

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

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

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

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

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

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

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

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

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

10 opportunity to speak on these important issues.

11 Thank you.

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

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

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

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1 through scientific-based remedies.

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

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

14 We know that most people are not
15 recognized. Rina Pandi published using the
16 NHANES database. You can see here that of the
17 7,500 patients over the age of 40, 647 of them
18 had PAD. Only 196 were diagnosed with
19 recognized PAD, whereas 451 weren't. This
20 corresponds to nearly five million Americans
21 who have undiagnosed PAD, five million
22 Americans.

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

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

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

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

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

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

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

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

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

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

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

5 What does coverage mean? These

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

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

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

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

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

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

7 PAD is common but your patient may
8 have never heard of it. This is an awareness
9 gap and public knowledge study that looked at
10 the awareness of PAD, and it compared to other
11 diseases such as multiple sclerosis, Lou
12 Gehrig's disease, cystic fibrosis, and as you
13 see here, the prevalence of PAD is over nine
14 million individuals, compared with multiple
15 sclerosis at 300,000, where the disease
16 awareness is only 26 percent; in other words,
17 76 percent of individuals did not know about
18 PAD.

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

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

4 addition, they were less likely to take
5 aspirin.

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

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

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

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

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

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

1 again, may reduce the risk of adverse

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

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

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

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

25 When you look at evidence for the

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

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

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

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

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

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

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

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

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

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

3 Dr. Jones referenced this article, the
4 AHRQ review, which specifically addressed the
5 comparative effectiveness between endovascular
6 therapy and surgical revascularization for
7 patients with critical limb ischemia, and as of
8 2015 we believe that endovascular therapy is at
9 least as effective as surgical
10 revascularization in the treatment of critical
11 limb ischemia with the goals of avoiding major
12 amputation in the affected limb.

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

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

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

25 who are interested solely in the diagnosis and

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1 management of patients with peripheral vascular
2 diseases.

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

15 I would also like to disclose that I
16 am the founder and medical director of VasCore,
17 the Vascular Ultrasound Core Laboratory, which
18 has participated in over 170 clinical trials in
19 66 countries; many of the PAD trials referenced
20 this morning and throughout the day, we
21 participated in. VasCore is solely owned by
22 the Massachusetts General Physicians
23 Organization. All agreements are provided

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

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1 of trials or performance of VasCore.

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

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

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

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1 claudication. In addition, we feel it's
2 critically important that all home medical
3 therapy be offered as first line treatment.
4 You've already seen an excellent
5 presentation by my colleagues from Duke about
6 this technology assessment, and you heard from
7 Dr. Dake about some of the information about a
8 drug-eluting stent. There were a number of
9 studies that were not included in that initial
10 presentation, and although reviewed today by
11 Drs. Schuyler Jones and Manesh Patel, there is
12 lots of information there worth this panel
13 understanding, and you can review that in the
14 slides.

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

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

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

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

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

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

25 DR. ARONOW: I would like to thank the

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

5 DR. BACH: My apologies.

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

8 My potential conflicts are shown here,
9 they're largely societal and not financial.

10 The American College of Cardiology did support
11 me in travel expenses for today. The ACC is a
12 nearly 50,000-member organization, a
13 not-for-profit, and its members are responsible
14 for caring for patients with cardiovascular,
15 and as it relates to today's presentation,
16 patients with lower extremity PAD.

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

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

25 I think before I launch into that I

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

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

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

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

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1 punt.

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

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

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

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

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

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

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

16 I'll end there, thank you very much

17 for your attention.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

12 reimbursed my flight here but has not
13 reimbursed anything else.
14 So, over the last 15 years of my
15 career, I've had the opportunity to work on
16 several writing panels. I've worked on
17 American Heart consensus panels and several ACC
18 agency panels. Here are my disclosures.

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

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

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

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

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

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

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

9 These are secondary interventions of

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

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

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

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

9 and further investigated with studies.

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

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

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

8 DR. BACH: Please try and wrap up.

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

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

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

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

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

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

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

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

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

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

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

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

4 So, the second thing I wanted to say

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

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

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

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

4 learned that there too, PAD patients are poorly
5 reimbursed.

6 DR. BACH: Please try and wrap up.

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

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

1 Comprehensive Wound Care.

2 DR. DENHAM: Thank you very much,

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

15 And the patients that we have helped
16 with the arterial pneumatic compression pumps
17 are extremely grateful for the help. The first
18 is a 97-year-old gentleman that I met with rest
19 pain so badly that I didn't appreciate how
20 mentally alert he was. He couldn't even sit
21 still in the office, constantly shuffling his
22 feet trying to get comfortable. We've all seen
23 patients like that. His wounds were wet
24 gangrene of his fifth toe. He quit smoking in
25 1937 and, as I said, was mentally alert. And

1 this is a photo of his wet gangrene, and you

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

16 For outcomes that matter to
17 patients --

18 DR. BACH: Please try to wrap up.

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

23 patients that will be evaluated.

