial.

Here's 21 consecutive trials. You heard the technical panel, supervised exercise

works. We strongly recommend that all patients in the Medicare population with claudication be offered exercise rehab like patients after PCI, CABG or heart valve surgery.

What does coverage mean? These

services should be covered because CMS has a vested interest in diagnosing atherosclerosis. The ABI is as reasonable as an ETT, an EKG or carotid ultrasound. We want to reduce mortality from atherosclerosis and want to improve functional capacity, just as we do after MI, CABG, or patients with stable angina. Thank you for your attention.

DR. BACH: Thank you very much, Dr. Beckman. I'd now like to introduce Dr. John Bartholomew, who is the president-elect of the Society of Vascular Medicine.

DR. BARTHOLOMEW: Thank you for this opportunity. This is my disclosure slide. I am president-elect of the Society of Vascular Medicine. We are over 500 members, we have been running for over 26 years.

One in every 20 Americans has PAD, and PAD raises your risk for heart attack and

stroke. It is common, it is underdiagnosed, it causes significant morbidity, poor quality of life, and it overlaps, as you well know, with coronary and cerebrovascular disease. And as

you've heard over and over today, it is a predictor of adverse prognosis.

PAD is common but your patient may have never heard of it. This is an awareness gap and public knowledge study that looked at the awareness of PAD, and it compared to other diseases such as multiple sclerosis, Lou Gehrig's disease, cystic fibrosis, and as you see here, the prevalence of PAD is over nine million individuals, compared with multiple sclerosis at 300,000, where the disease awareness is only 26 percent; in other words, 76 percent of individuals did not know about PAD.

This is an older study, done almost 20 years ago, but looking at patients with PAD, and it noted that they were less intensely treated than patients with coronary artery disease. In fact, PAD patients were less likely to recall a physician's advice to exercise, so important for their claudication.

PAD patients were significantly less likely to take cholesterol medications, or be offered or advised to follow a low cholesterol diet. In

addition, they were less likely to take aspirin.

And you've already heard that in the NHANES study, this is a study that is called the National Health and Nutritional Examination Study, and it looked at PAD patients and it found that statin use was reported in only 31 percent of the individuals, ACE or ARB in only, in approximately 25 percent, and aspirin in 36 percent. And as you've heard, this corresponds to over five million people not taking a statin, 5.4 not taking an ACE or an ARB, and 4.5 not taking aspirin.

This is the Reduction of Atherothrombosis for Continued Health, the REACH registry, and this looked at two-year rates of vascular-related hospitalization and associated costs in patients at risk of atherothrombosis. And what it found was that there was a higher rate of polyvascular disease for patients with PAD, more than with CAD or

cerebrovascular disease. There was a greater degree of undertreatment of atherosclerosis

risk factors in patients with PAD compared to coronary and cerebrovascular disease, and it revealed higher cardiovascular event rates for patients with PAD compared to CAD and CVD. in addition, it suggested that stable patients with asymptomatic PAD have high annual costs, largely because of the high rates of cardiovascular events and hospitalizations, and costs escalate in time as the PAD becomes more symptomatic.

PAD is a morbid disease. It's a major risk factor for lower extremity amputation. Quality of life impairment is more severe than heart failure or MI. Their functional impairment is common, even among patients with atypical leg symptoms. There's a decreased walking distance, a decreased walking velocity, and there's also objective evidence that depression is quite common among patients with PAD.

Millions of U.S. adults with PAD are not receiving secondary prevention therapy. These therapies, as you've heard over and over

again, may reduce the risk of adverse

cardiovascular events. Treatment with multiple therapies is associated with reduced all-cause mortality.

So the take-home message, PAD is common, underdiagnosed and undertreated. Most patients do not have classic symptoms. PAD is a coronary risk equivalent, and aggressive risk factor modification can save lives. Thank you.

DR. BACH: Thank you very much, Dr. Bartholomew. I'd like to introduce Dr. Robert Lookstein, from the Society of Interventional Radiology.

DR. LOOKSTEIN: Good morning, thank you to the panel for having the opportunity to speak. I'm representing the Society of Interventional Radiology. I'm a practicing interventional radiologist in New York City and I serve as the chair for the peripheral disease working group for the Society of Interventional Radiology. I have several comments I'd like to make within the theme of the coalition, as Dr. Rosenfield previously introduced. These are my disclosures.

When you look at evidence for the

treatment of asymptomatic lower extremity peripheral arterial disease, there are three consensus documents that have been written in the last decade. The first is authored by Dr. Hirsch, who sits on the panel today. This represents the ACC, the AHA, the SIR, the SVM, numerous other subspecialty organizations convening to provide recommendations for the care of asymptomatic patients.

The second is the TASC II document, again multiple specialties, including the North American Society of Vascular Surgeons and the European Society of Vascular Surgery, combining to provide recommendations for the treatment of asymptomatic patients.

And then most recently is the document that Dr. Conte referenced in his previous presentation.

This slide references the natural history of an asymptomatic patient, where we all believe as a unified multispecialty consensus that the major intervention in the asymptomatic cohort is to reduce the cardiovascular morbidity and the mortality associated with this disease. We do not

recommend revascularization as a primary therapy in the treatment of the asymptomatic population.

As previously mentioned, lifestyle modification, including smoking cessation, patient education regarding the diagnosis, blood pressure and lipid control are the primary benefits to reduce the all-cause cardiovascular events associated with this diagnosis. And again, just to be clear, none of us in these specialties recommend revascularization in the asymptomatic population.

With reference to critical limb ischemia, my colleague Dr. Shishehbor will reference this further, we are asked to determine whether or not there's sufficient evidence for an intervention to improve the life of patients with critical limb ischemia, and I would reference the article recently published by Dr. Hirsch, who again sits on this panel, the REACH study, who prospectively looked at almost 8,000 patients across the world, referencing them as patients who had undergone an ischemic lower extremity

amputation, against those with PAD who did not. This study demonstrated a significant increase, almost a hundred percent increase in the incidence of myocardial infarction, stroke, and all-cause cardiovascular death from patients who had undergone a lower extremity amputation. The evidence suggests that if we can avoid an amputation, we will reduce these risks. This risk was further confounded from patients having a more recent amputation, as compared to patients having a remote amputation.

Again, I will reference the AHA guideline documents. I had the privilege of sitting on the more recent guideline document which is currently in draft form for the AHA and ACC, SVS and SIR, SVM had a representative for this document as well, and specifically the recommendations on most recently published documents for critical limb ischemia from the TASC II document is revascularization is the optimal treatment for patients with critical limb ischemia, and according to the ACC and AHA guidelines, the treatment of critical limb ischemia is dependent on increasing blood flow to the affected extremity to relieve the

ischemic pain, heal the ischemic ulcerations, and avoid limb loss.

Dr. Jones referenced this article, the AHRQ review, which specifically addressed the comparative effectiveness between endovascular therapy and surgical revascularization for patients with critical limb ischemia, and as of 2015 we believe that endovascular therapy is at least as effective as surgical revascularization in the treatment of critical limb ischemia with the goals of avoiding major amputation in the affected limb.

The coalition previously referenced endorses the BEST-CLI trial. SIR participated actively in the BEST-CLI trial, which will further define the exact role of endovascular therapy for specific critical limb ischemia cohorts. Thank you for your attention.

DR. BACH: Thank you very much. I would like to introduce Dr. Michael Jaff, who is the president of VIVA Physicians.

DR. JAFF: Thank you, Mr. Chairman, and ladies and gentlemen. It's a privilege to be here to represent this group of physicians

who are interested solely in the diagnosis and

management of patients with peripheral vascular diseases.

My disclosures have been provided prior to my presentation this morning. I would note that that my presence here was funded by VIVA Physicians for all travel-related expenses. As Dr. Ansel mentioned, VIVA Physicians is a 501(c)(3) not-for-profit education and research consortium solely focused on peripheral vascular diseases. I am the president. All officers and board members receive a stipend for their service to the organization based on documentation of specific hours worked.

I would also like to disclose that I am the founder and medical director of VasCore, the Vascular Ultrasound Core Laboratory, which has participated in over 170 clinical trials in 66 countries; many of the PAD trials referenced this morning and throughout the day, we participated in. VasCore is solely owned by the Massachusetts General Physicians Organization. All agreements are provided

between the sponsor and the MGPO, not me, and my salary is not tied in any way to the number

of trials or performance of VasCore.

I'm going to be speaking specifically about intermittent claudication as the question at hand from the panel, and you've already heard all of the information that I was going to discuss about longevity, the limitations of patients with intermittent claudication. There is much more to this than just blockage of a pipe, but lots of cellular mechanistic problems that exist in PAD. You've already heard about the tremendous coexistent comorbidities of coronary disease, cerebrovascular disease and all-cause-related mortality. We understand the risk factors including diabetes, which is not only the Medicare population, but around the world as well.

The question about sufficient evidence about interventions that improve the immediate, near-term and long-term outcome is true, it's absolutely true if we're talking about improvement in functional ability. You've already seen all of the information about

exercise. We wholeheartedly support coverage of exercise therapy as a principal and primary treatment for patients with intermittent

claudication. In addition, we feel it's critically important that all home medical therapy be offered as first line treatment.

You've already seen an excellent presentation by my colleagues from Duke about this technology assessment, and you heard from Dr. Dake about some of the information about a drug-eluting stent. There were a number of studies that were not included in that initial presentation, and although reviewed today by Drs. Schuyler Jones and Manesh Patel, there is lots of information there worth this panel understanding, and you can review that in the slides.

What I would like to call your attention to is this: We now actually do have data demonstrating functional improvement in patients who are treated with an endovascular intervention. This is 12-month data from the IN.PACT SFA trial published in December in Circulation, demonstrating that although the

six-minute walk time did not change between the drug-eluting balloon and the bare balloon, there was a dramatic 88 percent reduction and fewer interventions in those patients who had

the drug-eluting balloon, suggesting that risks to patients for complications and costs are clearly to the advantage, and this is the first this has been shown.

We've also already heard about the CLEVER trial. The IRONIC trial, a similar study looking at quality of life, demonstrated in patients with claudication that if they received an endovascular intervention, they had an improvement not only in physical functioning but in quality of life.

Finally, I would like to remind you that one of the great parts about being in the field of vascular medicine and taking care of these patients is the dramatic advance in technology and the quality of the literature that has been generated over the past several years, with great anticipation for improved outcomes and data in the future. Thank you very much for your attention.

DR. BACH: Thank you very much, Dr. Jaff. I'd now like to introduce Dr. Herb Aronow, who's the chair of the American College of Cardiology.

DR. ARONOW: I would like to thank the

panel for the opportunity to speak today. I want to clarify, I'm actually not the chair of the ACC but of its peripheral vascular disease council and section.

DR. BACH: My apologies.

DR. EHRLICH: None taken, it would be quite an honor to be the chair of the College.

My potential conflicts are shown here, they're largely societal and not financial. The American College of Cardiology did support me in travel expenses for today. The ACC is a nearly 50,000-member organization, a not-for-profit, and its members are responsible for caring for patients with cardiovascular, and as it relates to today's presentation, patients with lower extremity PAD.

My task is a little easier than those who came before and who will come after me today in that I am here to ask questions rather

than answer them, and I'm going to specifically address a few gaps as it relates to the patient with intermittent claudication, long-term outcomes gaps, and some subgroups and the gaps associated with them.

I think before I launch into that I

would just reiterate points made earlier today in that the research paths we pursue, whenever possible, should be multidisciplinary, and should wherever possible include the wealth of registry data we have available to us through our quality improvement initiatives, the ACC NCDR and the SVS VQI.

With regard to long-term outcomes, there is a lot we don't know. We really don't know what the relative effects are of contemporary medical therapy versus revascularization on late functional status and quality of life. We really don't understand the relative patency of most contemporary intervascular therapies beyond two years.

We know little about the cost effectiveness of revascularization plus medical therapy, and when I say medical therapy I

include in that both medication and lifestyle interventions such as supervised exercise, versus medical therapy alone. We don't know whether if there were coverage for supervised exercise therapy, what would happen with endovascular and open surgical revascularization rates, they might very well

punt.

We also don't know what the rates of repeat revascularization would be after initial revascularization procedures were there coverage for supervised exercise therapy.

And finally, we don't know what the potential impact would be by improving functional status and quality of life on subsequent cardiovascular morbidity and mortality in this patient cohort who has such a high risk of atherothrombotic events.

As I mentioned, there are a number of subgroups in whom we must learn much more, the elderly, women and minorities, to name a few. The elderly, as you know, have a very high prevalence of lower extremity PAD, but their ability to report, to self-report, their

limitation is limited. Many of them are unable to perform treadmill testing to diagnose or quantify their limitations. Their procedural success is lower, their complication rate is higher, and it's a very costly demographic to treat. We must learn more.

In women who have a similar prevalence in PAD to men, they're often older and present

with a greater comorbidity burden. They less often have classic symptoms and are often more limited when they present with typical symptoms. Their outcomes after certain revascularization procedures may be worse than after others. We need to know more in this subgroup as well.

And finally in minorities, African Americans have a higher PAD prevalence than non-Hispanic whites, and Hispanics, African Americans and Hispanics are more likely than whites to present with CLI than claudication and they have outcomes that are worse after both endovascular and open surgical procedures. We must learn more in this subgroup as well.

I'll end there, thank you very much

for your attention.

DR. BACH: Thank you very much. I would like to introduce Mehdi Shishehbor, the director of endovascular services and staff, interventional cardiology and vascular medicine at the Cleveland Clinic.

DR. SHISHEHBOR: Thank you very much. I have no conflict of interest to report, and my travel was supported by my institution, and

I'm grateful and honored to be here today to represent the seven societies and organizations, but more importantly, my patients with critical limb ischemia that I see in my clinic and I take care of in the hospital.

As discussed, I will be discussing the interventions related to critical limb ischemia, which is the end stage of this condition, those with rest pain, tissue loss and gangrene. And let there be no doubt, as represented today, that all guidelines have recommended Class I indication for revascularization for patients with critical limb ischemia. That means the

revascularization is the cornerstone of therapy for patients with this specific condition with ulcers, tissue loss and gangrene, and that has been supported by every guideline that has been published to date, including the ACC/AHA guidelines.

Unfortunately if you look at the data, you see that a significant portion of the patients with critical limb ischemia are not getting this treatment. On the x axis is the

regional intensity of vascular care across the United States in patients that have Medicare. On the y axis the authors asked a very simple question, what's the proportion of patients that undergo amputation and get a vascular workup in the year prior to their amputation? And as you can see, depending on the intensity of the region, between 40 to 70 percent of the patients that get an amputation have no type of vascular workup or intervention prior to their amputation.

As alluded earlier, there is a direct correlation, very few things in medicine have a correlation of .87 between revascularization

and amputation-free survival. Again showing on the x axis is intensity of revascularization rates, meaning more revascularization, the rates of amputation were lower in those that had, in those regions that had higher rates of revascularization.

And again, the BASIL trial was mentioned earlier. The question is which approach is better, is it open or is it endo, and I think Dr. Ansel said it beautifully. This is not about open or endo, this is about a

personalized approach, an individualized approach to the patient. A particular patient may benefit better from endovascular while another may benefit better from open, and one may benefit from a hybrid approach. So the bottom line is that revascularization is a treatment that we need to offer to these patients, and individualize it to the particular patient that we are seeing in the clinic.

This condition has significant morbidity and mortality. The patients that have CLI have significant pain, they have

significant burden from a psychosocial standpoint, and obviously they have a significant decline in their functional ability. And we know that ulcers are a prelude to amputation. That's the time that we have to intervene and prevent amputation in these patients, given the morbidity and mortality associated with amputation.

This slide was shown earlier. There is a significant variation despite all this work and despite all the recommendations from the guidelines that revascularization is the

cornerstone of therapy for these patients, there remains a significant variation in the amputation in the country, but it's not just a variation, it's a variation that's linked to race, it's a variation that's linked to socioeconomic status.

You see rates of amputation across various races depending on intensity of revascularization, again showing that blacks have significantly more amputation rates than whites. And again, shown here in another form, when you link with socioeconomic status,

showing that those that are African American are from lower socioeconomic status, there is almost three times higher rates of amputation. These are the things that I think we need to put our attention to, and try to dilute these disparities.

Again, I would like to emphasize that patients with critical limb ischemia are complex, they require a multidisciplinary approach that encompasses vascular specialists, internists, family physicians, wound experts, podiatrists, and folks that are coming in to take care of these patients in order to

decrease the morbidity and mortality from this condition. Thank you very much.

DR. BACH: Thank you very much. I'd like to introduce Dr. Sanjay Misra, who's a professor of radiology at the Mayo Clinic.

DR. MISRA: So, thank you very much to the panel for allowing us to speak. I would like to state that I'm representing the Society of Interventional Radiology. I'm at the Mayo Clinic, but the views that I'm presenting do not represent the Mayo Clinic. The society has

reimbursed my flight here but has not reimbursed anything else.

So, over the last 15 years of my career, I've had the opportunity to work on several writing panels. I've worked on American Heart consensus panels and several ACC agency panels. Here are my disclosures.

I think before we start in the questions, I think it's very important to understand that we are talking about patient care, and I'm going to quote Dr. Mayo, who once said that the best interest of the patient is the only interest to be considered, and so when you think about taking care of patients with

vascular disease, they're very heterogeneous, and you can spend a lot of time and effort trying to define what the best goals are for each of the patients, and we've all discussed those as far as cardiovascular outcomes, but each patient is very different.

Recently President Obama laid out his precision medicine. What we really want to do is figure out for each patient when you see him, what is best for him or her. And so what

I'm going to try to talk about is, one, what is the role of endovascular treatment of SFA in patients with intermittent claudication versus supervised exercise therapy, and then, what is the role of endovascular SFA treatment in advanced chronic kidney disease.

And so, this is the ERASE trial, which was published only in abstract and presentation form, and it was presented at American Heart a few years ago, and it dealt with intermittent claudication patients and it was to compare the effectiveness of treatment versus SET, or plus SET, versus supervised exercise therapy for intermittent claudication. And this was the randomization scheme, and as you'll see, I'm

going to show you the results. At 12 months, patients that were revascularized all walked faster, so this is one of the important things. Unfortunately, supervised exercise therapy is not reimbursed in the U.S., and we would advocate for reimbursement for SET.

This is the VascuQol scores and these all improved as well.

These are secondary interventions of

patients that were treated with SET versus endovascular therapy, and as you can see, the secondary treatments were increased in patients that only underwent supervised exercise therapy.

What about advanced chronic kidney disease? I'm going to show you some single center data of our own in 440 patients that underwent PT or stent placement. These are the procedural details and what I want to show you is, this is the mortality for different stages of chronic kidney disease. We spoke earlier about not having outcomes based on all-cause mortality, and so if you were to stage patients into mild, moderate and severe chronic kidney disease, you would see that there are different

outcomes for all-cause mortality. This is our own data set from the Mayo Clinic Rochester.

What about amputation-free survival? This is the amputation-free survival curves, Kaplan-Meier estimates for the same data sets, so just based on different GFRs there are different outcomes, even for endovascular treatment. This needs to be further defined

and further investigated with studies.

So this is in part why we have a variation in lower extremity procedures for CLI, and I'll show you the Minnesota map. This is from Alan Hirsch and as you can see, Rochester and Minneapolis are outlined in the left, we're in the southeast corner, and there are different outcomes for lower extremity amputation in the state of Minnesota, mortality and stroke mortality.

So what are the gaps? We've heard from the SVC, SVS surgeons about the utility of bypass grafting. Unfortunately in the endovascular world, we don't know what is the best treatment for the different patients. We don't know when is best for using angioplasty alone or the different technologies. We don't

know what the clinical outcomes are. We've heard this from Manesh and Schuyler Jones. We don't know what the functional outcomes are. We need to understand this better. What is the differences in the mortality, the all-cause mortality, nonfatal MI and stroke in intermittent claudication patients?

DR. BACH: Please try and wrap up.

DR. MISRA: Thank you. Finally, we need to understand what are the individual roles for each of these technologies. Thank you.

DR. BACH: Thank you. I would now like to introduce Dr. James Froehlich, president of the Society for Vascular Medicine, and I'll ask again for people to please stay on time.

DR. FROEHLICH: I'd like to thank CMS for the opportunity to present here. I have been asked to talk about disparities and also to wrap up for the ten previous speakers who are part of this unique consortium.

I am currently professor of internal medicine at the University of Michigan and director of vascular medicine and assistant

chair of medicine for quality and innovation. These are my disclosures. I've consulted for all the companies that make anticoagulants. My travel and participation here today was supported by the regents of the University of Michigan. The University of Michigan is a

nonprofit educational organization that produces themselves as the finest higher education opportunity in the country and the finest football team. I have data to support that and I'll meet with anybody on the outside afterwards, but I want to point out that I think it's CMS policy that fisticuffs on campus are prohibited.

So, disparities, I want to say two things about disparities. First is, there are clear racial and socioeconomic disparities in terms of access to care and outcomes when it comes to PAD. This was alluded to and covered by Mehdi Shishehbor. I want to look at some different data, some registry data to support this.

These are amputation rates among black and non-black populations. You can see the disparity is astronomical, and this is true for

every age group. When you look at Dartmouth atlas data, you see that not only are there racial disparities in some of the amputation rates, but this varies also highly around the country. And excluded from my final slide set

was another similar map that looks at revascularization rate by race prior to amputation. As has already been covered by Dr. Mills and Dr. Shishehbor, clearly there's a lower incidence of amputation when a treatment strategy of revascularization has been tried.

We're also, there's a lot of evidence suggesting socioeconomic status also has a huge impact on the likelihood of receiving revascularization and amputation rate. These are data from UCLA using California state reimbursement data to show the marked disparity in terms of amputation rate based on income. These are ZIP codes, and this just shows how it varies widely throughout the Los Angeles area, and these graphical representations of these data show that there's a direct relationship between socioeconomic status and the likelihood of suffering amputation, as well as having access to revascularization prior. And you can

see the statistical outliers of Compton and East Los Angeles, where socioeconomic status is low and access to health care is low.

So, the second thing I wanted to say

about disparities is PAD is a disparity. You heard Dr. Beckman allude to this earlier. And what we mean by this is, patients with PAD are not receiving state-of-the-art health care either medically or interventionally, we believe.

These are data that we produced from the GRACE registry at the University of Massachusetts and the University of Michigan that showed that patients in the GRACE registry, which was a registry of acute coronary syndrome patients, you could see that those who had preexisting PAD were grossly undertreated compared with those who did not have PAD, and this included things like smoking cessation counseling, the provision of aspirin, and lipid lowering medication as well as aspirin at discharge.

The PVI registry is a statewide Michigan quality improvement consortium based on the partnership with BlueCross BlueShield of

Michigan, and it is an arrangement like Dr. Cronenwett alluded to, practitioners are paid to participate in the registry, and we've

learned that there too, PAD patients are poorly reimbursed.

DR. BACH: Please try and wrap up.

DR. FROEHLICH: I wanted to end by saying that I think this unique consortium of seven societies from multiple specialties brought together has raised four important points. One is PAD care is a team sport, and I think reimbursement should incentivize multidisciplinary programs. Evidence gaps exist. I support Dr. Cronenwett's suggestion that CMS should incentivize registry participation. Potentially the cheapest and arguably most effective therapy for PAD is not reimbursed by CMS, which I think is a potential huge cost savings. And I think the consortium gathered here is evidence of the fact that across all specialties, everyone believes that revascularization is an essential part of the armamentarium for PAD. Thank you.

DR. BACH: Thank you very much. I'd like to introduce Dr. Daphne Denham, from

Comprehensive Wound Care.

DR. DENHAM: Thank you very much,

ladies and gentlemen. I'm glad I'm at the end because rather than data, I've got some patient examples from my practice. I trained as a general surgeon about 20 years ago, started with Dr. Mills, and during the vascular rotations I was always impressed with the patients that we couldn't help and we couldn't revascularize. And over the 20 years, as you all know, there have been many things that have changed that have allowed improvement of that; however, there are still patients that we can't help. I do not have any disclosures.

And the patients that we have helped with the arterial pneumatic compression pumps are extremely grateful for the help. The first is a 97-year-old gentleman that I met with rest pain so badly that I didn't appreciate how mentally alert he was. He couldn't even sit still in the office, constantly shuffling his feet trying to get comfortable. We've all seen patients like that. His wounds were wet gangrene of his fifth toe. He quit smoking in 1937 and, as I said, was mentally alert. And

this is a photo of his wet gangrene, and you

can all appreciate the shininess, he's got some edema, he had a vascular bypass surgery years before, but by WIFI criteria, his amputation risk is greater than 50 percent. His ABIs, they couldn't even detect a toe pressure on his great toe on the right, and about 30 percent flow. Severe critical limb ischemia.

He declined further workup, he said I'm 97, I don't need this, but he was grateful to have any opportunity to get rid of the pain. He started wearing the pneumatic arterial compression pumps and instead of three hours a day, he would sit in his chair and wear them eight hours a day because he had some comfort during the time that he wore them. Within six weeks his rest pain was completely resolved and he was immensely grateful. His wound remained a dry stable eschar which, fortunately, we were able to hold off on everyone wanting to amputate him, and he died three months later in his sleep, but as I said, rest-pain-free.

The other was a 94-year-old, she's 95 now, I've known her several months. She presented with a simple blister. Her story,

she was not a diabetic, also quit smoking in the '40s, fairly mentally alert. Her wound demonstrates bone in the center of the wound. This is her Buerger's test, impressive critical limb ischemia. Her ABI is not as impressive, but a toe pressure of 37, which is below the 55 needed to heal.

Seven months later she actually has completely healed the wound, which has surprised all of us because at times we got hospice involved. Her rest pain has resolved also.

The next patient's 80 years old, had a previous amputation ten years ago, and I'll slip through quickly. He presented with this ulcer, but he also had an arm sarcoma that he was getting worked up and had surgery, so he wanted no further workup. But because of his amputation his PCP said I want you to see someone before you progress on all the other. You can see his prosthetic in the other picture.

After seven months he healed this wound just using the pneumatic arterial compression pumps and local wound care, and I

saw him back 11 months after we first initiated the pumps, and he actually came back to say I just want to thank you, my feet are warm. All of his wounds were healed, and considering that he had a golden limb, he was extremely grateful for the opportunity to have improved perfusion of his remaining limb.

This last patient, I was in my office the day the slides were due, like all of us we put it off until late, but he had severe critical limb ischemia as well, and he was not deemed a candidate for intervention, neither interventional radiology or by surgery. And in just four weeks time he too, his pain was much improved and he was grateful.

Over the past five years that I have been doing exclusively wound care, I have seen at least over a hundred patients, I think the numbers are up in the 130s, but I've moved around a little so my data was not clean. I know we've had 20 deaths, but we've had two amputations out of the patients that we have added pumps to. Some of these have been interventional candidates and we have added the pumps in conjunction with it, but all others

have healed or are healing, and are grateful for the opportunity. Thank you.

DR. BACH: Thank you very much. I'd next like to introduce Mark Turco, medical director, aortic and peripheral vascular at Medtronic. He is here representing Medtronic, Abbott Vascular, Boston Scientific, C.R. Bard, and Gore Medical.

DR. TURCO: That's a mouthful, Dr. Bach, thank you. It's great to be here, and thank you, Dr. Bach and committee members. So I was, before I transitioned to the medical device side, a former practicing interventional cardiologist, and I am very pleased to present on behalf of a consortium that we put together through AdvaMed of Abbott Vascular, Medtronic, Boston Scientific, C.R. Bard, and Gore Medical. These are my disclosures. I am a Medtronic employee and I am not a Yankee fan.

So what I'd like to do, you've heard a lot today already, what I'd like to do is truly emphasize three separate points. First, the significant advancements in endovascular therapies over the past decade. The second is the significant body of Level I evidence on

endovascular therapies that is not reflected in the AHRQ reports. And finally, the ongoing investments in clinical research that industry is making to advance endovascular therapies and improve treatment of PAD patients.

From a patient perspective PAD is a progressive and complex disease. Patients are now demanding that treatments be minimally invasive as possible, durable, limited complications, and not require reinterventions, and all of us certainly agree that this should be a multidisciplinary approach to patient care.

Over the last decade there has been marked improvements in endovascular therapy, which you can see well from this time line starting in 2005 out to where we are currently with two approved drug-eluting balloons on the market. With these advances there has been corresponding increase in Level I evidence. The advancements in these technologies need to be considered in any deliberation of this committee and any future reporting through AHRQ.

25 Since 2013's AHRQ report there have

1 been 35 comparative studies that have been
2 published that evaluate endovascular therapy
3 against an active comparator. These studies
4 represent over 25,000 patients. Of the 35
5 studies, 20 of these studies compared different
6 types of endovascular treatments which AHRQ
7 excluded in its review because AHRQ excludes
8 studies comparing treatments of the same type.
9 However, these studies met the rest of the AHRQ
10 inclusion criteria for rigor and are relevant
11 to today's discussion and deliberation.
12 Additionally, why should we exclude
13 trials that have less, that have 500 patients
14 or less than 500 patients? If we have a study
15 that is rigorous, that is well controlled and
16 it only has 450 patients, should that not be
17 included in the AHRQ criteria? If we look now
18 at the validity of these large and high quality
19 clinical trials and their outcomes, we see
20 there are statistically significant differences
21 favoring newer endovascular therapies over PTA.
22 If we look at the patients studied, we
23 can see that the results are generalizable to a

real world population. These patients had high rates of comorbidity, significant calcification

of long lesions and high prevalence of diabetes. These studies also helped to address the variability that you've heard today in care of the PAD patient, and deliver an evidence-based standard.

In addition to the clinical outcomes that you've seen, newer endovascular therapies have also demonstrated improvement in functional outcomes. Specifically we see improvements in walking distance and a reduction in claudication. We see these improvements despite the fact that patients in the PTA arm needed upwards of nine times more reinterventions to have the same level of function.

For outcomes that matter to patients --

DR. BACH: Please try to wrap up.

DR. TURCO: -- we see reductions in complications with endovascular therapies versus other treatments. There is currently 36 ongoing studies and an additional roughly 9,000

patients that will be evaluated.

So to conclude, there is a large growing body of Level I evidence supporting the

use of endovascular therapies for PAD patients. Many contemporary studies were not included in the AHRQ review. And while we agree with registries playing an important role in this space, mandating the reporting for a single registry could pose significant infrastructure and resource challenges to hospitals, particularly given that many providers are already participating in other long-term registries and studies. We are excited about the dramatic improvements we're seeing in patient outcomes and the newer endovascular therapies. Thank you very much.

DR. BACH: Thank you very much, Dr. Turco. I would like to introduce Terry Foust Litchfield, vice president of clinical operations at Lifeline.

MS. LITCHFIELD: Thank you very much for the opportunity to present today. I represent Lifeline Vascular Access. I would like to disclose, I am an employee.

We have 24 freestanding centers, including vascular surgeons, interventional radiologists, interventional cardiologists, focusing on outcomes, and our particular area

of expertise is the renal patient. You've heard about them from several of our speakers. Our system is accredited by the Joint Commission and we're an active member of the Cardiovascular Coalition.

The CKD and ESRD population is a really at-risk subgroup. You asked for groups that really were disadvantaged and fragile, and really when we look at high risk patients and we profile our database of in excess of a hundred thousand CKD patients, 81 percent meet consensus guidelines for risk of PAD.

The burden of amputation, the prevalence of ESRD, at commencement of ESRD and PAD is six percent already have amputation, and KDOQI, the quality standard for the renal community, suggests that every patient at the initiation of dialysis should be evaluated for the presence or absence of PAD. Our diabetic patients especially are at risk.

I'm not going to review slides that have already been talked about but the mortality and morbidity of these patients is very profound.

What we also see from the patient's

perspective in our patient engagement scores on CAPS type surveys are about 90 percent, but we see much obesity, we see 60 percent of the ESRD population being diabetic, and since so many are at risk, they often are second generation, their mothers or fathers had amputations, and many died on dialysis, and we find that less than five percent of our patients have regular PAD care.

So again, we do have very good outcomes. I will say that one of the things about freestanding outcomes, I do want to give disclosure that we do have a certain percentage in our group that actually goes for medical reasons to other places and that less than, about 45 percent of our patients actually require no intervention at all, patients that are referred to us.

This is the KDOQI, the renal guideline

on PAD. For those of you who aren't familiar with it, we are doing our best to educate the renal community about it.

And our conclusion is that chronic kidney disease, renal patients really could benefit from a comprehensive approach from

medications to interventions, and that patient engagement is a really important factor in this, and that the program goals really should include amputation reduction, and what I always refer to, many of the things we've talked about today add years to life, but what we'd also like to do is add life to those years. Thank you.

DR. BACH: Thank you very much. Our next and final scheduled speaker is Dr. Robert Thatcher, who's the chief healthcare policy officer at Cardiovascular Systems, Inc.

I'll also tell you, we're going to have open public comments, a few people signed up for it, immediately following this, so both Leslie Wise and Richard Conray should be ready to speak immediately after this.

MR. THATCHER: Thank you, Dr. Bach,

panel members, and CMS for the opportunity to speak today. I'm Bob Thatcher, I'm the chief healthcare policy officer for CSI and am an employee of the company. I want to tell the audience that the almost 700 employees at CSI work every day on behalf of physicians, hospitals, public and private payers and

patients who have a common goal of treating PAD in the most clinically and economically beneficial way possible.

We've heard much today about the PAD disease state. This slide depicts the prevalence of PAD in the United States and the fact that it ranks third behind kidney disease and diabetes, and while about 18 million people are affected by PAD in this country, a small percentage are diagnosed and even fewer are treated, as we've heard.

As we've heard today, CLI is the most severe form of PAD and these patients, if they're not revascularized, amputation rates of 40 percent and mortality rates of 20 percent occur, often within six months, and the macroeconomic burden, not just the index

procedure, exceeds a staggering $10 billion. A sad and dire commentary is the fact that amputation is the first and only therapy for over 60 percent of the CLI patients that present in this country. A majority of these patients never have any form of vascular diagnostic imaging prior to the amputation to see if the leg can be saved.

We note some key differences in CLI patients who are revascularized versus those who have amputations. Some of these have been highlighted before by other speakers, one-year mortality for Medicare beneficiaries is 48 percent and three-year mortality is 71 percent, versus two-year mortality of only 16 to 24 percent for those who are revascularized. 70 percent of amputation patients go on to an extended care facility versus only 20 percent who are revascularized, and 60 to 80 percent of amputees are unable to walk again, compared to two-year revascularization data showing 80 percent of these patients are walking and 90 percent of them are living independently.

And while the clinical and economic

outcomes for those amputated are shocking, the number of nontraumatic amputations performed each year is alarming. To put it in perspective, we amputate annually more legs in the United States than the combination of all amputations in every war or conflict since the U.S. Civil War, every single year.

The good news is we can dramatically reduce the percentage of amputations. Others

have talked about this. This is a single center experience in a community hospital where they've done two simple things. They basically had a multidisciplinary approach where every nontraumatic amputation is reviewed by a group of physicians from different specialty areas before the amputation occurs. And secondly, there's an angiogram or some form of vascular diagnostic imaging to see if the leg can be saved. While it sounds simple, it's not being applied today in most hospitals.

A new payment model from CMS which requires these two simple things to be implemented prior to any nontraumatic amputation will be the paradigm shift required

to dramatically reduce amputations in the United States. So we'd ask the panel to suggest via the meeting minutes that CMS look into a new payment model for amputation prevention, and if you choose not to do so, we would ask that a separate MedCAC meeting be held to review the level of evidence associated with lower extremity amputations in the United States today. Thank you very much.

DR. BACH: Thank you very much. Could

I ask Leslie Wise to come to this microphone right here in front of me? Thank you. And each of the speakers in this category of open public comment, each have one minute to speak.

MS. WISE: Hello. My name is Leslie Wise. I'm the vice president of global healthcare economics for AngioDynamics but actually I'm here today sort of just as a member of the public. I happen to know a lot about PAD because I worked in the industry for a long time and I used to work for Bristol-Myers Squibb when they launched their PAD indication for Plavix, and have worked on a number of other products in this space.

But I've grown up in a community where I saw my grandmother have her feet cut on and cut on and cut on until they went above her knee, and I've seen many many other people, so the issue of disparity in this disease state is really real. And I personally don't think there's an asymptomatic patient. I think we have not identified the symptoms they experience and I really think, and I implore CMS to consider that.

Today very often we tell patients, are

their feet pale? Every picture I've seen up there today, there was not one person that was of color, yet the burden of amputation in the African American male population is five times the national average. If we don't tell doctors how to recognize it, we'll continue to think it's asymptomatic. So I make the analogy to, we used to say that women just had silent heart attacks, women didn't have symptoms, because everything in the literature had done their research on men, and we looked for the symptoms that men experienced. Well, I'm telling you now, we know that women have their own set of

symptoms and they're real, they never were asymptomatic.

So, I just want to wrap it up there and just implore you guys to think about moving away from asymptomatic and to looking for what the actual symptoms are.

DR. BACH: Could I hold you one second? Thank you for the comments, which are deeply appreciated. Just a process issue. Can you tell us who paid for your transportation to this meeting?

MS. WISE: AngioDynamics.

DR. BACH: Great, thank you, and thank you for your comments.

May I have Richard Conray, from Around and About?

DR. CONRAY: Thank you for the privilege of being here. My name is Richard Conray, I have a family of Around and About, prosthetics, orthotics and physical therapy, and I've been in the physical fitness field, was a Jack LaLanne mentor for 50 years. I've built and designed spas all over the world and been on TV and radio shows all over the world

as well.

I'm here representing a gentleman that became a friend and also, the king of Sweden spent one million and a half to do a study on this gentleman who had a very bad disorder of circulatory problems. We became a friend of his, we helped him design and put Aqua Pulse International together, it's a revascular program, and we had it fully patented in the United States of America just recently.

This unit is now available that can be made and designed to cut down 47 to 50 percent of the problems with, the circulatory problems

that are causing all the problems, that we're having the diseases of circulation. I only have a moment here to speak but --

DR. BACH: Yes, please wrap up, actually.

MR. CONRAY: -- anyone interested in finding out more about it, take one of my business cards, we'll send you the research and report from the Kalinski Institute in Sweden and the famous physicians that did the study with him if you would like that information.

And also, this is cost effective for Medicare.

DR. BACH: Thank you very much. Can you tell us about your transportation expenses as well.

MR. CONRAY: I'm sorry?

DR. BACH: Who paid for your trip here?

MR. CONRAY: Our own company paid for it, we sponsored ourselves. I have a family-owned company called Around and About in Fort Lauderdale Plantation, Florida.

DR. BACH: Thank you very much, and thank you all for your patience this morning and for the excellent series of presentations.

We are going to -- we are ahead of schedule and I will be militant about maintaining that small advantage. It is now 11:37, we are breaking for lunch. We are, that puts us 13 minutes ahead of schedule. We will be back here at 12:22, we will begin the discussion.

(Luncheon recess.)

DR. BACH: Thank you very much, I hope everyone enjoyed their lunch. We're going to start the afternoon session. A small change to

the agenda, where I've added a break. There's two components here, the panel will ask questions of the presenters who have been nice enough to sit here in the front row or near the microphone here in front of me, and then we will have an open discussion in the tradition of a FACA committee, between one another. After that we're going to take a ten-minute break, which I'm estimating to happen at about 2:15, so we'll obviously see how this all goes.

I would just ask that as we ask questions of presenters, I've spoken with the panel in advance and also today, to ask questions that are precise as opposed to making statements. I will similarly ask the

presenters, there will be ample opportunity to provide more answers, but please provide answers, not sort of use the mic as open mic night, if you will, unless you have something really exciting to say and you're not a Wolverines fan.

So anyway, I will start with Dr. Carr, with questions from the panel, and then can I ask members of the panel, since it's hard for

me from here, just turn your tent card so I know you have a question.

DR. J.J. CARR: This is for Dr. Beckman from the American Heart Association.

DR. BACH: I'm sorry, Dr. Beckman is actually the only speaker who is no longer here.

DR. J.J. CARR: Okay. Then probably, let me go through the presentation -- well, how about Bartholomew? So the question is, we saw a lot of data on asymptomatic peripheral arterial disease as being underdiagnosed, and what are the opportunities for further refining that? In the public comment there was one individual that stated that she believed that

some of that was undiagnosed, that there really were symptoms in that. So I guess the question for you is, what is the feeling for further identification of people with asymptomatic peripheral arterial diseases, and are there primary and secondary prevention strategies that might work?

DR. BARTHOLOMEW: So, I think one

thing is, what is asymptomatic, and, you know, peripheral artery disease, we always think of these symptoms as intermittent claudication, but the majority of patients, as you've heard today, don't necessarily have intermittent claudication or for the audience, that's usually described as pain with walking, or discomfort, usually in the calf or buttocks or thighs with walking.

So I think one thing that we might need to do is also to educate physicians and caregivers in how to perform the ABI, at least to make that diagnosis, because I don't think everyone knows how to do that. Or, another simple thing that I know that some colleagues of mine have done, is to educate caregivers how to detect a pulse, simply by teaching them the

simple procedure of palpating a pulse in the dorsal pedis and the posterior tibial artery. So, I think those are a couple of things that one could do to educate the public more on what is PAD.

And as far as asymptomatic PAD, in answering your second part of the question, I

guess we would define that as an ABI less than 0.90 as asymptomatic PAD by my criteria, but I think that some of the things that can be done to prevent complications are not only once you recognize that, but perhaps to certainly monitor the individual's blood pressure, check the lipid panel, and advise him to quit smoking, but certainly the guidelines suggest if you had officially diagnosed with PAD you'd want to get the LDL cholesterol under 70, you'd want to make sure their blood pressure was 140 over 90 or lower, you'd want them to quit smoking, you would like them to follow a good diet, a low cholesterol diet, and exercise regularly. Did that answer your question?

DR. J.J. CARR: Thank you.

DR. BACH: Okay. Please introduce yourself, Joe.

DR. CHIN: Joe CHIN, deputy director of the coverage group. I just wanted to clarify a comment about the ABI, specifically for screening in asymptomatic patients. Under our authority, Medicare's authority to cover preventive services, one of the criteria is an A or

B grade from the Task Force, U.S. Preventative Services Task Force, and also through an NCD it has to be reasonable and necessary and appropriate for the Medicare population for us to actually cover specific screening with ABI. Right now it's not recommended by the Task Force so there is no mechanism right now to cover screening for peripheral artery disease with random ABI.

DR. J.J. CARR: Can I ask you a quick follow-up question?

DR. CHIN: Please.

DR. J.J. CARR: If somebody doesn't have a pulse, that would mean that it was then a diagnostic test under your reasoning?

DR. CHIN: Right. So typically the way we define asymptomatic is there is no sign or symptoms of that specific disease, so basically if you're not detecting a sign or symptom, that's how we classify it, if through

a regular exam you have a finding, for example a wound or an ulceration, and did an examination to detect a lower reduced pulse, that's diagnostic.

THE COURT: Dr. Deyo, question?

DR. DEYO: Yeah, a question for Drs. Jones and Patel. You reviewed the efficacy of a couple of different types of medications, but there are some things that I see coming up in various guidelines, including ACE inhibitors, statins and so forth, that you didn't cover. And I'm just wondering if you're aware of clinical trials of those agents for, specifically for peripheral artery disease.

DR. PATEL: So, I think Schuyler, you can jump in, but the guidelines are based on several cohorts of patients with PAD in larger cohort studies that have coronary artery disease that was being evaluated. So for example ACE inhibitors, some of that data is from the HOPE trial where ACE inhibitors were used in diabetic patients, some of whom had PAD, and so they're subgroup analyses of that data.

Data for specific populations where it

was just studied as a primary prevention in only PAD patients diagnosed with an ABI or something, I'm not sure of a direct large cohort study. Aside from some of the

antiplatelet studies we discussed, statin and the ACE inhibitor data is based on larger trial data where PAD was represented as cohorts of that population. Does that answer your question?

DR. DEYO: So it sounds like evidence is mostly from other types of vascular disease?

DR. PATEL: Certainly there was, like you've heard for a lot of primary prevention, or secondary prevention, PAD observationally has been known to be a cardiovascular risk equivalent, and then as you said, observations of other trials with patients that have a broader population than just PAD, but some of them might obviously be undiagnosed with that.

DR. DEYO: Thank you.

DR. BACH: Dr. Lefevre, can you put up your tent card if you have a question? Dr. Zuckerman, please.

DR. ZUCKERMAN: Also for the AHRQ center, you had so much data it was very hard

to keep track of everything. I did have a question about when there's inconsistency between data showing improved quality of life,

and I think we would all agree, quality of life is very important, but quality of life and pain, both being very subjective compared to some of the other measures, and were you able to have any, a determination of placebo effect where there was a control adequate to get a better sense of to what extent when there were inconsistencies, it had to do potentially with a placebo effect, as opposed to an impact of the actual intervention?

DR. JONES: Thanks for the question. I think, when we really constructed the questions it was hard to figure out how to evaluate differences in usual care and/or placebo, compared to the interventions. So what we had to do based on the available evidence was actually look at specific interventions compared to those things. There was no clear evidence that a placebo effect exited. However, we all know that in many of these cases they do, we just weren't able to detect that. And so along with heterogeneity,

along with mixed populations, it was very difficult to tease that out. I'm not sure that

answered your question, but that was the difficulty in trying to determine that.

DR. ZUCKERMAN: So, just to follow up, so it sounds like you didn't try to take that into consideration as you interpreted the strength of the relationship?

DR. JONES: Right. I guess what I would say is that qualitatively we were able to determine that there was a likelihood of that, but quantitatively there were no methods of fixed effects or a network meta-analysis that we could do.

DR. ZUCKERMAN: And if I may, I had another question for you, and that had to do with some of the -- I just want to make sure I was clear that when you updated your analysis and you looked at new studies, and you didn't look at them exactly the same way, you didn't include them in a meta-analysis, you just looked at them. So I'm assuming that when you looked at which studies were the best and so on, that the results were consistent with the previous results, otherwise you would have said

so?

DR. JONES: So, one of my slides said there was limited evidence to suggest that there was, that new evidence would suggest a difference in what we found given the comparisons that we made and given the fact that three months ago we didn't know this was occurring, so we did a very, I'd say rapid review of the almost 2,000 articles in a qualitative, not quantitative review of that evidence, but from a qualitative standpoint, I would say it does not suggest that we would have concluded anything differently.

DR. PATEL: Just to make one clarification too, our analysis was very specific at comparative strategies of endovascular versus medical or endovascular plus exercise, so some of the data that was excluded may have been newer therapies within one strategy, so that I think should be clear. The second is, I think another way of saying qualitatively is to say that we wouldn't have suggested from the data that the point estimate was going to change qualitatively.

DR. BACH: Dr. Cuyjet.

DR. CUYJET: I have two questions, one for Dr. Ansel, who kind of tweaked my curiosity. I did not know that Italy has the lowest amputation rate in the entire world, but it reminded me of Ancel Keys' original seven-country study from the late '40s or early '50s where they plotted cardiovascular disease from the Mediterranean to north of Finland and came up with a saturated fat diet.

So, is there an explanation for why Italy has such a low rate, is it diet related, is it lifestyle-related, what's the explanation for that, if we know?

DR. ANSEL: Thank you very much. So, Italy has three hospitals that focus on critical limb ischemia for the entire country, so they're high volume institutions that do exactly what we've been talking about here, which is use a cooperative integrated approach between the different specialties. So these patients have very focused clinics, but they're very aggressive and their number of endovascular procedures has skyrocketed in the last few years. They've actually led the world in how to get through these small vessels,

they've been teaching us how to go through toe vessels to get blockages opened up, so it's a very aggressive country from that standpoint.

DR. CUYJET: Okay. And the second question relates to, I guess Dr. Cronenwett can answer this best. In my former life I was the chairman for an institute for health equity in Nassau County in Long Island. Depending on whose numbers you believe, Nassau is either 10th or 11th in the country in terms of median income, so it's a very wealthy county. But within that county we have communities, predominantly African American communities like Roosevelt and Hempstead, and Uniondale, where the lower extremity amputation rate was 2.8 times compared to the North Shore LIJ Health System. So I've seen these maps where the amputation rates are high.

It's not frequently appreciated, but about 70 percent of U.S. blacks live in 10 percent of the U.S. ZIP codes, about 3,000 ZIP codes. If anybody has a map of those areas of high incidence of amputation rates with the ZIP codes, and what the demographics of the ZIP codes are, and if that holds up, Gary Puffin

has done some interesting stuff with this, but the Vascular Quality Initiative looks like a method, and I'll put my public health hat on now, where primary prevention beats everything else out of the gate in terms of secondary and tertiary interventions. So, has anybody looked at that data to look at it?

DR. ANSEL: I don't have an answer but these guys are pointing to each other, so I will let them do that.

Dr. Cronenwett: There are, as you saw this morning, there were several slides presented that correlated both race, socioeconomic status and amputation rate, and that's been done by several people and there's a pretty high correlation across the U.S. The explanations aren't completely clear about whether it's late presentation or late diagnosis, or other biologic factors, but at VQI we do have the ability to look at patients' ZIP code and obviously race ethnicity, and correlate it with imputed socioeconomic factors to try to answer some of these questions, but we haven't focused on that yet as a particular initiative.

DR. CUYJET: Can I just ask, one of

the things we've found is people refer to access and there's two different kinds of access. One is when you get your foot in the door, the other access is what happens on the other side of the door, and so that's why your intervention tweaked my interest, because that's where the rubber hits the road in terms of what happens to the patient when they access and have an encounter with the health care provider.

Dr. Cronenwett: It's a great question and a great opportunity for us to look at.

DR. CUYJET: Okay.

DR. BACH: Thank you. Can I ask panelists if you asked your question to put your tent card down, and if you have additional questions, that's great. Dr. Campos Outcalt.

DR. CAMPOS OUTCALT: Yeah, I have a question for Dr. Jones and Patel, and then a question, a follow-up question after they respond to that, my first question, and my next question will be for Dr. Turco.

So, Dr. Turco mentioned a number of studies that he felt were not included in your

25 assessment. Could you comment on his comments,

1 please?
2 DR. PATEL: This should get exciting,
3 I think. So, I think rightly so, Dr. Turco is
4 pointing to several studies that have occurred
5 in the last few years where specific
6 interventions, potentially in the endovascular
7 space, were compared against each other in a
8 fairly rigorous fashion. As I stated, I think
9 just a few moments ago, our analysis starting
10 with AHRQ in 2012 and even our update, was
11 looking at sort of larger strategies, looking
12 at endovascular plus exercise therapy versus,
13 say, exercise therapy alone.
14 So when we did the update, we saw some
15 of those randomized trials and others, but they
16 were excluded as they would have been excluded
17 from 2008 to 2012, again, because they didn't
18 meet the key questions that we were addressing
19 during that time. It should be important to
20 recognize that the AHRQ evidence base doesn't
21 speak to specific interventions within, say,
22 endovascular, surgery, or other types of
23 potential interventions.

DR. CAMPOS-OUTCALT: So my question, then, to Dr. Turco is, you mentioned that there

are, I forget the number of studies that you mentioned, and then you said they were rated as Level I evidence. I would like to know what criteria you used to get to Level I evidence, who made that assessment, and whether that assessment is open to scrutiny from outside groups.

DR. TURCO: So what we had looked at, and thank you for the question, was since the AHRQ report that came out in 2013, 2012 was the stop of where, the cutoff of the studies that Dr. Jones and Dr. Patel looked at. There were 35 additional studies. Of those 35, 20 studies looked at endovascular versus endovascular interventional procedures, and they were excluded by definition because it was not comparing to, it was comparing to another comparative treatment group.

So there are 20 studies just in the newer endovascular treatments that were excluded from that, you know, that data set, which I think is critically important when you

folks deliberate and look at that data. Of those 20 studies, all of them met every other criteria for inclusion from rigor within the

AHRQ data, so they would have all met Level I evidence, and rigor as randomized controlled trials, that fit the criteria for the AHRQ.

DR. CAMPOS-OUTCALT: And who conducted that assessment, and is it open for review?

DR. TURCO: We could provide it for review. What we did as the consortium of the five companies that worked together, we actually asked Boston HealthCare to basically conduct that independent assessment, and they provided that independent assessment to us for review and then presentation here today. And I can check as to whether we can provide all of those, that data set to you, and I think we should be able to do that.

DR. CAMPOS-OUTCALT: And what level of PAD were those studies on?

DR. TURCO: So it goes across the board, intermittent claudication, chronic limb ischemia, and then also a mixed population of chronic limb ischemia and intermittent

claudication, so it was across the board in all three categories of those patient populations.

DR. BACH: And actually, can I ask a followup? I'm just trying to understand within

those endovascular intervention studies, I'm not going to try to put words in your mouth, I'm going to throw out an idea and then you tell me if I've got it all wrong. Are you saying that the new -- let me just -- newer devices that would constitute one or more arms of these trials relative to the comparator, would move the mean effect within the category such that the AHRQ report would have a different approach? Another way of saying it, you're saying that endovascular interventions are better on net because of these new devices to an extent that (inaudible).

DR. TURCO: So, just one thing. Dr. Patel and Dr. Jones did a great job with this report. So we would need, one would need to go back and do that assessment looking at the results of those particular trials. I would assume, and it's my own personal feeling that the level of evidence would change in the

AHRQ report if we were to add in some of those missing pieces of information. Again, that's almost 25,000 patients that could have been added back in.

Now, the other point to consider,

which was one of my next to last slides, is that there are 9,000 patients almost that are being studied, close to 9,000 patients on even newer technologies, with those trials looking to endpoints out to five years, so truly durable results out to five years. So that could be an additional 9,000 patients that are added to the information pool and evidence pool looking at intermittent claudication and critical limb ischemia.

DR. SALIVE: Can I ask a follow-up question?

DR. BACH: Sure. Is your follow-up question on the same topic?

DR. SALIVE: Yes.

DR. BACH: Okay. We can go ahead.

DR. SALIVE: So, I did appreciate, Dr. Turco, the comment you just made about the ongoing trials for newer technologies, but I

looked at your slides, and many of those studies are not randomized trials, and could you comment on why that is the case? They are mainly one-armed studies, I guess, of the device under investigation.

DR. TURCO: So, I can only -- it's

hard for me to comment on all of the other industry trials. If you have a particular trial in mind, we do have representatives from Bard and Gore, Boston Scientific and Abbott here that can comment. I can certainly comment if you have a specific question about one of the trials that is a Medtronic-sponsored trial.

DR. SALIVE: Okay. You listed 35 trials or something that are ongoing, and I appreciate that, and you said there are 9,000 patients in these trials, but most of them are not trials and most of them are observational studies, and one is very much driving that 9,000 number and I think it's one of yours, of 5,000 right there. So many of them are small single-armed studies, not randomized trials, so I'm not sure why you think that would drive some of this.

DR. TURCO: Well, I think, again, we have two separate topics, we have the newer trials and then we have the body of evidence that is already in the literature that is peer reviewed from 2012 to the current time, so we would have to see what happens with the newer body of evidence, but we do have 25,000

patients, patient level evidence of rigorous evaluation that could be added in to the totals.

With regards to your question, I agree with you, some of those trials are observation and single-armed trials, but there are also trials in there that are randomized and meet the rigorous criteria that AHRQ has set forward, and I think are worthy of inclusion and consideration.

DR. SALIVE: One last question.

DR. BACH: Marcel, hold on. Dr. Jones has something to say as well.

DR. JONES: I'd just like to say, I don't disagree at all with Dr. Turco. This is about how you slice the pie, slice the data. So when we were asked by AHRQ to do this

evidence review, if we had five years and 50 people and $500 million to slice this data, we could have sliced it in every single way and looked at each of the comparisons. We did very broad strokes or very big pieces of pie to look at the comparisons that we presented, and part of this I think may have been how I presented it.

We also did a separate review of supervised exercise and home exercise, which is a subtopic. We could have done angioplasty versus stenting versus atherectomy as a separate topic. We could have done surgical techniques as a separate topic. So this is how you slice the data as much as it is about the data itself.

DR. BACH: Thank you. Dr. Swain.

DR. SALIVE: I had one last question --

DR. BACH: Oh, I'm sorry. Go ahead.

DR. SALIVE: -- about the small studies of new investigational devices. So, it would seem to me that those would only provide safety data. Is that true, or are they really

going to provide some data on effectiveness of the device?

DR. TURCO: It's hard to take a broad swath without looking at each individual study that you want, you know, are trying to consider. You know, certainly if these studies, you know, are -- you have to look at both safety and efficacy if we're trying to change a label or trying to get a United States

approval, so I think some of those would probably be looking at both aspects. If it's just kind of a postmarket evaluation that is in that list, then in particular that may be looking purely at a safety indication.

But I mean, your questions, I think are very valid. I would, however, suggest that the large pool of evidence there since 2012 does have some rigorously controlled trials that if we just exclude those patients with new endovascular evaluations, I think it would give us a misleading interpretation of the level of evidence that's available for our patient sufferers.

DR. BACH: Thank you. My apologies,

Dr. Salive. Dr. Kormos is next.

DR. KORMOS: Thank you. I enjoyed this today, this was really an eye opener, but it opened my eyes to a greater problem in cardiovascular disease, and my question relates to the first challenge that we have in asymptomatic peripheral vascular disease, and I'm going to direct my question to Dr. Bartholomew if he's here.

You gave a very impassioned plea for

us to take a closer look at the fact that undiagnosed peripheral vascular disease is rampant, and I'm gathering that argument was made because we need to look for it, and to look for it, you know, ABI is probably the only thing that you have right now that would do that. But my question to you is, are we looking at ABI as a surrogate marker for cardiovascular disease in general? Because what people are dying from aren't their legs necessarily, but if you find something on an ABI, they're dying from cardiovascular disease and strokes and other things.

So I'm trying to put this together.

There's a little bit of a disconnect here. How do you present this case for a better study or assessment of cardiovascular disease in patients such as those that smoke and they have diabetes, they're obese, et cetera, et cetera, because isn't that really the challenge, to pick this up in some way that you can then add the lifestyle modifications that you're going to do if you picked up an ABI that was abnormal?

Because what I'm a little bit thinking

as a second part of my question is, how do you keep people from doing something when you have an abnormal ABI, how do you keep that chain going down the road and then doing an angiogram, doing a vascular study, and then someone says oh, there's a 50 percent lesion, let's open it up? I know there are guidelines, but there's also a rampant increase in these procedures.

So the first question is, is this, are you using ABI as a marker for cardiovascular disease, or is this specific to the vascular problem?

DR. BARTHOLOMEW: Well, we routinely perform an ABI in our vascular medicine clinic on all our patients and we, again, use it as a marker for pan vascular disease. I mean, we think of each individual who has an abnormal ABI as likely having some cardiac problem or disease, or even cardiovascular disease, or even cerebrovascular disease. So, I'm not sure that I'm answering that exactly how you wanted it, but that's how I work with my patients with abnormal ABI.

Now, that being said, I always go back

to a careful and extreme physical exam as well, so if we're thinking about any type of intervention, if they're asymptomatic for their PAD, certainly that individual does not need an intervention for their lower extremities, certainly at that point. But on the other hand, if the ABI is abnormal and they do have claudication or do have a nonhealing ulcer, that would be a different story.

As far as looking at the rest of their anatomy, I mean, their heart or their carotid vessels, again, I think a careful history is

important, and questioning the patient about any cerebrovascular symptoms to see if there is a suggestion of carotid disease, loss of vision, difficulty with speech, arm or leg weakness or anything of that line, and then again, a careful history of their cardiac status as well.

So, again, an ABI may be an indication that that patient has pan vascular disease if it's abnormal.

DR. KORMOS: But you're doing this in a vascular clinic?

DR. BARTHOLOMEW: Uh-huh.

DR. KORMOS: If this gets approved, are you going to say it's approved for use in a vascular clinic, or is it going to be approved for general medicine and general practitioners, where you're going to get millions of ABIs being done because it's paid for, but the question is, then what do you do with it?

DR. BARTHOLOMEW: Well, again, I think it doesn't have to be done in a vascular clinic, I think maybe, if I can use Dr. Hirsch as an example, he's long promoted the use of an

ABI for internists, family practitioners and other individuals. It's a very simple test to do, but I think it gives us a lot of information by having that abnormal ABI, so I think that knowing that there is peripheral arterial disease, again, translates into the thought that that individual may have pan vascular disease.

DR. BACH: Rick, can I come back to you? Dr. Swain is next.

DR. SWAIN: Yeah, an interesting conversation there. I do have a question for Dr. Turco, but for you, the question is, you know, you have an asymptomatic patient --

DR. BACH: Should we get him a chair?

DR. SWAIN: Yeah.

DR. BARTHOLOMEW: I'm from Michigan, by the way.

DR. SWAIN: -- asymptomatic patients that get ABIs, and then you tell us that many patients don't have typical claudication, limitations with walking. Some, and I could elicit, I'm sure, a symptom from every person in this audience of something relating to their

legs. So you have the practitioners, primary care practitioners who get an ABI and there is something related to, your legs jump or something, you don't think that's going to lead to overuse?

And it's not like atypical angina, as a cardiovascular surgeon I can tell you, that's different, you can't compare it to that, so it seems to be an issue.

DR. BARTHOLOMEW: Well, I actually think this should be part of a physical exam that patients perform. If you're going to do a complete physical on an individual, I think it's such an easy test to do but it has a lot of rewards if it is abnormal, so again, I'm

going back to saying I think general doctors should do it, internists, advanced practice nurses. And I don't know, will it really result in overuse? I don't know how you can overuse something that has so much information, how could one overuse that test?

DR. SWAIN: Well, overuse of what that might lead to.

DR. BARTHOLOMEW: Oh, I see. Well

then, more education must come with that, and that means that just because the abnormal -- I can remember actually going back to my first day at my job, and I'm a hematologist by training, and where I went in Michigan they didn't have enough work for me so they sent me off to a general clinic, and I went in and I tried to feel the pulses on this person's legs and I couldn't feel them, so I panicked and called a vascular surgeon. He said don't worry about it, take a good history and physical, and he said do an ABI. Well, I don't think I even knew what an ABI was at that time, but -- and I said, well, gee, ABI, what is that, and he translated it for me in English and I was able to understand, and I performed it, and

certainly I felt more reassured.

So I think, again, education must go along, but I think the ABI is a very valuable tool.

DR. SWAIN: So the question I --

DR. BACH: Hold on, Dr. Swain. Rick, did you have, Dr. Deyo, did you have a followup on that?

DR. DEYO: A quick followup to that. As a primary care doc I routinely ask essentially every patient, do you smoke, and I follow guidelines for screening for diabetes, for high cholesterol, for hypertension, and I intervene with all of those things when I find them. What would I do differently because the ABI is abnormal, above and beyond those things?

DR. BARTHOLOMEW: Well, again, that implies that the patient has vascular disease and I think that, you know, many people smoke, they think nothing is going to happen to me, my cholesterol is a little bit high, I'm overweight, I don't exercise. But if you tell them that they have peripheral arterial disease, first of all, they won't know it because they don't recognize it. If you'll

recall in my slide, 80 percent of people don't know what PAD is. But then as you explain to them that this is a pan vascular disease and may imply they have a more serious problem, I think that may make a difference. You have a marker for them, you have something that you can put down that says your ABI is abnormal,

that means you have some blockage.

DR. DEYO: So the interventions are the same but you think the compliance from patients would be better?

DR. BACH: If the test results in a behavioral intervention.

DR. BARTHOLOMEW: I think it might.

DR. J.J. CARR: Let me just -- the AHA guidelines, ACC guidelines, 2013, if the risk, if you have a risk marker for coronary artery disease then you might intensify to statin therapy or a variety of things, so documenting the presence of subclinical disease could change the dynamics, and Alan, if you'd like to --

DR. HIRSCH: I'd be happy to make a comment.

DR. BACH: Wait, Alan, I want to try

and maintain some sequence based on questions, but we will have a chance to come back, of course, to these things, so I hope that's all right. Dr. Lefevre was next.

DR. LEFEVRE: So I had a question, actually two questions about the populations in

these studies, one for question one and one for question two. So I'm trying to understand the results in terms of, in relation to the populations in the studies. So in question one we're asked about the efficacy of antiplatelet agents in asymptomatic PAD, so my question is, Dr. Jones and Dr. Patel, in these studies, were these simply healthy patients or patients in the general population who were then screened for PAD and found to have asymptomatic PAD without other risk factors, or were they somehow chosen first for other risk factors? And the reason I ask is this is because I think what we know about antiplatelet agents is they have some efficacy for preventing coronary events. We know they work better in secondary prevention than primary prevention. We know probably that your risk of coronary disease is probably a big factor in whether they work.

So I'm trying to understand, the risk of these patients in the population, were they patients with an average ABI of .9 without other risk factors or were they very severe PAD patients, a lot of risk factors, and would that

have influenced, do you think that might have influenced the results?

And the second comment I had is, the difference between those studies and the secondary analysis of the RCTs like the CAPRIE study which, I assume the CAPRIE study was patients with CAD, if I'm not mistaken. So those were, again, patients with CAD plus PAD, which is probably a particularly severe population. And so I'm wondering if you can say something about the effect in those studies in relation to the population, and do you think there was an influence there?

DR. JONES: Sure. So, because of our effort to identify modifiers of effectiveness, we looked at all of those things. Unfortunately, they're poorly characterized in many of these studies. What I will say is that PAD was used as a risk enrichment criteria in many of these cases. To get into these

studies, you're right, the CAPRIE and other studies, they involved patients with vascular disease or coronary disease, or both.

DR. PATEL: If I might, so for the

aspirin versus placebo asymptomatic patient trials, it wasn't just an ABI, it could be risk of enhancement, so it could be that they had diabetes, hypertension and the diagnosis of PAD, for example, or patients that were felt to be at risk for atherosclerotic events because of age, so there's a broad inclusion set of criteria, some of which included PAD, defined variably across the trials which were put together.

For CAPRIE, that's a secondary study from a larger randomized control trial where patients, some had prior MI, some had prior stroke, some had PAD. The PAD patients had overlap sometimes with other vascular diseases and there were probably a few patients that just had PAD there too, so the subgroup, again, represents an amalgam.

We didn't find a statistical finding that we could show because it's poorly characterized, as Dr. Jones has said, about the

disease severity. We've showed you other observational data around disease severity but in those studies, again, because of the way

they were characterized, there's not a tremendous information on lower ABI, more symptomatic patients, and let's say antiplatelet agents.

DR. LEFEVRE: And in those studies you would get, in those asymptomatic PAD patients, there was a range of severity, and that makes sense.

DR. PATEL: That's right, and so it's not that we can give you such a well characterized asymptomatic patient population that's been described.

And to Dr. Carr's point, simply that, again, from the secondary statin studies and others, PAD is considered a CAD risk equivalent so if you did identify it, you might push their LDL target lower or use more of a high intensity statin.

DR. LEFEVRE: So, my second question is about the populations in key question two. This relates to the studies that compared exercise with interventional therapy, and my

question is, I mean, the guidelines for interventional therapy are, obviously, that you

have to fail exercise first. So my question in these studies, are these patients who initially present with symptomatic PAD and then you choose a treatment, either nonoperative or operative, or are these patients who have already failed exercise therapy and then are randomized to either continued exercise therapy or intervention? I think that would be very different.

DR. JONES: To give you a background, some of our technical expert panel is actually in this room, who helped us form this question. What we really wanted to look at are these patients who underwent exercise and failed, and therefore this treatment strategy is what we were comparing. We couldn't find it. There just wasn't available trial evidence or study evidence to look at those specific things. And so when you look at the ACC guidelines it's failed to benefit from either medication or exercise, or the risk-benefit ratio favored revascularization. And so I would say in many of these cases, we don't know if they had

failed exercise and then went on to

endovascular. All we were able to do was when they actually stated their rules and stated their results and methods, say that these were endovascular and exercise, and this was exercise, and compared those findings, or endovascular versus exercise, so on and so forth.

DR. PATEL: That's exactly right, and I just might say one thing. It seems less likely that they're going to be failed exercise patients because we believe that investigators would likely document that or describe that for us. So we don't have it documented and can't say either way. But if you went to the trouble of ensuring the patients failed supervised exercise, you would likely produce that information in your journal article, because we believe that would raise the impact that showed you're being guideline-based.

And then secondly, as many people mentioned, supervised exercise has not been reimbursed, and so a lot of this trial evidence is probably based on clinical practice.

DR. BACH: Dr. Lawrence, please.

DR. LAWRENCE: Yeah. From the perspective of the public and many of our specialists and specialty societies who presented here, there has been a great concern about the overuse of procedures, particularly in patients with claudication. So I'd just like to ask Dr. Carr questions related to the freestanding centers that he mentioned that he represents, and just a philosophy about whether or not you believe that all specialists should be able to treat PAD, if you were a primary care physician or an interventional nephrologist, or a psychiatrist. My understanding is in a freestanding center that there aren't the same privileging criteria as there are in a hospital.

So first, who do you think should be treating these patients, and secondly, as far as practice guidelines or standards, do you believe that there's a certain range of ABIs that should be used as criteria as well as symptoms of leg pain, to control the overuse of procedures, particularly for claudication?

DR. J. CARR: Well, thank you for your question, it's an excellent question. The

reason I stand here is because we care about that, and we established a society to do exactly that. As you know, the office space, the interventional space has grown over the last several years, and many like-minded physicians came together to establish guidelines, to establish standards and to set the bar, and we feel very strongly as a society at OEIS that we set the bar and match the established guidelines in proof of therapy.

As far as other participants, certain qualified physicians should be performing these procedures by all means, and most of our physicians are members of established societies represented in this room already. We follow and adopt those. We don't have a mandate yet, because we're new. We have designs on creating our societal standards for an office-based location site of service, because we know that presents unique needs and controls, and insurance that the patient is safe and secure, to have an effective safe outcome, so that is in the works right now.

We have established statements of quality and we have encouraged accreditation of

every facility that is operating. We are moving toward more and more of a certification process, but again, we're young, and we're moving very quickly in that regard.

DR. LAWRENCE: So just to follow up to be clear, should CMS be reimbursing someone who has had no training in vascular disease management or procedural endovascular? I'll just use as an extreme a psychiatrist or, you know, someone who we know has had absolutely no training in that, does your society believe that those people should have privileges or be allowed to do them in a freestanding facility, or should they have to join a society or demonstrate expertise before getting reimbursed by the federal government for endovascular procedures?

DR. J. CARR: We firmly believe that operators should all be trained, formally trained in these endovascular procedures in an office setting, we clearly believe in that. There are established specialties that warrant that and have training programs, and there are certainly outliers that are entering in this space that we're very careful to assess their

qualifications, but I believe everyone should be qualified if they go through a training program. We have vascular medicine folks that get into an interventional program, and are we going to restrict them because of the type of specialty? I think you need to prove adequate accredited training to do this, and I think as far as reimbursement goes, I think what we hold for institutions should be mandated for everyone, and so I think we would like to partner and educate more and more about the value of this.

It's a preferred site of access for most patients because of the ease of use. We see this also as an opportunity for access. We talked about the disparity of care amongst different areas and by having office space at local interventional facilities, we believe strongly that we can assist with access. But we appreciate exactly what you're saying, and we're moving very quickly as a society to set those standards.

DR. BACH: Dr. Swain, you had another question?

25 DR. SWAIN: Yes, a followup to the

1 first set of questions with Dr. Turco. Two
2 things. One is, you mentioned that you've got
3 all these studies going, and again, registries,
4 even a couple thousand registries are not going
5 to be hugely helpful in comparative efficacy
6 and safety, but I've seen a lot of K-M curves
7 today, and only a few had confidence levels,
8 and a few less than that had Ns at five years,
9 one of them I think has N of nine patients, or
10 16 at risk, or something like that, so the idea
11 that there's five-year data available is
12 questionable.
13 Do you know how many of these patients
14 have a considerable amount of data after five
15 years, like over 50 percent of the study, so
16 can you say something about the durability?
17 DR. TURCO: Yes. So, I can speak to
18 the durability in our particular DCB trial. So
19 to give you an example, if you take the impact
20 on the Medtronic drug-coated balloon trial, we
21 will be presenting this year data out to 24
22 months, and we will continue followup on those
23 patients so, you know, as the years go we'll

have more and more data. The data's still somewhat incomplete and I think, you know, in

the PAD space we all need to realize that, you know, maybe in contradistinction a little bit to where we are in the coronary space, you know, we're still a little bit immature.

And the beauty, I think, of what I tried to show in that last slide of the 36 trials that are ongoing, nine of those 36 are truly randomized control trials looking at endovascular interventions that have mean followup out to 3.8 years, and will follow those patients anywhere between 3.8 and five years, so we just probably need to be a little bit patient to be able to get some of that long data around the durability of some of these procedures.

But if you take drug-eluting stents for the periphery, if you take certainly bare metal stent data, self-expanding bare metal stent data, if you take some of the graft data that we have, and now two-year data on drug-coated balloons, we're starting to get that longer-term data that patients want. And

if you look even at the 12-month data comparing endovascular technologies, take a look at the patency rates and the revascularization rates,

if you take just our particular DCB trial at 12 months, you see a target lesion revascularization rate that is at 2.4 percent. That's hard to beat in an intermittent claudication SFA population.

DR. SWAIN: That actually brings up a good point and your slide ten I think was the meat of it. You compared six different trials and you've got it out to .1 percent results. And unfortunately when you showed that slide, and it's not your fault, the footnote was off the bottom of the screen, you couldn't see the footnote. The footnote says, the definitions for -- these are comparing out to the .1 percent level. The definitions for primary patency and TLR windows and analysis windows were different, varied from trial to trial, and data is presented for illustrative purposes only.

What does that mean when you're presenting .1 percent? And I kind of viewed

the presentation of the Dukies for not including this so, you know, these are not data that I would view as quantitative data.

DR. TURCO: I never criticize the

Dukies except in basketball, you know, that's the only time we criticize them.

But Dr. Swain, your pushback and comments I think are valid, but realize that when we try, it's like putting together a meta-analysis, you know, you can only try to compare apples and apples. So in the consortium of folks that I stood up here today to try to represent, we have industry sponsors from five different companies that were running five different trials. We are now trying to bring uniform definitions to things like patency and so forth, so that we can understand them better.

And your point about Kaplan-Meier, is Kaplan-Meier the best way to look at some of these results, or should we be looking at other indices for patency as opposed to looking at Kaplan-Meier patency and so forth. So your point of that one slide, ten I believe it was,

you know, where it had the eight or so trials --

DR. SWAIN: Six.

DR. TURCO: Six that have very significant p values, most of them going out

to, you know, .001. They are comparing somewhat different entities, but it was illustrative of the fact that they were comparing endovascular to endovascular treatments, and they were very statistically significant.

DR. SWAIN: Yeah, and unfortunately none of it, you presented no data of patient-centered data, you know, just TLR and patency, which is, again, you know, do they live longer, function better and feel better.

DR. TURCO: And it's, again, a valid point. However, I did mention the issues of quality of life, and one of the issues when we look at quality of life in PAD studies is the confounder of repeat reintervention, so I tried to make the point, and it's hard to do everything in four minutes, but I tried to make the point that in the PTA group, those patients

who have the same level of function as the drug-coated balloon or other technology group, had upwards of nine times more repeat vascularization than patients in the other experimental arm.

So that's pretty significant to me

because one of the points that I did try to emphasize is what patients want. Patients want minimally invasive procedures, they want procedures that are durable with no complications and without repeat revascularization, and I think that's what we're all trying to do with bringing these newer endovascular technologies to the floor.

DR. SWAIN: That's very good, because that's my criticism of the primary endpoint of the BEST trial. The secondary endpoint should be the primary endpoint because by that, what you said is exactly right, because the way the BEST trial is set up now, if you do surgery and then redo surgery it's a failure. If you do a stent of an angioplasty and then redo it every single day for the rest of the patient's life it's a win, so, you know, that's not what

patients want.

DR. TURCO: You didn't say a win for whom.

(Laughter.)

DR. BACH: Dr. Lewis.

DR. LEWIS: So, I want to ask the Dukies a question and this is from a little

different perspective, but one of your early slides identifies male gender as a risk factor, and that concerns me in that if you look at your absolute numbers, there are probably more men in the older age groups but there are a significant number of women, and psychologically and through our experience with coronary disease, if you say that male gender is a risk factor, there can be an underdiagnosis of this in women. I'm particularly concerned because of the increase in diabetes and the fact that this will become progressively a disease of both men and women. How do we deal with this perception?

As you have noted, they are different, they have higher risks when they have the disease for women. It really isn't a men's

disease, nor is that really a risk factor with some of the complications.

DR. PATEL: Yeah, I think that's a very good point on this slide, which maybe shouldn't have been so hastily taken from existing sort of dogma, guidelines, information about risk factors.

A couple of points with respect to

that. As I think everybody in this room knows that there are more women alive than men right now in the United States, and women live probably between two and four years longer than men, and for atherosclerosis not related to peripheral arterial disease when they present with it, they present on average five years later, and maybe not with the symptoms that we read in the textbook, and we've learned all these different things.

So very much so we want to make sure it's clear that women certainly get PAD, in fact there are probably more women than men with PAD. Women are disproportionately having amputations, as you've already heard, and women certainly have potentially even different sort

of disease burden than men because they're presenting later, so I want to dispel any ideas that might have been presented that women don't have PAD, women don't suffer from it, and it's not a risk factor. It may be the age when you're evaluating the patient, perhaps you haven't even thought about it before. So certainly all those points are valid and we should stand corrected if it was

misinterpreted.

DR. BACH: Dr. Zuckerman, do you have your tent card up?

DR. ZUCKERMAN: I have a question for Dr. Menard. I was very interested to hear about the study design and I had some questions about it as it struck me as unusual, so I just want to make sure I understood it correctly. So I gather there is some kind of randomization in the study, but that was in the randomization each doctor does his or her own thing and that, I think you said that can vary quite a bit and it's very individualized, and I gather that means it can even be off-label uses of devices which have never been approved for those

indications or for those patients.

And I guess I have a couple of concerns, one being that the FDA when they approve devices usually don't require clinical trials and so we may actually know very little about the safety, and certainly not about long-term effectiveness of the devices, but you're putting them in a trial where you'll have relatively small numbers of patients getting the same kind of treatment, and that

makes it very difficult, I would think, to analyze in a way that would help us understand which treatments are most effective for which kinds of patients, men or women, people of different races, people with different comorbid conditions, so I just wanted to get a better sense of that design.

DR. MENARD: Absolutely. I mean, you've highlighted the challenge that we faced, and anyone who's trying to design a large trial faces, and there's two ways to do this. One, you could do what we look on in the cardiology world and envy their huge well designed trials where they pick off one specific question at a

time, try to answer that question and get a very concise answer.

The other way to do it is what we ultimately opted to do, which is to try to be all-inclusive. Clearly it's a messier way to do it, the limitations are you have a much more heterogeneous data set, and you struggle to make very specific comparisons, which everyone in the room would obviously want, so clearly that was a challenge.

What we did not want to do was limit

the treatment arm to a particular strategy or particular platform ala the BASIL trial, which many of us that treated patients felt was not relevant to our practice by the time the trial was finished, and again, it was four years ago. So that was perceived as a bit of a fatal flaw that supported our pragmatic design and favors that design. The kind of corollary in asking investigators to enter support of a trial that's challenging to enroll and asking them to do things differently than they typically do, again, I guess is the generalizability of the trial and the results, and ultimately we felt

that was going to be too limiting.

So absolutely, limitations in the way we've done it. At the end of the day we felt if we could achieve an appropriate power, hopefully we will be able to answer the questions that we wanted answered. But you're absolutely right, once the patient's randomized, the individual investigators can do exactly what they want.

Just one more sort of point to that. So, our effort to look at in a critical fashion new technology that's come on line and decide

whether it's appropriate for the trial has been questioned by some, so we've looked at the data for the two drug-eluting balloons that have been recently FDA-approved and decided to include them in the trial, so there's no data on those in the CLI space over a long period of time, and why is that appropriate for the trial? But the counter to that is the vast majority of things we do, there's no long-term data for what we're trying to do, so we felt rather than have a trial that at the end of the day, that those patients that got treated with

those technologies were not allowed, we felt it was better to include them.

DR. ZUCKERMAN: Thank you. And I'm sorry, I just have a followup about the outcome measures. As I recall the outcome measure, the primary outcome measure was amputation-free survival, and are there other outcome measures that are also being looked at?

DR. MENARD: Yes, so, and I was going to make a comment earlier on the critique of the primary endpoint. A lot of thought and discussion went into that. The primary endpoint is not amputation-free survival,

amputation-free survival is severely flawed for the express point that was made earlier, if you do an open endovascular intervention and then there's some outcome that's other than death or amputation, there's no accountability for that reintervention or that secondary event.

MALE-free survival, yes, it's limited to major events, and reintervention and amputation-free survival, which is our primary secondary endpoint, also includes minor reinterventions. There are two clear reasons

why we decided not to have that be the primary endpoint. There was the impact on the patient, so we felt that major reinterventions have significant major impacts on patients and their burden was what we were hoping to focus on, and so the minor interventions, yes, are very important, but the overall impact on the patient was less.

And the second point, perhaps more importantly, is when we use an endovascular first strategy, we presume that there will be more interventions, that's an accepted reason to use endovascular therapy, and it did not seem fair to jeopardize or hinder the

endovascular arm for that reason. So we are hopefully going to have a very clear ability to make comments on the burden of reinterventions, we recognize the importance of that, it was just not part of the primary endpoint.

DR. ZUCKERMAN: I'm sorry, I just didn't understand. So what is the primary endpoint?

DR. MENARD: The primary endpoint is MALE-free survival, so it is not

amputation-free survival, and we're well powered for amputation-free survival, but a major adverse limb event, which was an endpoint that is somewhat novel, other people are not familiar with it. It came out of the SVS working group on endpoints, and it includes a major amputation and a major reintervention, so a new bypass graft, a thrombolysis or thrombectomy, any major surgical intervention such as a jump graft. What it does not include is balloon angioplasty, a surgical patch angioplasty, quite frankly many of those are date procedures and the impact of those reinterventions, while very very important, again, was not felt to represent a big burden

to the patient.

DR. ZUCKERMAN: Thank you. And I'm sorry, how long is the longitudinal study?

DR. MENARD: How long is the study?

DR. ZUCKERMAN: Yeah.

DR. MENARD: Yes, so each patient will have at least two years followup, so ultimately four years, possibly five years.

DR. ZUCKERMAN: Sorry, so the patients

could go up to four or five years, or that's how long it will take?

DR. MENARD: Yes, the first patient in could have over four years of followup.

DR. BACH: Thank you very much. Dr. Lawrence, and Dr. Lefevre, do you have another question? Okay. And then I would like to call an end to this part of the discussion, although if there are burning questions, we will proceed. Go ahead.

DR. LAWRENCE: I had a question for Mike Dake. One of the great concerns is followup on my previous question about appropriateness and the potential for overuse. And you presented, one of the concerns is that endovascular procedures, although very

successful initially, don't have the durability that many, and there's been changes that I know you presented, and you had some excellent long-term data out to five years. But what impressed me was you didn't present any physiologic data, you presented TLR but didn't present what we have been talking about here today, which is ABI, possibly treadmill walking

or, post-exercise ABI.

So my question is, with those great long-term five-year results, did you measure ABI? If so, was there a physiologic improvement in your study that would indicate that there is durability at least, if you use a drug-eluting approach, as opposed to a non-drug-eluting approach? So it has to do with the role of ABI as a physiologic measure, which has sort of been a standard of care in the field for 20 or 30 years, and why you didn't present it here today?

DR. DAKE: Thank you, Dr. Lawrence, it's a very good question, and we did measure all those physiologic parameters at regular intervals, yearly. One of the problems with the trial design was that when someone came in

symptomatic, they weren't repeated prior to the intervention, and so consequently by sampling only at regular interval times annually, you mask any of the real benefits.

Now if we censor all those people who basically had a reintervention, of course you're going to show a benefit, but it's a

somewhat limitation of the trial design for that particular trial that obviously all of these things weren't captured prior to the intervention. If that were the case, we would be able to do that evaluation. Does that make sense?

DR. LAWRENCE: Yeah. So, do you believe that ABI should be a standard as a physiologic test for all the interventions that we're talking about today?

DR. DAKE: Yes.

DR. BACH: Dr. Lefevre.

DR. LEFEVRE: Yeah, my question was on the evidence for key question three, it's for Drs. Jones and Patel, although I think some other people may want to weigh in. So, you reviewed the evidence on critical limb ischemia in terms of the comparative effect and efficacy

of endovascular versus surgical treatment, and I would have thought that was the correct framing because I think you have the starting point that you have to do something in those situations, you can't do nothing. But then we heard other evidence that came out later,

people pointed to the fact that amputations were reduced, you know, a correlative procedure, there was a correlation between workup for PAD and reduced amputations.

So my question is, when you do your evidence review, did you review evidence of interventions versus no interventions for critical limb ischemia, or did you think that that was just not a relevant question, you didn't look at it, or did you look at the evidence and there wasn't any evidence?

DR. JONES: Thanks for the question. We did review for all studies, and the way the literature search was constructed was to put in every intervention, every comparator, the patient population and the outcomes, and whatever came out within the filter would be put into buckets. When they fell into these buckets, however, only four looked at

endovascular versus surgical or, sorry, endovascular versus usual care.

Remember that surgery versus usual care had been done but it was done before 1995, which is when our study started, so it didn't

actually meet entry into our study. And so of those four, none were good quality studies because the good quality studies ended up being endovascular versus usual versus care. So we looked at them, we could not do a quantitative meta-analysis on those studies, and that's why we really chose to focus on endovascular versus surgical.

DR. LEFEVRE: Okay. So there was no evidence on intervention versus no intervention. Thank you.

DR. PATEL: And of course all the patients you saw had to be, somebody had to feel comfortable that they could get revascularization, and most of the guidelines during this period were saying do some type of revascularization.

DR. BACH: Any other questions? Great. Okay. At this point, thank you, speakers, and we're going to have an open panel

discussion along these lines, and I did want, Dr. Hirsch, I did cut you off earlier, and this might be, if you had something you wanted to say that was related to this earlier

conversation, we'd love to hear it. I don't want to put you on the spot, though. And please, also, tent cards or just interrupt each other, I don't really care.

DR. HIRSCH: I always have something to say but it's hard to know where to focus. First of all, you know, to all the presenters, great job. And to the panel, I'd love to assist you with Medicare. I have two general domains that may take three minutes, or six minutes.

The first is, the PAD burden is obviously gigantic and if I were a CMS beneficiary, I'd want to look for the sweet spot where the evidence overlaps with efficacy and cost effectiveness, so for the moment I'm going to ignore the asymptomatic population where hopefully risk reduction therapy will be given, and for the moment I'm going to ignore the 100,000 ischemic amputations for which my heart breaks every day, and look at the one to

three million Americans, most of whom are Medicare beneficiaries, who have claudication.

What I didn't hear today, I was going

to address this to our Duke guys, but, is whether we really know that there's a relationship between ankle pressure patency and patient-focused symptoms, as Dr. Swain said. In other words, there's a question coming. If I know that medication works because there's over 2,000 patients in controlled clinical trials with no change in ankle pressure, and I know that supervised exercise works, I think, Dr. Jones, you showed that in your report, so how important really is patency anyway to the average Medicare beneficiary with claudication?

My question is, in America at the current time, what fraction of beneficiaries do receive a claudication medication, an exercise program or an endovascular approach? I think we know that; the panel and the audience might want to know.

DR. JONES: You're asking us?

DR. HIRSCH: Yes.

DR. JONES: Since you said Duke guys --

DR. HIRSCH: I did.

DR. JONES: We prefer national

champion Dukies.

DR. HIRSCH: I love your championships, Minnesotans love what you're doing, it's okay.

DR. JONES: So, Dr. Hirsch, when we look at various data sets, and you've looked at them as well as we have, there are upcoming areas of study with which we have all been involved with today that can answer some of these questions. From a CMS or Medicare standpoint from what we've looked at, I would say that it's unable to be determined what percentage of patients get supervised exercise. I would guess that it's near zero.

DR. HIRSCH: That's a good guess.

DR. JONES: Near zero. It depends on how you define it so it depends on where it is. Now for cilostazol and pentoxifylline, specifically these modifying agents per se, it looks like about 10 percent of patients get those medications, sometimes surrounding a vascular intervention. Does that answer your question?

DR. HIRSCH: Manesh?

DR. PATEL: I guess the only other question you were hinting to was the relationship between hemodynamics, patency and symptoms.

DR. HIRSCH: Yes, physiology is important in understanding the results of all of these trials.

DR. PATEL: That's right. So, there are relationships in individual trials. The meta-analysis and AHRQ work you saw that we presented has not looked to investigate how direct that relationship is. We all know from several other presentations that it's not a direct one-to-one relationship, there is a relationship but from what we've seen it's not a direct one-to-one. We did not do a systematic analysis of the physiology to the patency to the symptoms.

DR. HIRSCH: Thank you. I have a follow-up question because I do care about claudication, but I also care about the many hundreds of thousands of ischemic amputations, and I loved the speaker who said that there are more amputations of PAD than there are from,

many ways of saying it, land mines in the world, trauma, motorcycle accidents, anything.

There was a relationship discussed, I'm not sure if we addressed this with you, that amputations have decreased in the country, and the implication of this is because of endovascular therapy, which may very well be the case. Straight line flow is important, my patients get that. But I think as an epidemiologist and as we think about this from a CMS perspective, are there other variables that could lead to the decrease, does it really exist in amputation rate, like the temporal decrease between 15 to 25 percent, and then sort of 12 percent of current smoking, or the temporal concomitant increase in use of aspirin, other antithrombotic agents that has about doubled over the last ten years, again in the same population. Or the use of statins, you know, in adults has gone from near zero to nearly 60 or 70 percent.

So the question I guess I'm asking, do we really know about the causality of the temporal trends and the decrease, do these temporal trends decrease all of the ischemic

outcomes of all the atherosclerotic diseases? Anybody want to take that, Dr. Patel?

DR. BACH: And let me pile on. I looked at some of these graphs and I saw what appeared to be the slope in reduction of cardiovascular mortality, which is unlikely due to peripheral endovascular intervention.

UNIDENTIFIED PANELIST: And they started before a lot of them.

DR. PATEL: We showed one slide, and others are welcome to come in, we showed one slide of just temporal trends. Of course it's always tempting but there is no causality information there, as you know. What we would say is there are multiple confounders, as you stated, other known things that affect cardiovascular mortality and probably patient outcomes such as risk modification, smoking, statins, antiplatelet agents. The antiplatelet agents, we gave you some evidence on what the effectiveness of that is.

Second, of course, which we didn't show you, is that the population's aging, the burden of disease is going up, the rates of diabetes are going up, so certainly the number

of patients in the country that are at risk for any one of these may also be changing at a rate that we didn't quantify, so we can't speak to either, except to say that there are probably confounders on both sides.

DR. HIRSCH: We're here to find knowledge gaps and I just want to make sure the gaps are well known and that non-gaps, for example, the supervised exercise signal, is also well known, separate the gaps from the knowledge.

DR. BACH: Great. So, we can use this time to -- oh, sorry, go ahead.

DR. CAMPOS-OUTCALT: So, for purposes of discussion, which keep us within the FACA rules, I'd like to express some discomfort I have with the wording of the questions, and then make sure that we're all answering the same questions when we vote.

So for instance, for number one, for adults with asymptomatic lower extremity PAD, how confident are you that there is sufficient evidence for an intervention that improves, A, intermediate and near-term health outcomes, and B, long-term health outcomes as well? If I

knew what health outcomes we were talking about and that we agreed on, I would have a lot better chance of answering that consistently with everybody else here.

So I guess my question is, are those outcomes related to the extremity or are they total cardiovascular outcomes, that's question number one. And then the interventions, there's just a wide array of potential interventions here. I mean, if I really took a broad view of this question I'd say sure, yes, I have high confidence because there's lots of interventions that could increase lots of outcomes, but that's true of everybody in America, whether they have PAD or not.

And so I'd like to narrow the questions down as a panel, if we could, and get to specific outcomes, that would help a lot, and then the interventions would follow.

DR. LEFEVRE: If I could just add to the question, because I think -- first of all, I just want to clarify that it says do you believe that there's interventions that are effective, so first of all, I mean, I assume

it's saying do we believe the evidence

demonstrates that. I mean, you don't want us to bring in our personal beliefs about exercise or things like that, correct?

Dr. Salive: It's confidence, not belief.

DR. LEFEVRE: I mean, I might be confident that exercise works, but it might not be based on this evidence. I assume we're voting on this evidence, is that correct?

DR. BACH: I think that's an excellent set of guideposts because this is an evidence development coverage advisory committee, so it should be, your responses should emanate from interpretations of the evidence.

DR. LEFEVRE: Okay, and that's the easy question. The harder one, I think, is the comparisons and what we're comparing. And again, I think the question is, when you say do you have confidence for efficacy of an intervention, is that efficacy an absolute term or is that comparative efficacy, and I think question three says that the best.

I mean, you might say that you're

confident that surgery leads to improved outcomes but you're not at all confident that

the comparator of surgery versus endovascular has good evidence. So I think that's really a sticking point for me on how we're going to vote. Are we voting just in isolation for each of these technologies or are we voting on comparative evidence? Because most of the evidence presented was related to comparative effectiveness, especially for questions two and three, it was mostly comparative effectiveness, but then the question's not really structured that way, so I'm not really sure what I'm voting on.

DR. BACH: I think that one, I'm going to do my best for that one, that one's actually easier for me to answer. The issue is in general terms against no intervention, even if we don't have high quality evidence for it. And remember, and there was some tussle over this in the ACA about whether or not comparative evidence could even be part of coverage decisions, and I think the general tenor of the law is against that, but we're not

here to make coverage decisions, simply to give a view of the landscape.

So I would think even if we're looking

only at, you know, head to head or intervention versus intervention, the nested notion is against a comparator of no intervention. The question is, do we pay for X, or should the government pay for X, compared to not. It's not so, if you will, variable. Marcel.

DR. SALIVE: So, I want to comment on the question about question one. I think if the person is asymptomatic, their health outcomes are mostly bad, so in terms of what you're interested in, they have no symptoms, you can't prove their symptoms, right, because they have none. So all your outcomes would be, then, in the area of the harms from interventions to prevent death later, right?

I do not think that the outcomes that CMS listed in their slide as to what outcomes are of interest to CMS at the very beginning come into play for the asymptomatic person.

So, a second point on this question, you know, time frame, I guess for intermediate

versus long-term it doesn't matter, but I have a general ballpark I use, but they're similar points for the symptomatic or asymptomatic.

Finally, you know, this question is

focused on asymptomatic but has peripheral artery disease, so based on some criteria they have peripheral artery disease. I don't want to get into, for me, this question of what else they might have, so they may well have a lot of other things and there may be a lot of lifestyle interventions that can prevent disease in those people, but we're focused on peripheral artery disease interventions, so to me this is not as hard of a question as you made it out to be, and hopefully that would clarify it.

DR. BACH: Thank you, Dr. Salive. Dr. Lystig, I'm going to get to you in a second here, but I want to, actually, I want to circle back.

Dr. Carr made a point about the AHA guidelines which I wasn't immediately familiar with, but I got the implication, and let me restate it. Is there a way to look at this

first question that proposes that the discovery of PAD through a series of actions which alters cholesterol, actions taken against a person's systemic cholesterol level, alters their outcomes? So this is not treatment of the PAD,

it's essentially marked PAD in the marker, and I'm throwing that out there, I feel quite naive in this clinical space.

DR. SALIVE: One last comment from me. So, the coverage program in Medicare doesn't deal a lot with pills, so I don't think we have to focus on pills in this discussion. I mean, I believe there was a Cochrane review that talked about lipid lowering in PAD that was very positive and it wasn't yet mentioned either, but was circulated to the panel. So I mean, I believe that intervention is quite good for PAD patients, lipid lowering, so we can say yes, we believe that's the intervention, and that's another easy way to answer this question, but it doesn't help the coverage program too much.

DR. BACH: Dr. Lystig, and then Dr. Hirsch.

DR. LYSTIG: So with the comparative effectiveness issue, it also brings up the related issue about using data from registries, and the extent to which we should also be basing our conclusions upon other types of nonrandomized trial comparisons. Several

speakers have pointed out the interest in what might be done, for instance with the Vascular Quality Initiative, but if one were to take the approach that registries would be a desired mechanism to get additional data, then yet in the sponsored reviews that we are to see from AHRQ, for example, that use available data, that those questions are set up in a screening process where such registry data would be structurally removed from consideration as valid evidence, it seems hard to say why, how that could be effective.

We are moving towards a state where we are trying to find better mechanisms to synthesize evidence from a variety of sources. Obviously a well-run randomized clinical trial is a great source of evidence, but randomization as a mechanism for treatment

assignment is a pretty poor proxy for overall quality of the study. It's often the case that there's a high quality randomized clinical trial but it's not the case that only randomized clinical trials can provide strong evidence.

So if we're thinking about scenarios

where we're trying to understand what real evidence exists for multiple therapies to inform our judgment, we should consider not only how it is that we would fairly evaluate the contributions from registries, but also to move into saying in single-arm studies and other observational mechanisms, what are approaches we can take that allows us to decide this evidence fairly so that we can make better decisions, and I think that general concept develops better use of more information that will very much help in making these decisions.

DR. BACH: Okay. Who's next? Dr. Swain, were you next?

DR. SWAIN: I have one quick question for the center. Give me your definition of long-term. Is it two years, five years? My

general definition, even though it's not long-term, is five.

DR. BACH: Let me take a crack at that, I certainly don't speak for the Agency, correct me if I'm wrong, but I think to some extent this spoke to the clinical situation, and by looking at some of these overall survival curves in this population, I think

what we'd often think of as long-term for preventive interventions is appropriate, and I'd say sort of after the period where the adverse, potentially adverse effects of the intervention had sort of cleared. It would probably be in the longer term after six months for many of these trials, that that would constitute maybe the beginning of a long-term window, maybe a year. These looked like populations of patients who had fairly brief average survival, so I think looking at a five-year outcome when there's serious, a large number of gaps prior to that, might not be appropriate.

DR. SWAIN: CLI, for CLI that's a for sure, claudication that occurs, you know, on

the 17th hole when you're carrying your bags is probably five years, so it's just a difficult question the way it's asked.

And I guess the general comment for today is I appreciate all the speakers, and viewing all the literature as a cardiovascular surgeon, you know, it's embarrassing that we haven't done better. And as a former FDA person it's embarrassing that more data, better

data wasn't required for approving devices.

So we can see that the world's changing now and there's great studies upcoming for which we don't have any answers yet, they haven't been published and able to be peer reviewed or FDA committee or whatever, so I think that in the future we will have data and the registry I think can be important, it's only a recent registry, there's only a hundred thousand peripheral vascular so far, but, you know, to beef up that registry, to make it required, and there's incentives. Just like in cardiac surgery, you don't get paid by insurance companies unless you're in the STS. That may well be useful in the future for

propensities for scoring of studies and using it as a historical control like we use some of the UNOS database and the InterMax database and things like that.

So I think that, you know, we have things coming, but right now the lack of data is just impressive and very disappointing, but I think the future and the idea that we have these six randomized studies that were listed by Dr. Turco, and when the PARC committee

started in 2011, you've just got to have common definitions and common endpoints in order to be able to compare anything, and we appreciate the problems our Duke friends have doing those comparisons because it's where cardiac valve disease was 30 years ago, you know, everybody did everything differently. So I think CMS has a problem right now of using evidence-based medicine because there's very little good evidence of not only comparison to comparison, it's kind of like comparing in my family, you know, we could compare who could dunk a basketball best, but that doesn't really, you know, we need to be able to compare in a lot of

these things; an intervention versus things like exercise and we just don't have any of that data, and I don't know that we're going to get any of that data now because kind of the horse is out of the barn, so I appreciate the problem that CMS has had.

DR. BACH: I'm sure our colleagues from Duke appreciate the basketball metaphor as well. Dr. Hirsch, did you have a comment?

DR. HIRSCH: Yeah. I made a comment earlier about claudication with CLI and I

wanted to come back to the asymptomatic cohort. This term asymptomatic is extremely problematic, it probably should be discarded. There is other evidence not presented today that suggests, as one of our public speakers said, that no one is truly asymptomatic. If you have an ABI of .85 and you stop walking and you don't speak English, you don't complain as well, you have a functional limitation, and that's what Mary McDermott of Northwestern published in multiple sources. The challenge is if we wait again in the post-ACA world where we're not RVU-based and we're trying to keep

the Medicare population healthy, if we wait for people to complain in the English language the way we understand, we only detect one out of ten, or actually one out of 20 patients with PAD.

So when the AHA guideline was written the thought was that, again, in all the trials that existed, we don't really use the term asymptomatic very often. If my colleague here had leg intervention 20 years ago but no longer complains because the intervention was successful, he still has very severe PAD

despite that success. If my next colleague has PAD with the same ABI but, again, has stopped walking, his event rate is not driven by his risk factor, the question earlier, it's no longer one or two percent for ten years, it's now at least four to five percent, probably six to eight percent of the community population. So the time frame of risk is as short or shorter than a patient discharged with a stenting.

In other words, the PAD diagnosis in an asymptomatic patient unmasks the functional

limitation, unmasks the cardiovascular risk, and although we don't have a primary USPSTF A grade, that's true, we don't have a prospective single randomized trial, that's a knowledge gap, I could probably reference five additional studies, the old CAPRIE study, the current PRA2P study, the previous ramipril trials, and the heart protection study with statins and ACE inhibitors whereby within one year those coronary event rates declined by a lot, 15 to 20 percent, and absolute risk reduction in the first year of one percent, and these drops in rates are short-term, meaning the first six

months to one year according to the definitions, and never go away, they persist.

So I just want us to caution ourselves that, not to be too cynical as Dr. Beckman is no longer here, but there probably is no such thing as asymptomatic.

Final one, knowledge gap. Of the critical limb ischemia patients that actually present in our country, fully half of the presentations are first CLI, they're not stage of disease. So you're asymptomatic today and

tomorrow your first presentation is a black toe, so there is the opportunity to provide surveillance for early detection if we detect, quote, asymptomatic PAD. In other words, you, Peter, may have a severe lung nodule but not be coughing yet. We have to be careful. Unlike lung cancer with microscopic lesions, here we do have therapies that actually are fairly well proven to change the natural history. Hope that's helpful.

DR. BACH: Dr. Deyo.

DR. DEYO: I guess those comments confuse me a little further actually, rather than helping me. If there's no such thing as

asymptomatic, then I assume that everybody in this room who's had a leg symptom has potentially got PAD.

DR. HIRSCH: Well, no. I mean, it's like everybody with chest pain doesn't have coronary disease. The goal is to detect the ischemic symptom and accurately define it by a diagnostic test.

DR. DEYO: I guess an underlying concern that I have here is that in other areas

of medicine we're learning more and more that screening in general populations may not have the benefits that we really think it does, in part because there are adverse consequences to screening itself, even in non-sick patients. And in the absence of a clinical trial, for example, demonstrating the benefit of a screening strategy, I guess I'd be reluctant to endorse a screening strategy, and it seems to me that's in part what underlies this question about treating asymptomatic patients.

DR. HIRSCH: You're right on the money. We have to be very careful about the term screening without a prospective randomized trial. The analogy is we can't have confidence

of the benefits (inaudible).

DR. BACH: I think, and let me rephrase, Dr. Hirsch, what you said. I don't think Dr. Hirsch, I think he was saying asymptomatic was a problematic moniker because of all the stuff we assume it means about the patient, but then you were listing actual changes in behavior, functional status, things like that, that we as clinicians may not be

particularly skilled at picking up or if we do find them, we don't naturally reflex to logical explanations like PAD.

I think that's what he was saying, and Rick characterized it as, you know, any leg symptom, but I think it's probably somewhere between these two things, is what you intended to say, not any leg symptom. If you stub your toe, that's not an indication for screening.

DR. HIRSCH: You're absolutely correct. I have tremendous respect for the evidence-based process of USPSTF, and we don't have prospective Level I data, true Level I data with a control group, or with long enough followup to know about the benefits versus harm. However, we should have caution that we

don't discard the asymptomatic group entirely because there are interventions that, if you were in my office and you had an abnormal pulse but you felt fine, or your ABI was .5 and you felt fine, you could be maintained in health with Medicare-based medical interventions that are known to be effective.

DR. CAMPOS-OUTCALT: Yeah. I just

have to correct an implication that the USPSTF only accepts randomized control trials as high level evidence, that's entirely not true. They have a process where they do look at observational studies, observational studies can be upgraded because of quality, consistency of results, magnitude of effect and so forth. It does not require a randomized control trial to get an A or B from USPSTF. And the rating when it comes to screening using ABI for peripheral artery disease is an I, which is insufficient evidence, which is where I think we're at, so I don't think we really have a disagreement with USPSTF on this particular point.

DR. SALIVE: And I think their review that was provided to us was positive on the ABI

for detection. It did reflect that the intervention needed to be proved to be beneficial after that, so there was a path forward to something that might be useful, so I don't think we need to endorse or disendorse that, I think it's a reasonable approach to take, and hopefully there will be some

interventions eventually.

DR. BACH: Dr. Cuyjet.

DR. CUYJET: I'm going back to not so much a question but just a comment really to the evidence. Most people don't just have one risk factor or two risk factors for PAD or CVD, and there's some evidence in trials going back to if you know that you have one risk factor, or two risk factors, or three risk factors, for diabetes, for example, and this is basically what economics means: if you're going to invest the time and energy to manage your diabetes, you're not going to ignore your hypertension or your smoking or your other stuff, so it's not really an answer, but we mentioned that we're going from an RVU to an outcome-based medical encounter.

My comments don't really help us

answer these particular questions, but it's just a general framework about how patients will modify and invest, even older patients with a marginal return on investment in terms of health outcomes will be less than 30 years before, but it's not a factor that should be

underestimated in what patients do to commit to maintain a good outcome.

DR. BACH: Dr. Kormos.

DR. KORMOS: So, I may unmask my naivete, but in my world there are very few devices, everything is a clinical trial. I'm trying to understand, and I guess as we decide about whether interventions make a difference, the word I heard in a lot of the presentations today was heterogeneity, there's a lot of heterogeneity both in the disease, the presentations, the patient populations, and today I heard that in fact how these devices are used are very heterogeneous, there's all sorts of different methodologies and strategies per implication, and that's where I get a little bit fuzzy about how definite I can be and how I'm going to try to answer these questions.

Because, you know, is one 510(k) device the same as the other? You know, when was the predicate device laid down, how long ago? How much are we following the same path but the devices have really changed now, so at

what point do you say okay, it's really time to do a full clinical trial? I don't know.

And so when you ask me to, you know, what's the evidence that any -- I mean, some of these I think I've got a handle on, interventions that clearly help. But as I get into the more esoteric device area, then I'm having a little more trouble understanding how to make that interpretation given the variety of devices, how they're used, and the variety of the disease states, so that's where I'm struggling, and I don't think there's an answer, it's just a comment.

DR. BACH: Dr. Lefevre.

DR. LEFEVRE: I just want to make a comment about the issue of RCTs and registries because I think there's a lot of comments made here, and I'm certainly in favor of registries, and I think the presentation by Dr. Cronenwett was very good in terms of what registries can

do and what they can't do, but I think sometimes we go beyond what registries can do and we expect to be able to get treatment effect information from registries. And I

think there's only very few situations where you actually can get treatment efficacy or comparative effectiveness of treatments from registries, and those are when you have relatively unconfounded interventions and a homogeneous population.

Here we have very much the opposite. We have heterogeneous populations with very highly confounded outcomes, and then we have cardiovascular disease with very highly confounded outcomes. So I think we absolutely need to insist on RCTs for the primary questions. For the issues of intervention versus medical therapy, for example, we need to insist on RCTs for those questions. And if we try to get by with lesser data, registry data, we'll end up ten years or 20 years in the same situation we are now, we won't know, we won't be able to answer the question. We'll have some suggestive data, we won't be able to answer it.

So I think we need to be very clear about what kind of studies we need, where we need RCTs, and what registries can do, but not

to mix those, and be very clear where the RCTs are needed and what questions cannot be answered by registries.

DR. BACH: Thank you. Dr. Lystig, did you have something else?

DR. LYSTIG: Yes, but it actually comes back to this most recent comment again with respect to the registries issue. So first off to the prior comment, I agree that there are mechanisms out there that exist, primarily in many journals, about how you can view observational studies as being equivalent to, or at least the same level as a randomized trial.

My point that I was trying to make earlier was that if there is interest from CMS in the use of registry data to make informed decisions in a panel such as this, then there seems to be a problem between having a commission review that has as part of its requirements that the data to be summarized has to be a randomized clinical trial, so you're

structurally throwing away that information from saying that, okay, how can we learn from

the registries?

And to this most recent point about what we can learn from the registries, again, I think there are many endpoints that we are interested in, and for things such as quality of life, that sometimes can be something that is easier to get out of a registry framework, provided that the analysis plan is done appropriately and steps are taken to find subsets of the population where you can find homogeneity and you can get rid of some of that underlying heterogeneity. So there are scenarios where it is almost a requirement to have randomized clinical trials, I'm not saying that. I'm just saying that if we want to make the most use of information that is being generated, we should consider avenues that would allow that nonrandomized trial information into the committee's deliberations.

DR. BACH: Thank you. Dr. Lefevre, your card is still up, and Dr. Kormos, your card is still up. I don't know if you have more to say. This is very stimulating

discussion and I appreciate the panel members

pushing each other to be clear on their points. We're going to take a break, but before we do that, when we come back from the break I'm going to ask you to vote, so I would actually like the panel to take a moment before we break and think carefully if you feel like you have the bounds of the questions adequately defined or whatever, so that we can go through a voting process and the discussion around our questions. And if not -- Dr. Carr.

DR. J.J. CARR: Just a point of information. So on question one, long-term health outcomes, those would be cardiovascular death, coronary heart disease death, cerebrovascular events, those would be the long-term health outcomes we would be voting on?

DR. BACH: So on the voting sheet, there's a list of the clinical outcomes of interest, it's the second half of the third paragraph in your packet, and it lists a set of outcomes which includes the ones you just listed as well as a number of others. I can just read them, reduction in pain, avoidance of

amputation, improvement in quality of life and/or functional capacity including walking distance, wound healing, avoidance of cardiovascular events -- these are the ones you listed, MI, stroke, cardiovascular death and all-cause mortality, and avoidance of harm from the interventions. So that's the sort of market basket of outcomes.

DR. J.J. CARR: I mean, there was some discussion among us to limit the scope of that question to just peripheral vascular disease outcomes, but our mandate clearly includes cardiovascular events, death, cerebrovascular accident. So when I'm voting, I'm voting according to the instructions on the sheet, and we really presented very little to no evidence on prevention of those outcomes for asymptomatic people, but there is a robust literature in that area that would indicate that peripheral arterial disease is a CVD equivalent much akin to diabetes, and that we have prevention strategies that are highly effective.

DR. BACH: Right, so I understand the question, and I'm just doing the best I can as

well, but the first level question allows for a range of responses which, my read of it would be you would express the level of confidence you have for the highest effective intervention on the highest outcome, because the subsidiary questions, the follow-on discussion allows us to then bifurcate or trifurcate the space with the discussion.

If intermediate confidence, on all these interventions in your head, please discuss the specific interventions and associated outcomes. So that gives you the discussion around each of those questions, one, two and three, which allows you to segregate, okay, I'm talking about CV events, cardiac events or peripheral events, these are the events I'm talking about. I hope that helps.

And then beneath that there's a question in each of the, there's a sub-discussion in each of the questions saying, considering the heterogeneity of the Medicare population, discuss which subgroups of the population are likely to benefit or likely to not benefit from that intervention.

DR. J.J. CARR: So I mean, just point

of information, we really have six voting questions as I look at the green sheet, right, so we're going to rate for questions one, two and three, an A and B on each question, that's just a point of information, are we?

DR. BACH: Yes, that's right. I believe we're voting six times, one immediate and near-term, and then long-term.

DR. J.J. CARR: And each of those have the outcomes that are in the instructions.

DR. BACH: That's right, and then after each one there's a discussion, about which outcomes, okay, which interventions. I hope that helps.

DR. J.J. CARR: Right. I'm just making sure that we didn't change the instructions when we vote when we come back.

DR. BACH: Right, the only thing we cannot change is this piece of paper.

DR. J.J. CARR: Okay.

DR. BACH: Please.

DR. ZUCKERMAN: It seemed that there's some differences of opinion about long-term data and what that means, and also obviously that long-term is different for the different

groups, and certainly I was not comfortable with the idea of looking at just long-term data regarding what happens immediately after the intervention, because there are a lot, because if the intervention is successful for a short period of time and then not successful, that's important too. So, I don't know if that can be clarified by CMS, or if you don't want to clarify it, but I'm just trying to get a better sense of what we're talking about.

DR. BACH: What I would propose, I don't think it's particularly productive if each of you voting has a different definition. I don't know if we could easily converge on one but I propose we try right now to try and separate those two questions for us collectively, and then CMS will take, within the context of the definition we arrive at, the answers we give. So, the floor is open to the difficult distinction for short- and long-term outcomes.

DR. LEWIS: I think for number three, the short-term outcome being wound healing, with knowing that sometimes these things can

fail at eight months or 12 months, that would

be long-term, and if the wound had healed in the interim, that still might be a short-term outcome.

DR. BACH: So, can you put a time frame around that?

DR. LEWIS: I guess six months for wound healing.

DR. BACH: I'm totally comfortable with choosing a different breakpoint for each of the three questions also, I mean, I think within reason, does that solve our problem? I'm just trying to get to a structure before we vote.

DR. LEWIS: That's why I started with three, it seems like it would be very different than one.

DR. BACH: And it's easier than one.

DR. LEWIS: Well, one seems almost easy in its own way too, because long-term outcomes would be the cardiovascular events that would start in maybe two to five years.

DR. BACH: Okay. So I think the proposal on the table very loosely is a

six-month cutoff for critical limb ischemia between short and intermediate versus

long-term. Are people comfortable with that?

DR. LEWIS: I mean, I was just giving a number. People could choose a different number.

DR. BACH: In the critical limb ischemia, question number three, we're going to use six months as the breakpoint between --

DR. HIRSCH: It's hard to know, Peter, you know, what time frame is appropriate. Let me just give an alternate perspective, but I don't know the answer. If we were the patient, not the trialist, not the company, not me, you know, when I get an intervention in a doctor's office, I'd like it to work, I'm just going to say out loud for at least a year, I don't want to be coming back every three to six months. And if I were thinking long-term, what I'd want my wife or my best friend to have, it would be five years.

Of course the reality for PAD is we don't have any outcomes generally beyond one year or two years for almost anything, but we

could take all three questions and, I hate to say it, but kind of merge them, since all we really have is one year for almost everything.

For question three, even for wounds even if they heal at three or six months, we all know they recycle and reopen, and then reclose and reopen, so in our trials it's very hard to pick a time point that makes sense. So for the panel, you could choose one and three, one and five, but be careful if it's anything much shorter, because I don't think patients necessarily value that.

DR. LEWIS: Months?

DR. HIRSCH: Years. Durability is important, so I'm advocating for longer time frames.

DR. BACH: So the counterproposal, I'm just trying to triangulate on something here, the counterproposal is a one-year, short-term outcomes mean outcomes out to a year, and then there's a separate thing which I think is largely constrained by trial design and followup, which is five years arbitrarily, meaning gives us a view into the long-term

durability.

Are people comfortable with that? That's across all three questions now.

DR. SWAIN: But I think it's just so

different. In group one you may be talking about a 40-year-old with an ABI of .9 or something, you know, so aspirin is an intervention, you'd really want to know five- to ten-year data.

Whereas in the second one, intermittent claudication, which could be, again, not able to walk across this room, versus the other end of the spectrum is claudication when you're carrying your bag of golf clubs on the 17th hole, so you've got a huge thing, so I would throw out five years for that as long-term, if you're going to study device or drugs or whatever.

And then for the horrible limbs, the CLI, you know, one to two years is long-term, and then intermediate may be six months to a year, and acute is less than that.

DR. BACH: Does anyone have a view on that? I think the first decision we're making

now is are we going to use a common standard for all three questions, or if we want it to be sort of a moving cutpoint, and I'm not hearing a clear consensus.

UNIDENTIFIED PANELIST: There's three

different populations so I think there should be a different cutpoint for each.

UNIDENTIFIED PANELIST: I agree.

DR. BACH: I'm seeing nodding heads. We're not going to vote on this. Is there some articulate difference of opinion around that or are we going to use a moving cutpoint?

DR. LEFEVRE: I think question three is different, but on questions one and two I would agree with Dr. Hirsch. Like less than one year short, one to five years intermediate, and greater than five years long, I think that's a general standard. But I think here we should just make it simple and say one year and less, or greater than one year, because we say immediate and near-term and then long-term, so we don't really have an intermediate step, so I would just make it simple, one year and over one year.

DR. BACH: So the proposal on the table for question one is up to one year, up to five years, for the immediate/near-term versus long-term. Are there objections to that? One year and five years.

We haven't talked about intermediate

claudication, so let's go to question three and resolve that. Are we comfortable with one year and five years, or do we want to talk about six months and two years?

DR. LEWIS: I guess I'm uncomfortable with the one year, because the data don't support that people even live much longer than that. If they have pain control immediately, that would be a good outcome for many people, so is it what I want, no, but it is what happens.

DR. BACH: I think the important dichotomy is actually separating the research into its appropriate buckets as well as sort of the clinical experience of patients. I'm throwing out a number here, I don't have a preference, six months and two years for question three? Okay, six months and two years

for question three.

And then for the one that's between, the intermittent claudication group, is this also one-year and five-year, or is there some other? Dr. Lystig.

DR. LYSTIG: The proposal I heard before sounded like it was saying that we

should consider this not in terms of an average of one-year or average of five-year with a one to five split, but things less than one-year and things greater that one-year, so I'm confused.

DR. BACH: That's for question one and two.

DR. LYSTIG: Yes, that makes more sense to me.

DR. BACH: Okay. So, can you rearticulate that in a statistical sense so that we can all know what you're saying, or what the distinction is?

DR. LYSTIG: Less than or equal to 12 months, versus greater than 12 months, and have that be short-term versus long-term, because you're just splitting the space up into two

adjacent areas, rather than targeting things just at one area versus targeting things just at five years. So there's two spaces, and the questions are set up in terms of essentially an endpoint for a therapy for which you have the most evidence, and it's just where that time point falls in within that dichotomy.

DR. BACH: So those are outcomes, so,

I'm trying to make sure I have this distinction clear. So we're not talking about experiencing, for example, outcome improvement through one year as the short-term, you know, by continuing to experience that outcome up to 365 days, versus up to five years. You're talking about experiencing improvement in outcome within the zero to one time interval, but that could decay and it would still qualify as a short-term health benefit, but then having the continued experience between one year and five years would count as the long-term.

DR. LYSTIG: That being said, for many of the outcomes that are like survival analysis, so you're effectively making your inference based upon 12 months, which is a

function of what had happened up until 12 months.

DR. BACH: Agreed.

DR. LYSTIG: So effectively, just saying the information available within the first 365 days, versus the information available after that time point.

DR. BACH: Okay. Is there comfort on the panel about that?

DR. ZUCKERMAN: No. I mean, I just want to say, we certainly don't want a study that's two days long. I understand that not every study's going to be up to a year, but I don't think we can just say anything up to a year is a short-term benefit, because a one-week study is, I think, too weak to be --

UNIDENTIFIED PANELIST: But we're not talking about a one-week study for any of this.

DR. BACH: Okay. So the distinction on the table, speaking just about the short-term outcomes here, is the distinction between, is a short-term benefit, can it occur before the end of a year and for example disappear and it still counts, or

alternatively, does it have to be durable to 365 days to count? I think, Ted, is that the distinction you're making? I think it is.

DR. LYSTIG: My distinction had to do with just trying to split the time scale into two adjacent regions, right, so things happening up to a year, things happening after a year. Again, the way I'm reading the question, and maybe I'm reading it incorrectly, is how confident are you that there exists, A,

therapy for which there's sufficient evidence for immediate or near-term health outcomes? So it's the best evidence for some therapy in one of these three areas in a particular time interval. So it's not to say on average across all therapies for all outcomes, it's what's the outcome with the best evidence.

DR. SWAIN: I mean, again, you're comparing the third question to the first question, and the idea that a 13-month, evidence of something for 13 months in an asymptomatic patient doesn't, I could never use the term long-term for that. So I don't know what the solution to this one is, other than we

qualitatively define it when we vote on it, what we mean by it, and CMS can look at the transcript, which we know you'll do.

DR. ZUCKERMAN: Yeah. I don't know why it has to be adjacent, I don't see the benefit. I also just want to say even if you have a five-year study and not everybody lives to five years, that doesn't mean it's not worth looking for as long as you can look, for those patients who live longer.

DR. BACH: We've done a more

sophisticated interpretation of the document in front of us, and short-term is the, we're going to go, if this works for you and everyone, with Dr. Lystig's definition, which is during the time interval up to, for example, a year, there is an intervention that alters health outcomes.

But the second question, long-term has a reasonable time point of durability, call it three years, four years, five years, something like that. We're limited by data on that, so if you're sort of, the cartoon version of this is if you have an intervention, at 364 days you're doing fabulous, that's short-term. If

you're doing fabulous at day 367 and 368, you're not, you haven't satisfied the long-term benefit, you have to be at five years, or, I think we acknowledge that data run out before we would like, so, you know, in the projection across the time horizon.

Does that work with everyone, that distinction? So if you will, there's a large doughnut hole between those two endpoints.

DR. LAWRENCE: Just so I understand, so if it's 366 days for an intervention, that would be a successful short-term?

DR. BACH: That's right.

DR. LAWRENCE: It seems short to me for surgery, it doesn't for medication, but for surgery and interventions that seems like a very short period of time. And as was pointed out, from a patient perspective I don't think they would consider a success to be if they went one day over 365, I think maybe two years.

DR. BACH: Let me say it again. First of all we get to answer both, right, but my understanding is, if you will, over that time period if you get a blip of benefit in the

short-term, we're counting that, and there's obviously the discussion, but that is a benefit. And then if it's a question of durability, and let's imagine that we had perfect follow-up data past five years, to get an outcome benefit that is long-term you have to see that benefit at five years, that's what we're going to go with, all right, or three or four years, a long period.

I would like to take, I promised everyone a ten-minute break, I would like to stick with ten minutes, and then we are going to vote.

(Afternoon break.)

DR. BACH: Okay, thank you all. Can I ask you to either take your seats or have your conversations in the hall, please? This is the moment everyone has been waiting for.

One more clarification. In thinking about this issue about question one, the issue of asymptomatic, I'm going to try as best I can to remap this onto a regulatory framework with Dr. Hirsch's comments very much in my mind.

I think what is intended, in fact I'm

confident that what is intended from the question regarding asymptomatic patients is patients whose PAD is discovered through screening. So whether it is a narrow view of the symptoms that trigger the doctor, or the evaluation, or a broader view such as happening to catch a history of reduced walking distance or something, that would be off the table. It is sort of systematic screening of patients without symptoms of the disease, if that's the trigger, that's the bucket, so it's essentially the chain of event following screening that's the question.

Go ahead, Dr. Hirsch.

DR. HIRSCH: Just to be clear, that's excluding the fact that five years ago I had a right ilial angioplasty and I'd been feeling just fine, seeing my primary care doctor. We're not dealing with that beneficiary, all right?

UNIDENTIFIED PANELIST: That's not an intervention at all.

DR. BACH: I would think that's a documented prior history of PAD, assuming that

was an intervention for PAD, right?

DR. HIRSCH: Yes.

DR. BACH: I would think that documented PAD puts you into a different category. Go ahead, Rick. I'm doing the best I can here.

Dr. Deyo: Let me just press you a little bit. It seems to me you've reframed the question from whether there are benefits for asymptomatic patients to the advisability of a screening program.

DR. BACH: No, Rick. What I believe is, I'm trying to define the cohort, not the question of screening itself, right? So if we were going to conduct a study, I think the

entry criteria would probably be screening, but then it could have different interventions, but I'm just trying to narrow the cohort into those, but I think those two things are related ideas. I'm open to other definitions. We just need to be able to give Medicare some guidance regarding the cascade of events that could occur after a screening test is done.

DR. HIRSCH: So, Peter, I don't know

the best answer, these are very tough questions. But I'm going to, again, take a patient centric CMS perspective. If in the United States of America fully half of the population, more or less, has no identifiable chief complaint but has PAD with both functional impairment and high event rate, that means our meeting and our panel is really excluding a huge population of beneficiaries. In contrast, a member of the USPSTF screening population really hasn't been studied, so we're taking the first question and truncating it to a tiny fraction of the actual PAD cohort, and I'm just asking myself, or CMS, is that wise.

DR. BACH: We're going to take the questions I believe as written, and I take your

point, of course, but I think it's perfectly okay, quite commonplace for the discussions to focus on narrow populations, and there's lots of people with lots of conditions who are not being considered, and it's sort of the best -- I don't know how else to constrain this so we're voting on the same thing.

MS. ELLIS: All voting panel members,

you should have your keypads. When it's time to vote, please press your vote of choice hard so that it will register. Also, when it's time to vote, we will need you to state your name and your vote for the transcriptionist and for those individuals on the webcast. So again, please speak into the mic, state your name and your vote, and we can begin.

DR. BACH: Okay. So I'm going to read the questions. The first question is, for adults with -- and remember, we're voting twice here. For adults with asymptomatic lower extremity PAD, how confident are you that there is sufficient evidence for an intervention that improves immediate/near-term health outcomes, which we as a panel decided constituted outcomes occurring within the first year after

identification?

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

MS. ELLIS: We're waiting on three, two, one. If you're not sure, would you just push your button again.

MS. JENSEN: And just as a reminder,

every panel member should vote.

DR. BACH: Okay. The mean is 1.4, you can see it on this screen. I don't know if we can fix this screen up here which doesn't show the bottom. Oh, there we go. The mean value is 1.4, and that's with all ten panel members voting.

So, I'm going to ask on the second question, which is essentially 1(b), let me read that. The same question, for adults with asymptomatic lower extremity PAD, how confident are you that there is sufficient evidence for an intervention that improves long-term health outcomes, which we agreed as a panel is outcomes that were assessable up to five years, or I should say at five years, given the constraints of the data.

(The panel voted and votes were

recorded by staff.)

DR. BACH: Okay, the mean was 2.8 there. Hold on a second. I apologize, I've missed a process step which I knew, and I apologize. Hopefully we can regenerate this. I actually have to poll you now for your

responses, so if we could return to 1(a), you don't have to vote again but hopefully everyone remembers what they voted 15 seconds ago. On question 1(a) on the asymptomatic near-term health outcomes, Dr. Campos-Outcalt, will you tell us how you voted?

DR. CAMPOS-OUTCALT: I voted one.

DR. BACH: Dr. Carr? You can identify yourself, or I can identify you.

DR. J.J. CARR: Three.

DR. BACH: Dr. Carr. Dr. Cuyjet?

DR. CUYJET: One.

DR. BACH: Dr. Deyo.

DR. DEYO: Two.

DR. BACH: Dr. Lawrence.

DR. LAWRENCE: One.

DR. LEFEVRE: Two.

DR. BACH: That's Dr. Lefevre. Dr. Lewis?

DR. LEWIS: One.

DR. BACH: Dr. Salive?

DR. SALIVE: One.

DR. BACH: Dr. Swain?

DR. SWAIN: One.

DR. BACH: Dr. Zuckerman.

DR. ZUCKERMAN: One.

DR. BACH: Okay, and what are we doing now?

MS. ELLIS: Go ahead, Dr. Kormos.

DR. KORMOS: One.

DR. BACH: That's Dr. Kormos. Dr. Lystig.

DR. LYSTIG: One.

DR. BACH: Dr. Hirsch?

DR. HIRSCH: The outlier, three.

DR. BACH: Okay. And I would like to do the same for 1(b), and actually, can I ask you to identify yourselves so I don't have to do that?

DR. CAMPOS-OUTCALT: Campos-Outcalt, two.

DR. J.J. CARR: Jeff Carr, four.

DR. CUYJET: Al Cuyjet, two.

DR. DEYO: Richard Deyo, four.

DR. LAWRENCE: Peter Lawrence, four.

DR. LEFEVRE: Frank Lefevre, two.

DR. LEWIS: Sandra Lewis, four.

DR. SALIVE: Salive, two.

DR. SWAIN: Swain, two.

DR. ZUCKERMAN: Zuckerman, two.

DR. KORMOS: Kormos, two.

DR. LYSTIG: Lystig, two.

DR. HIRSCH: Hirsch, four.

DR. BACH: All right. My preference is we're going to do the other voting and then we will return to the discussion of each topic, okay, so we're on to question two. For adults with lower extremity intermittent claudication, how confident are you that there is sufficient evidence for an intervention that improves immediate/near-term health outcomes?

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

MS. ELLIS: We're waiting on one vote. There we go.

DR. BACH: 3.2. Can I poll you?

DR. CAMPOS-OUTCALT: Campos-Outcalt, three.

DR. J.J. CARR: Jeff Carr, two.

DR. CUYJET: Al Cuyjet, three.

DR. DEYO: Deyo, four.

DR. LAWRENCE: Peter Lawrence, three.

DR. LEFEVRE: Frank Lefevre, three.

DR. LEWIS: Sandra Lewis, three.

DR. SALIVE: Salive, four.

DR. SWAIN: Swain, four, and we're not copying each other.

DR. ZUCKERMAN: Zuckerman, three.

DR. KORMOS: Kormos, three.

DR. LYSTIG: Lystig, four.

DR. HIRSCH: Fascinating. Hirsch, five.

DR. BACH: All right. And for 2(b), for adults with lower extremity intermittent claudication, how confident are you that there is sufficient evidence for an intervention that improves long-term health outcomes?

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

MS. ELLIS: We're waiting on one vote.

DR. BACH: Okay. Doug, go ahead.

DR. CAMPOS-OUTCALT: Campos-Outcalt, two.

DR. J.J. CARR: Jeff Carr, three.

DR. CUYJET: Al Cuyjet, three.

DR. DEYO: Deyo, four.

DR. LAWRENCE: Peter Lawrence, five.

DR. LEFEVRE: Frank Lefevre, two.

DR. LEWIS: Sandra Lewis, four.

DR. SALIVE: Salive, four.

DR. SWAIN: Swain, four.

DR. ZUCKERMAN: Zuckerman, two.

DR. KORMOS: Kormos, four.

DR. LYSTIG: Lystig, four.

DR. HIRSCH: Hirsch, five.

DR. BACH: Okay, and on to question 3(a). For adults with lower extremity critical limb ischemia, how confident are you that there is sufficient evidence for an intervention that improves immediate/near-term health outcomes?

And remember, in this case we decided that these were health outcomes experienced within the first six months.

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

MS. ELLIS: We're waiting on two votes, now one. We need one more vote, just one. Can everyone just press your button one more time? There we go.

DR. BACH: Doug?

DR. CAMPOS-OUTCALT: Campos-Outcalt, four.

DR. J.J. CARR: Jeff Carr, three.

DR. CUYJET: Al Cuyjet, five.

DR. DEYO: Deyo, three.

DR. LAWRENCE: Peter Lawrence, five.

DR. LEFEVRE: Lefevre, three.

DR. LEWIS: Lewis, five.

DR. SALIVE: Salive, two.

DR. SWAIN: Swain, four.

DR. ZUCKERMAN: Zuckerman, two.

DR. KORMOS: Kormos, four.

DR. LYSTIG: Lystig, three.

DR. HIRSCH: Hirsch, five.

DR. BACH: Hold on a second. Okay, great. The last question, which people are already answering, it's 3(b). For adults with lower extremity critical limb ischemia, how confident are you that there is sufficient evidence for an intervention that improves long-term health outcomes?

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

DR. BACH: Okay, go ahead.

DR. CAMPOS-OUTCALT: Campos-Outcalt, two.

DR. J.J. CARR: Carr, two.

DR. CUYJET: Al Cuyjet, three.

DR. DEYO: Deyo, four. Or, correction, three.

DR. LAWRENCE: Peter Lawrence, five.

DR. LEFEVRE: Lefevre, two.

DR. LEWIS: Lewis, five.

DR. SALIVE: Salive, two.

DR. SWAIN: Swain, four.

DR. ZUCKERMAN: Zuckerman, two.

DR. KORMOS: Kormos, three.

DR. LYSTIG: Lystig, three.

DR. HIRSCH: Hirsch, three.

DR. BACH: Thank you very much. We're going to now cycle back to the discussion on each of the questions, and in the context of these questions, the discussions have thresholds so if the vote is below, I can't remember if it's less than or equal. Yeah. So a vote, an average vote less than 2.5 means that we will not further discuss the particular intervention, so in this context, 1(a) referred to near-term outcomes of asymptomatic patients,

that received a score below the cutoff, I believe it was 2.2 or something like that, so -- right, 1(a), the mean was 1.4, which means we won't now discuss the questions related to it.

But the next one, 1(b), the long-term health outcomes with asymptomatic disease was over the threshold, it was 2.8, so the question to the panel, this, if you will, allows you to flesh out the question and the discussion and things like that, so, please identify the specific interventions and associated outcomes in terms of long-term outcomes in asymptomatic PAD. And the floor is open.

One of the, I don't want to call it a shortcut, but one approach that we all can take, or some of you can take, is you can actually point to some of the literature, reviews and other presentations that we've heard today, if you don't feel that cataloging every single thing is an efficient use of time. But the floor is open, and we're talking about long-term outcomes for asymptomatic patients. Go ahead.

DR. J.J. CARR: I would just say

current guidelines for both primary and secondary prevention have significant benefit on cardiovascular, heart and -- cardiovascular mortality, anywhere from 20 to 40 percent, and that was the intervention I was thinking of, basically lifestyle, control of risk factors, and medical intervention where appropriate.

DR. BACH: Thank you very much. So systemic interventions aimed at non-peripheral limb outcomes. I won't -- I in no way want to curtail the conversation, but I would take the view that that's a consistent theme we've heard throughout the morning. If there's a difference of opinion over these things then let's continue to pursue it. I would rather now put that to the side, again, with any objections I won't do that, I'm just trying to keep the process going.

With that off to the side, I would turn the question to both directed interventions and peripheral outcomes, given that you've just, I think, covered the waterfront of systemic interventions and non-peripheral outcomes. I'm looking for interventions in the peripheral space amongst

asymptomatic patients, evidence supporting those.

DR. HIRSCH: Just because there's silence, I mean, I think we heard from every speaker and from our Dukies that there is no role in space for that if we're saying, again, as you defined this, this is a truly ischemic limb population, then there is nothing to do.

DR. BACH: Dr. Swain.

DR. SWAIN: With the exceptions of popliteal aneurysms and the AHA exceptions.

DR. BACH: Okay, understood. Thank you for pointing to it, and we know exactly where to look for the AHA exception as it relates to peripheral disease. Dr. Lefevre.

DR. LEFEVRE: I do agree with the first commenter, we expect there is efficacy for antiplatelet and other interventions for patients with vascular disease. However, I think the reasons why I would rate this lower is I don't think we know what populations this is directed at. We say asymptomatic lower extremity PAD; I think we've heard here that's a very nebulous population, I think we heard

the studies include a whole range of patients

with all kinds of risks, so I don't think we can say who needs to be treated, so I rated it lower because of that, because of the populations being ill defined.

DR. BACH: Okay. Dr. Deyo.

DR. DEYO: Just to add slightly to that, I agree with the argument about systemic therapy, I think there's little question in my mind that that is effective and will have some benefit for these patients, but I have real reservations about recommending a screening program specifically for PAD, as opposed to screening for risk factors in general.

DR. BACH: Point taken, and, you know, the point of this discussion, we do not need to reach conclusion, if you will, during the discussion, but I want very much to get the impressions and conclusions aired for the purpose of the transcript and for the purpose of aiding CMS in the future.

DR. HIRSCH: So maybe for the purpose of the transcript, there's qualitative data unpublished, probably about one-fourth of

current CMS beneficiaries have an ABI done, or any PAD diagnosis, or at high risk. So even

though we're not advocating screening, Peter, and we don't know its role and there's no randomized trial, we unfortunately live in that world, as Dr. Beckman said, between marked profound under diagnosis and the disease that becomes evident. So I'm just putting it out there for the record.

DR. BACH: Okay, large reservoir of undiagnosed --

DR. HIRSCH: Just that it's having real cost and real effects.

DR. BACH: In bifurcating this discussion, I want to make sure that I have not shortchanged the possibility that some of the systemic therapies have peripheral benefits. I didn't hear that brought up, I didn't hear it in the evidence, but I don't want to -- that is a version of the two-by-two table that I should at least explicitly bring up and ask members of the panel if they feel the evidence supports peripheral benefits in the asymptomatic population of systemic therapy per se. I

focused on, if you will, cardiovascular and cerebrovascular outcomes in the way I separated things. So that's the question to you also.

Do you have a --

DR. J.J. CARR: I agree with what you said. I was just going to, for the record, there are prospective data comparing Framingham risk score, family history, ankle-brachial index, carotid IMT and coronary calcium in the NHLBI multiethnic study of atherosclerosis, a cohort of 7,000 people, Yeboah, published in JAMA, 2012, that could be used to evaluate the efficacy of a primary intervention with those tools.

DR. BACH: That was Dr. Carr speaking. Dr. Cuyjet.

DR. CUYJET: I would just add the comment, there was one slide that correlated GFR with outcomes, and we know that if your blood pressure and diabetes are well managed, renal insufficiency disease declines, so I would add that to systemic interventions.

DR. BACH: Thank you, Dr. Cuyjet. Okay. Go ahead, Dr. Salive.

DR. SALIVE: I didn't hear any direct evidence and so I'm kind of the opposing view on that.

DR. BACH: Could you speak closer to

the microphone, please?

DR. SALIVE: Sorry. I didn't hear any direct evidence that was positive on this. I felt that this was negative, and although the evaluation was, the average met our criteria, and I think that would be valid for a screening test, but I think this was negative. The presenters showed two aspirin trials that were both negative after screening for ankle-brachial index, and then there was some discussion about lipid lowering, which I believe was, you know, maybe in the high risk people, but lipid lowering is now widely recommended anyway, so I don't see why high risk would need to be identified through the ankle-brachial index.

DR. BACH: Okay. So Dr. Salive, when you said this, you're talking about the long-term outcomes with systemic therapy.

DR. SALIVE: Yes.

DR. BACH: Okay. Does anyone want to pick up on this point, because that differs from what I think Dr. Carr concluded, so is there a way to fill this in with evidence?

DR. HIRSCH: Well, if we're here to

highlight evidence gaps because, again, I've been very careful in saying what we know and then say what we don't know, so CMS, AHRQ and the investigators can fill in the gaps, we hardly reviewed the totality of evidence in this data-focused meeting today and there's no way we could have done that.

So there are at least two prospective trials, 4S was the one simvastatin trial, I can't remember the other lipid trial, where asymptomatic patients did not develop incident claudication, a robust pre-hoc defined endpoint. It's never been repeated, it's not been the focus of care, but there is some evidence out there, it's an evidence gap. Just because we don't know doesn't mean it might not be effective. And in the current Vorapaxar power one antagonist antiplatelet domain, there is initial evidence, a Bonaca paper in

Circulation a year and a half ago suggesting, again, that limb events actually are decreased by that particular antithrombotic agent.

But we haven't gotten that granular today, so these are evidence gaps that could be filled in.

DR. BACH: Okay, I appreciate it. I'd like to move on to question 2(a), which had a 3.2 mean score which, again, asks for, or leads to a discussion about which interventions and which outcomes in the context of immediate or near-term health outcomes for patients with intermittent claudication.

And let me actually propose, and we'll further curtail it within the limb, the peripheral outcomes, they need not be peripheral interventions but peripheral outcomes, as opposed to this kind of global set of cardiovascular and cerebrovascular outcomes. Dr. Swain.

DR. SWAIN: I think the exercise results are very reasonable for the short-term and I'll make my comment for the next question, for the long-term too, so I think exercise for

sure.

And then there's the question of whether endovascular revascularization does, and I think I agree with the Dukies, that that's an intermediate level of evidence for that.

DR. BACH: Do you want to distinguish

between supervised and home-based exercise?

DR. SWAIN: Oh, supervised, yeah. I know the results of this is whether CMS will cover that, and I think CMS should cover supervised exercise for all these reasons.

DR. BACH: Other -- Dr. Zuckerman?

DR. ZUCKERMAN: I'm just happy to agree with that.

DR. BACH: Oh, great, I love these comments. Dr. Lawrence.

DR. LAWRENCE: Yeah, I gave it a three, and the reason I did was because it really to me is dependent on the level of disease. So in intermittent claudication, the more proximal, the more the intervention is likely to be successful initially, so a claudicator with iliac disease will do

dramatically well and have a very long survival with a procedure. In fact, a juxtarenal aortic occlusion can benefit greatly from an aortofemoral bypass, immediate benefit.

But as the disease moves more distally, as in SFA or infrapopliteal, then claudication becomes to me a much less compelling indication for doing either a bypass

or intervention. So it's sort of in the middle where to me if it's distal, then it's a medical problem and it fits in with Dr. Swain about exercise and maybe cilostazol, whereas if it's proximal, you have a 90 percent success with any of the open or any of the endovascular approaches, so level of disease becomes critical to me in claudication.

DR. BACH: Other comments? Dr. Lefevre.

DR. LEFEVRE: I just want to say, I don't think it's quite right to say supervised versus unsupervised are different interventions. I think it's better to say, you know, exercise improves walking distance and supervised exercise more than unsupervised

exercise, indicating like a dose-response effect, it's a more intensive exercise intervention. So I don't think we should just say supervised is effective and unsupervised is not, we should just say exercise is effective and the greater the intensity of the intervention, the greater outcome benefits you get.

DR. BACH: Okay. And same question,

then, for long-term health outcomes for intermittent claudication.

DR. HIRSCH: Well, actually I'll speak up and --

DR. BACH: And actually you need not if -- no, no, no, Dr. Hirsch, I did not mean you need not speak up. What I was about to -- although that would be fine. No. I was about to say it may actually help for everyone else here who doesn't have a list of how everyone voted to say what your vote is. And you need not do that if you'd rather just speak, but it might help everyone to anchor your comments. So go ahead, Dr. Hirsch, I'm sorry for cutting you off.

DR. HIRSCH: I'm not sure I exactly followed that. Just to push the panel to have an open discussion, again for CMS and the audience, I was surprised at the relative downgrading of all of the interventions for claudication, and so just to provoke you all to speak up, whether it was the Duke presentation or the primary information offered, we have been presented evidence that pharmacotherapy that supervised exercise, yes, based on a

dose-response, endovascular and surgical intervention all work and they have been studied, each of these at least one year back to the bimodal TED distribution. So why is the level of evidence and confidence not higher? I'm confused.

DR. BACH: Also, that's a great way of asking a question that will also help answer some of the other discussion points, so I actually open the floor up to answer Dr. Hirsch's question. Dr. Lawrence.

DR. LAWRENCE: I would say the answer is because the superficial femoral artery is the key of a lot of the discussions here, and

the perception is that it's not durable so that it may get immediate success but there's a lack of durability. So it has to do, with me, again, the level of disease, not that it can't be initially successful, but that the durability is a major question with both open and endovascular approaches.

DR. HIRSCH: Peter makes a very good point, and for the audience that's not endo focused, it is true that from mid thigh down our patencies are not quite what we want them

to be, although they have certainly markedly improved.

But this gets to, our questions are difficult because we have three interventions, right? We have exercise, we have pharmacotherapy, and we have a range of anatomic possibilities, and yet we're asked to vote on all of them on one vote. What's challenging, if I were reading the transcript as a CMS officer later, I might be quite dour about the confidence that we can approve claudication interventions for Medicare beneficiaries when my level of confidence might be very high overall.

DR. BACH: Dr. Campos.

DR. CAMPOS-OUTCALT: Yeah. I voted three and two. That's because the evidence report showed a moderate level of confidence, moderate level of evidence, and it didn't go past a couple years, so I voted a three and two for that reason.

DR. LEFEVRE: I would agree. They were also very small studies, there were no large scale studies, and I think the effect size wasn't great, the walking distance improvement was not that great.

MS. JENSEN: Can you identify yourself for the record, please?

DR. BACH: That was Dr. Lefevre, I'm sorry. Dr. Swain.

DR. SWAIN: I voted four but it was, again, the heterogeneity on durability because, again, if it's a minimal claudication, I think durability should be defined out to five years, that's how I define long term. If it were somebody that couldn't walk, you know, 20 feet, that's a whole different patient. So the heterogeneity in this question makes it almost

impossible to answer, but we don't have good durability for endovascular or open surgical interventions, and I don't believe we have good five-year durability for things like exercise.

DR. HIRSCH: So Julie, I think you're making a very good point. What the group is saying is they want longer outcome studies for all interventions, and you're right, even for CLEVER it was 18 months only. Although if you had angina or if you had some other symptoms that migrate, my guess is you got 18 months of relief, my guess is you would be happy.

DR. SWAIN: That was my original --

DR. HIRSCH: Let's not minimize what 18 months means.

UNIDENTIFIED PANELIST: And also --

DR. BACH: Wait. I don't think anyone's minimizing it, but they have been separated into different categories. Dr. Lawrence, or, I'm sorry, go ahead, Dr. Lefevre.

DR. LEFEVRE: I think another way to look at the outcomes would be if they defined the minimal clinically important improvement in

walking distance and then we have a response rate, that would be much more meaningful to me than just an average.

DR. SWAIN: And we saw no MCIDs or anything.

DR. BACH: Dr. Lawrence?

DR. LAWRENCE: Yeah. Without a quote because this is from memory, but within the last year there has been a paper, I believe it was in JAC, that looked at patients and interventions, and I think it was exclusively in claudicators. In the United States there are almost as many procedures done for reintervention in less than two years than

there are the initial procedure. So in other words, we've almost reached a point where the initial procedures are occurring at about the same rate as reinterventions, and that addresses the issue of durability.

DR. BACH: Great, thank you. Other comments? No. Dr. Zuckerman, you still have your card up, I think. Go ahead.

DR. ZUCKERMAN: I just wanted to say, I think for many of these, and this was one, it

was a conflict between what seems logically likely and what the data show, and the data just aren't very good. And so even though it seems like if people exercise or have some kind of successful short-term benefit that would help them in the long-term, but we just don't have the data to show it.

DR. BACH: Okay, thank you. On to question three, the issue is critical limb ischemia in terms of interventions and outcomes affecting immediate and near-term health outcomes interventions and again, separating out those things that are systemic and targeting other parts of the body other than peripheral.

DR. SWAIN: Julie Swain. Again, you know, as I think it was AHA or ACC, you know, more blood flow. I think that's established, more blood flow will heal wounds, so for short-term into the heal wounds, get rid of pain, I think the evidence is fairly good that that occurs, I voted a four on that one.

DR. BACH: Let me ask you a point of clarification, and again, this is not my area

of expertise. What I heard was that there were no comparative studies that were at least a high enough level of evidence to get into the Duke review or they predated the Duke review, where usual care or nonintervention was the control?

DR. SWAIN: Yeah. Nowadays really, the standard of care is to intervene, I mean, that's the standard of care. So the idea that you're going to have a comparative study to do nothing and let them sit there and have a stinking wound before you amputate, or do something, and, you know, on this particular subset I think it's the provide more blood flow, we have good short-term healing, and we've seen it from the practitioners and all of

us who do vascular surgery, heal and get rid of pain and make the patient more comfortable.

And long-term wise, most of them are going to die pretty soon anyhow, so if we say long-term is seven months or eight months, then make them more comfortable, as part of the interventions and the outcomes that you all are looking for.

DR. BACH: Thank you.

Dr. Campos-Outcalt.

DR. CAMPOS-OUTCALT: Yeah. I think this is the classic example where observational data can be upgraded, because the magnitude of effect of doing nothing versus doing this is quite large, and so you don't have great studies but you could upgrade them because of the observational magnitude of effect. So that's why I gave it a four, even though I don't think the studies are particularly robust.

DR. SWAIN: Yeah, and I have a big problem with the graphs we saw on several slides of length of life for vascular intervention or those that were amputated, and people may have a shorter lifetime. I mean,

there is no comparability between those two groups of patients, and I saw no propensity for analysis studies done for that, so I think those are just, the idea of having another MedCAC panel on amputations, I don't see the reason for that.

DR. BACH: Dr. Lewis.

DR. LEWIS: One of the evidence gaps with the compression devices and hyperbaric treatment may be in the patients who are not candidates for that intervention.

DR. BACH: Yeah, we didn't hear much evidence of that, although we did see some dramatic pictures. Dr. Lefevre, did you want to say something?

DR. LEFEVRE: Yeah, I just wanted to comment. I gave it a three. I do agree that this is an issue where we could accept a lower level of evidence, we don't necessarily need an RCT. If you have a patient population that truly has no other alternative and is heading for a limb loss, then certainly these are improved outcomes. The reason I only gave it a three and not higher is because I think that's a slippery slope at selecting the patients, and

it's very easy to think, you know, it's not easy to select just the patients who are going to lose their limb, it's going to be hard, you know, and you might end up selecting patients with less disease and end up potentially even doing harm.

So I think that kind of threshold of where to intervene and could we truly define a population that has no other alternatives than to lose their leg, I think is questionable, so that's why I gave it a three.

DR. BACH: Dr. Carr.

DR. J.J. CARR: My thinking on this question, and I voted a three and two, is that an ounce of prevention is worth a pound of cure, that there's tremendous investment in resources here at the end, and I think the speakers and the public speakers did a good job indicating that there's a huge reservoir of PAD out in the community that is undiagnosed, and I would urge CMS to develop strategies to uncover clinical disease that's simply not manifest, and encourage trials that would allow us to better risk stratify these people with disease and develop strategies, rather than continually

going from simply asymptomatic to symptomatic in critical limb ischemia.

I think there's a lot of opportunity to target, you know, identify through biomarkers, through genomics, through risk

factors, not necessarily imaging or diagnostic testing, but there are probably ways that could more effectively risk stratify and identify at-risk women and minorities that have evidence of peripheral arterial disease, as well as treatments that could be more effective.

DR. BACH: Dr. Salive.

DR. SALIVE: Yeah, I guess I downgraded it because there was only the one trial, but I did actually appreciate that there was quite a lot of observational evidence presented in the TA, and so it was helpful but it didn't sway me further. I just think that it is too weak, and other speakers have commented that some of these can be studied observationally and stronger evidence could be provided that way, so that's what I was thinking.

I think the trial that's underway that was presented was helpful as well, in terms of

answering this question farther down the road.

DR. BACH: Dr. Lawrence.

DR. LAWRENCE: I think the reason that there are not prospective randomized trials is

because it would be unconscionable to not treat patients who have critical limb ischemia lesions. So I mean, this is evidence that's 40 and 50 years old, and it would be like saying we need a new randomized trial to justify the use of Heparin and warfarin for PE. It's not going to happen because it would literally be negligent to have the patient with an arterial lesion and true critical limb ischemia.

Now, rest pain is always a little questionable because that can go either way and sometimes patients can sit with that, but if you truly have an ischemic ulcer, gangrene, and don't treat the patient, I can't see any rationale or justification as long as they have a treatable lesion.

So to me, this has to go to both early results and long-term, they need to be a five. This is the only option for these patients, and it's just a question of what kind of treatment they're going to get, not whether they get

treatment of not.

DR. BACH: Okay, thank you. Marcel, did you have something else? Let me move on to

(b) then, which scored slightly lower than the immediate and near-term outcomes. The long-term health outcomes for critical limb ischemia, and using the rule that we established this is outcomes durable to two years amongst these interventions.

So again, it's a limited number of interventions that have come up and I guess the question is, you know, discussion around those interventions and outcomes, is there more detail or texture that we can give CMS around these outcomes or interventions? Great, I managed to pose a question where I silenced everyone, which of course is my goal.

(Laughter.)

All right. And I'm going to circle back one more time here through the three questions, there is another discussion point that we need to bring up, and I grouped these because I think to some extent they go together, but the second bullet reads considering, and this is for each of the three

questions, considering the heterogeneity of the Medicare population, discuss which subgroups of

the Medicare population the evidence shows are likely to benefit or likely not to benefit from intervention.

And so I'll take these in order beginning with the asymptomatic population, but then again, disagree with me as you like, I believe these are, the answers to these will generalize across the three questions, but again, correct me if I'm wrong. Dr. Carr, you still have your tent card up. Dr. Swain.

DR. SWAIN: I just don't think we have enough data for subset analysis, that's the problem, and the biggest subset I see is diabetes or no diabetes. It may be that doing, let's say an open surgical or endovascular intervention in diabetics may well give you better long-term results or it may well have a blended long-term effect depending on the control of the diabetes and all that. So again, the data is just, if there's not enough data for the aggregate, there's certainly not enough data for subset analysis in different Medicare populations.

DR. BACH: And would your view of that

cut across all three categories, all three questions?

DR. SWAIN: Pretty much so.

DR. BACH: Okay, fair enough.

DR. SWAIN: I don't know about critical limb ischemia, again, I do think you'd supply blood, but the other two for sure.

DR. BACH: Fair enough. Dr. Carr.

DR. J.J. CARR: For question one in the asymptomatic, there's a fair amount of large scale data that subclinical atherosclerosis in people with peripheral arterial disease predicts cardiovascular morbidity and death, especially in women and minorities in an untreated group, and so I think that there are data that could be reviewed that would justify more aggressive prevention in the at-risk populations and reduce morbidity later in Medicare-aged beneficiaries.

DR. BACH: More on that point, or something else. Dr. Cuyjet.

DR. CUYJET: I'd just make a general comment. I mean, the literature regarding

depression as a comorbidity and its impact on coronary heart disease is irrefutable, and there's been not much discussion, we had one case presented of a gentleman who continued to smoke and did all this other stuff, but I did hear the word depression come up in the presentation. So when we talk about general care of the total patient, I think depression screening is indicated and recommended for it to be a general part of the evaluation of patients with suspected PAD.

DR. BACH: Thank you. Dr. Salive.

DR. SALIVE: Yeah, so I think to generalize maybe the last couple comments, I think it is the multiple chronic condition people in the Medicare population who benefit greatly, so yes, it might be the diabetic, it might be depression, and there's many other chronic diseases. And I think there was a nice slide from someone about kind of the overlap of coronary artery disease, cerebrovascular disease and PAD, but I would just say it extends to a variety of chronic diseases and, you know, we don't know much, it would be nice to know more, so the studies need to kind of

ascertain the chronic deceases, the comorbid diseases that are accompanying this so that it can be understood a little bit better and, you know, this is really a very high risk group with the PAD group.

DR. BACH: Yes, please.

DR. KORMOS: So just following up on what Dr. Swain said, I also saw a fair amount of data, getting back to the issue that there's a differential in presentation, especially in intermittent claudication based on gender, race, age, we mentioned diabetes, and there were a few others in there as well that if trials are going to be designed in the future, then they probably need to adjust for some of these differences and it goes with some of these things.

And it actually gets to the point that, I think that Dr. Hirsch meant, that we talked about asymptomatics, but those asymptomatics could include people with previous peripheral vascular disease, and that's a subset that doesn't really get addressed in any of this.

DR. BACH: Thank you. Okay. Moving

on, then, that's the end of the discussion of the questions and the voting and the subsidiary discussions around those.

I do want to leave, the floor is open and if we in the next discussion come back to some of those things, that's fine. This is supposed to be a free ranging discussion.

But we do have some additional discussion topics that I think we've already, some of the comments have sort of bled into this area already. They are to discuss the important evidence gaps that have not been previously or sufficiently addressed by the literature, and to discuss any apparent lower extremity PAD treatment disparities and how they may affect the health outcomes of Medicare beneficiaries.

I'll start. I'm not providing the answers, I'm just going to repeat some of the things I've heard during the course of the discussion in terms of evidence gaps. I've heard very consistently today that there are important subsets, of course this is not my disease area, but diabetics, nondiabetics; gender or, pardon me, sex difference; race,

particularly African Americans; location of the lesion. These are all themes that I've heard from multiple people over the course of the day as important ways of thinking about this condition.

And then interplay between other types of vascular disease, nonvascular disease such as depression is another evidence gap that has come up, and then the issue that really has revolved initially around the questions, but very much around the discussion around clinical trials design, the tightness of the definition of the cohort, the tightness of the definition of the outcome, and in the middle of there is the tightness or looseness of the interventions given a rapidly changing, particularly on the device side, rapidly changing landscape of devices. So I have already heard all those things; if you want to take any of those off the list, let me know. If you want to add things to the list, please have at it. Dr. Lawrence.

DR. LAWRENCE: Yeah, there are two that I would just suggest you consider adding,

25 although you touched on them. One is the

1 unreconstructible patient, the patient who
2 either because of prior interventions or prior
3 procedures, or they just have such diffuse
4 disease that there's no available treatment,
5 has a high likelihood, and particularly those
6 that have wounds or have a chronic disease
7 which will, like a wound, which takes a
8 tremendous amount of resources.
9 And then the other is to address
10 specifically infrapopliteal disease. I think
11 that maybe aortoiliac has gotten most clearly
12 defined as far as management. Fem-pop, as
13 we've heard today, has a lot more evidence
14 coming up, but infrapopliteal disease and very
15 distal disease, it particularly occurs in
16 diabetics, and I think that that's going to be
17 an area that needs to have much more
18 investigation and many more studies than we
19 currently have.
20 DR. BACH: Fair enough.
21 Dr. Campos-Outcalt. Sorry, Doug.
22 DR. CAMPOS-OUTCALT: That's all right.
23 I think the diabetes question is particularly

interesting and important. Peripheral vascular disease and diabetes together is a bad

combination, and I just think that there's going to be differences in treatment that need to be fleshed out.

Secondly, the disparities, we've documented disparities but I'm not sure we've got a lot of research on why the disparities exist.

DR. BACH: We're going to get to that. We're not on that question.

DR. CAMPOS-OUTCALT: Okay, so I'll hold that one. I think the research on better ways to find symptoms, which has been discussed, is probably another one I would add, and then the obvious one is comparative effectiveness. We just don't have very good comparative effectiveness data.

DR. BACH: Thank you. Dr. Deyo.

DR. DEYO: Yeah. In terms of subsets that I think need more attention, we tend to think of everybody in the Medicare population as old, but I think there's an important difference between young old and old old, and

the risk/benefit equation may change with increasing age, and I'd like to see more studies that segregate out the old old

population and help inform us better about that group.

DR. BACH: Fair enough, and I assume for all of us that cutpoint moves up about a year every year. No, the point is taken. I'm sorry, I don't mean to be silly. Dr. Carr?

DR. J.J. CARR: Just for the record, I was going to point out that, and this may be obvious, but atherosclerosis is the disease, and within atherosclerosis there are manifestations within different vascular beds, renovascular, peripheral arterial, coronary disease, cerebrovascular. And then I would just for the record say that there are large and medium arteries that could be involved with the disease, and small vessel disease in the kidneys or in the distal legs, and that as CMS thinks about this, just like they would lung cancer, realize that it's one disease that may have multiple manifestations based on where the disease metastasized to or the organ system

involved.

That complexity confounds a lot of this discussion, but an understanding of that pathobiology will be very helpful as we move to

precision medicine where we look at genetics, we look at evolving treatments that are near to being available to the Medicare population that will have multiple organ system effects across the vascular system.

So, I think thinking of peripheral arterial disease in isolation from these other manifestations of atherosclerosis will not give us a comprehensive picture of how we can best manage it in the Medicare population.

DR. BACH: Thank you, Dr. Carr. Dr. Deyo, is it your card or are you done? Dr. Lefevre.

DR. LEFEVRE: One more subpopulation I think would be by severity of the PAD. I didn't see any studies that restricted or stratified patients by mild, moderate or severe level of disease, and I think I'd like to see studies segregated by either ABI or maybe even better, functional status, in terms of

interventions directed at different stages of disease.

DR. BACH: Thank you. Dr. Salive, I guess you don't have a question. Dr. Swain.

DR. SWAIN: A subpopulation of those

who are having a second intervention, because that's a specific one, and I disagree again with the BEST trial that, you know, an intervention that can lead to death or limb loss, which is endovascular, surgery or anything, that it is not a minor procedure. So we have that particular subset of reintervention, which apparently is very common.

DR. BACH: Dr. Zuckerman. Thank you.

DR. ZUCKERMAN: I don't think it was part of this discussion so much, but to emphasize what someone else said before about the importance of having better data earlier in the process, so that when they're more likely to be short- and long-term benefits and just having better data on, we have to figure out how to do screening that works and that leads to interventions that work, and I don't think

we have research that shows that. Maybe there is no way to do it, but maybe there is and we just haven't gotten the research done yet.

DR. BACH: Okay, thank you.

Dr. Lawrence.

DR. LAWRENCE: Just a brief comment.

It's interesting to me that in all of the discussion today, I haven't heard the word stem cell mentioned once, and yet there have been like five or six trials of stem cells, and many people in the cardiovascular community think of the lower extremity as the place where the role of stem cells will be investigated. So not that it should be thought of now as a therapy, but when you're talking about gaps in knowledge, I think that approaches, that's why I mentioned unreconstructible disease and restenosis, the patient has multiple procedures, is that stem cell may have a role there, and that's certainly something we can encourage CMS to support, and there will, I think there will be research, and that may be all that we're talking about at a conference like this, is the role of stem cells in PAD.

DR. BACH: Okay. Well, that goes into the, if you will, to categorize it, that's sort of, let me call it new technologies, or not well understood.

I actually wanted to ask a question about that, which is the compression devices. We've heard a fair amount about it. It's not

an area that I know much about. Is there an evidence gap there, or was it that our reviews didn't take in what we should have taken in? Dr. Hirsch.

DR. HIRSCH: Yes, there's an evidence gap. Clearly we were presented with a number of trials that demonstrated some initial efficacy but the sample sizes are small, the descriptive populations are not necessarily representative, but there is at least a biological reason to presume there might be efficacy, so there is a research gap.

DR. BACH: And again, apologies for the naivete. Is it possible that could be side by side with other interventions for critical limb ischemia, or does it only have to, is it your expectation this will only be for

nonoperable patients?

DR. HIRSCH: Once again, this may come off Peter's comment. For all the things we study, when we tend to combine different syndromes, CLI and claudication, asymptomatic and claudication, we tend to learn very little, because already the panel doesn't like the sample sizes, so it's always wise to have a

relatively well described single population. A CLI compression trial would likely be distinct from a claudication compression trial.

Peter, your comment about cell therapy, you know, the National Heart Lung and Blood Institute sponsors the CCT-based trial, I'm the national co-PI looking at claudication cell therapy, but there's only 80 patients, and if you didn't like CLEVER and you didn't like the other studies of a hundred, you're not going to like this either. So I think what we're maybe saying to ourselves back to CMS is since it's been very, very, very, very, very, how many very's, hard to get people to be actually aware of the trials and to be randomized. Again, like other new therapies,

if there isn't a reason to incentivize research participation to have adequate enrollment and adequate sample sizes, this field will never move.

DR. BACH: Point made, thank you. Dr. Swain.

DR. SWAIN: I'd like to second that for virtually all the trials. You know, I think CMS was, one of the first ones to require

payment be, that you be in a trial was lung volume reduction surgery, and I think for a whole lot of these devices and trials that they should go on, and the way to incentivize if you're going to pay for it is you be in the trial. And that works well, because the off-label use and everything is impossible.

DR. HIRSCH: But Julie, if you're going to ask for that, I'm going to ask for parity, it's not just device trials, my device maven, but it's equal for pharmacotherapy and behavioral therapies. Thank you.

DR. SWAIN: Very good.

DR. BACH: Dr. Zuckerman, do you have another comment?

DR. ZUCKERMAN: No, I'm sorry.

DR. BACH: That's all right, thank you.

So along the lines I have heard a call for coverage under evidence development, is the technical term for that. There were also discussions about registries and quality improvement in the context of registries. We heard about a large registry going. Is it reasonable to argue that there would be subset

differences in outcomes based on institutions participating in those registries or not? I'm seeing head nods, which is one of the things we can't record in this meeting.

DR. SWAIN: Swain says yes.

DR. BACH: Dr. Lewis.

DR. LEWIS: Well, we certainly saw differences in rates of such things as amputation, et cetera. I don't know why we would think that there would be homogeneity across the country in these things, so I think looking at heterogeneity of site is very reasonable.

DR. BACH: Dr. Salive.

DR. SALIVE: So yeah, I think one thing to incentivize also is the pragmatic trial, and I think we heard a pretty good example of one, although I didn't hear enough details today about that trial. But I think that the reason to do it is to allow for wider strategies for treating these problems and, you know, have some ability to compare them and enroll a variety of different specialties, I think as we heard, to do the procedures and treat the patients.

So I think, you know, that pragmatic trial idea, it didn't sound like it was fully pragmatic, and I know it's a spectrum of pragmaticness, but to me also, I think this gets to the idea that people were mentioning of personalized medicine but, you know, an individualized approach that involves the patient is needed, I think, in this, that I don't think we heard too much about, because what are their priorities? And older people have different priorities, they don't all have the same priorities, and it's not related to the diameter of a certain vessel in their leg,

so it may be related to their functional status, and I think that was reasonably examined here.

So I think the studies of patient preference are also a gap that we should try to get, encourage some work there.

DR. BACH: Okay, thank you.

Dr. Lystig.

DR. LYSTIG: So, you'd asked the question about the registries and about seeing heterogeneity by sites, so I think in the presentation we've seen from the registry

result I did not see what would deem to be sufficient accounting for the possible differences in the patient populations by sites, so I'm less interested in seeing that sites have differential performance than seeing after having made appropriate adjustments to see a comparable patient population between those sites, you might then have differential performance. So when we are looking at these observational data sources, we have to take appropriate steps so we can draw the appropriate inferences from it and make fair

comparisons.

But then I'd also just point out too that within the context of registries, there is a difference between doing a census and doing a sample. If you do the samples right, within stratified sampling, for example, you can make very good inferences about targeted subgroups. It is not necessarily a requirement that in order to have effective findings from a registry it needs to be a census of everyone with a particular condition, it's appropriate not to conflate those two issues.

DR. BACH: Agreed. Dr. Hirsch.

DR. HIRSCH: I was going to add one more positive comment to get us out of our depressive rut.

No, but seriously, I'm worried a little bit today about disparities and to answer questions that focus on what we don't know, we don't know, we don't know. And for those who presented, there's an awful lot of consensus out there that is well grounded, I'm conservative in the scientific base, and gosh, I don't have quite the date right, but PAD

performance measures, these six to seven things that every vascular site thought were appropriate exist and have been published and peer reviewed, there's no controversy.

It was simple things, as you've said before, like statins, appropriate antiplatelet therapy, appropriate ABI use, appropriate graft surveillance once you've had your bypass graft, and these disparities that exist within registries and practices are a problem, aren't they? Because even if we know what, you know, a CMS beneficiary should do if there's this huge disparity, we already know scientifically with dissemination research it's easy to

abolish disparity by measuring these and then having appropriate pay interventions.

So I just want to put on the record that the performance measures that exists for CMS is an excellent guidepost to a bare minimum of what we know.

DR. BACH: Okay, thank you. Dr. Swain, do you have another comment?

DR. SWAIN: This is totally different than the others, but is there a possibility

that CMS with their big bucket of money that they have, to support, help support the registry? Because the biggest lack I see in the SVS compared to the STS is on-site audit. Once you start doing some, it doesn't matter how many you do, it's amazing how the data get changed when you're at risk of having an audit, not just a statistical audit, that's certainly important, but on-site audits, and then a requirement to enter data in the registry for payment, I think would go a long way in helping. And audits are the most expensive part of any of these, is having help pay for at least some number or percentage of sites' audits.

DR. BACH: Let me move on to the last -- I can answer that question, which is I think it's unlikely to have a mechanism in place. But, you know, as a condition of coverage, there are other financial incentives for institutions to do it.

The last question is, discuss any apparent lower extremity PAD treatment disparities and how they may affect the health

outcomes of Medicare beneficiaries.

Dr. Cuyjet.

DR. CUYJET: Al Cuyjet. Obviously we've seen disparities in outcomes among different populations and given the evidence gaps, it begs the question as to how we're expected as primary care providers to assess and manage these patients. You can look at the, New York's just in its seventh month of the Nurse Practitioner Modernization Act, I think we're the 17th or 18th state.

And so the point is, it brings me back to 2002 with the ALL HAT trial and we all got carted off down to Texas for dissemination training, and I think a big piece of this needs to be, when we have the evidence, it's fine

that we know it, but it needs to be disseminated and diffused into the practice population so when patients do show up, they're assessed and managed accordingly, and I think CMS can play a big part in that.

DR. BACH: Okay. Thank you for that comment. So you skipped over the answer to the question so let me fill it in, which is that

there are, appear to be at least outcome disparities and large treatment disparities in terms of amputation rates at least by race, this is what I saw on the slides, correct me if I'm wrong, and that very large effects due to income as well, or at least using ecologic metrics of income as well, such as income or ZIP code or something like that. And I think you went further and said okay, given that, what should we start thinking doing about it; is that right?

DR. CUYJET: I can tell you just as a simple example, I mean thiazides are the cheapest way to treat hypertension. The prescription rate was tracked actually with an implementation dissemination product and the curve kind of went like this, it had been going

like that for some time. So it's an effective intervention that does work and it does improve control rates, depending on what your target is.

DR. BACH: Other comments about disparities? There was an earlier comment that suggested that subsets of patients, probably

the ones showing high rates of amputation, for example African Americans, might be evaluated differently, that maybe, I think what I was at least reading between the lines, that the approach in African Americans, maybe the screening approach should be more aggressive or started earlier, or that the triggers for evaluation of vascular disease might be set at a different threshold in populations at higher risk of these very bad outcomes. If I didn't hear that, then please correct me.

DR. HIRSCH: You heard correctly. So, the general global epidemiologically accurate disparities is African Americans, Hispanics, Native Americans, yes, the extreme elderly who are still viable, smokers, diabetics, and people with Stage III and Stage IV CKD all have the highest CLI and amputation disparity rates.

But the disparity has at least four components which could all be solved. One is access to research again; it's true that women are underrepresented, there's almost no minorities in our current research portfolio, it's unbelievably adverse. Access to

diagnostic interventions, a simple ABI or duplex. The third is access, again, to treatments; the thiazide motif is true, more potent antiplatelet agents are better, and they're not used as well in the lower socioeconomic groups. And then lastly, again, obviously rehab and outcomes.

All these disparities exist. As my colleague Dr. Beckman says, PAD by itself is the disparity. It doesn't matter if you're white, black, you live in downtown Minneapolis or Rochester, you're not going to do very well, but yes, we could serve to focus on those high risk groups very very easily.

DR. BACH: Further comments? Dr. Cuyjet, did you have another comment? Okay, great.

I want to thank the audience for putting up with us, I want to thank the panel

for putting up with me, and for Medicare for giving us the opportunity to have this discussion, and for the presenters for what is obviously hundreds of hours preparing for this combined, for a very, if you will, very long

runs for very short jumps in some cases, but thank you very much for the broad perspective and for the academic discussion.

We have, we are going to essentially wrap up. That is essentially my closing remarks. The purpose of this committee and of FACA type activities is to have an open public dialogue around issues that hopefully will do a number of things, not only to help the Agency contemplate important problems, but also drive a research agenda, and this room is full of people who are thinking about research agendas, and hopefully eventually drive policy, although Medicare would never say that is true. You know, when you hear calls for supporting registries, hopefully the folk a few miles south of here are hearing that as well. So thank you again, all of you, for your time, and I want to give the microphone to Tamara.

MS. JENSEN: Thank you, Dr. Bach,

thank you for being the chair today. It was a great panel, it was a great day, very impressive presentations, a very impressive panel. So let me reiterate what Dr. Bach said,

and thank you very much for everything you've done today, it's been very helpful. We have a lot to take back and we will be looking at this over the next six to eight months to see what we will be doing next. So, again, thank you very much.

DR. BACH: We are adjourned.

(Whereupon, the committee adjourned at 3:53 p.m.)