24 So to conclude, there is a large

25 growing body of Level I evidence supporting the

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1 use of endovascular therapies for PAD patients.

2 Many contemporary studies were not included in

3 the AHRQ review. And while we agree with

4 registries playing an important role in this

5 space, mandating the reporting for a single

6 registry could pose significant infrastructure

7 and resource challenges to hospitals,

8 particularly given that many providers are

9 already participating in other long-term

10 registries and studies. We are excited about

11 the dramatic improvements we're seeing in

12 patient outcomes and the newer endovascular

13 therapies. Thank you very much.

14 DR. BACH: Thank you very much,

15 Dr. Turco. I would like to introduce Terry

16 Foust Litchfield, vice president of clinical

17 operations at Lifeline.

18 MS. LITCHFIELD: Thank you very much

19 for the opportunity to present today. I

20 represent Lifeline Vascular Access. I would

21 like to disclose, I am an employee.

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

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

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

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

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

25 What we also see from the patient's

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

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

19 This is the KDOQI, the renal guideline

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

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

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

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

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

18 MR. THATCHER: Thank you, Dr. Bach,

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

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

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

12 As we've heard today, CLI is the most
13 severe form of PAD and these patients, if
14 they're not revascularized, amputation rates of
15 40 percent and mortality rates of 20 percent
16 occur, often within six months, and the
17 macroeconomic burden, not just the index

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

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1 We note some key differences in CLI
2 patients who are revascularized versus those
3 who have amputations. Some of these have been
4 highlighted before by other speakers, one-year
5 mortality for Medicare beneficiaries is 48
6 percent and three-year mortality is 71 percent,
7 versus two-year mortality of only 16 to 24
8 percent for those who are revascularized. 70
9 percent of amputation patients go on to an
10 extended care facility versus only 20 percent
11 who are revascularized, and 60 to 80 percent of
12 amputees are unable to walk again, compared to
13 two-year revascularization data showing 80
14 percent of these patients are walking and 90
15 percent of them are living independently.
16 And while the clinical and economic

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

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

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

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

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

25 DR. BACH: Thank you very much. Could

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

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

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

25 Today very often we tell patients, are

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

14 symptoms and they're real, they never were
15 asymptomatic.
16 So, I just want to wrap it up there
17 and just implore you guys to think about moving
18 away from asymptomatic and to looking for what
19 the actual symptoms are.

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

25 MS. WISE: AngioDynamics.

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

3 May I have Richard Conray, from Around
4 and About?

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

13 as well.

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

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

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

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

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

12 And also, this is cost effective for Medicare.

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

16 MR. CONRAY: I'm sorry?

17 DR. BACH: Who paid for your trip
18 here?

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

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

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1 We are going to -- we are ahead of schedule and
2 I will be militant about maintaining that small
3 advantage. It is now 11:37, we are breaking
4 for lunch. We are, that puts us 13 minutes
5 ahead of schedule. We will be back here at
6 12:22, we will begin the discussion.

7 (Luncheon recess.)

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

11 the agenda, where I've added a break. There's
12 two components here, the panel will ask
13 questions of the presenters who have been nice
14 enough to sit here in the front row or near the
15 microphone here in front of me, and then we
16 will have an open discussion in the tradition
17 of a FACA committee, between one another.
18 After that we're going to take a ten-minute
19 break, which I'm estimating to happen at about
20 2:15, so we'll obviously see how this all goes.

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

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

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

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

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

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

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

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

8 DR. BARTHOLOMEW: So, I think one

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

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

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

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

8 guess we would define that as an ABI less than
9 0.90 as asymptomatic PAD by my criteria, but I
10 think that some of the things that can be done
11 to prevent complications are not only once you
12 recognize that, but perhaps to certainly
13 monitor the individual's blood pressure, check
14 the lipid panel, and advise him to quit
15 smoking, but certainly the guidelines suggest
16 if you had officially diagnosed with PAD you'd
17 want to get the LDL cholesterol under 70, you'd
18 want to make sure their blood pressure was 140
19 over 90 or lower, you'd want them to quit
20 smoking, you would like them to follow a good
21 diet, a low cholesterol diet, and exercise
22 regularly. Did that answer your question?

23 DR. J.J. CARR: Thank you.

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

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

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

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

17 DR. CHIN: Please.

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

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

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

5 THE COURT: Dr. Deyo, question?

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

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

25 Data for specific populations where it

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

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

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

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

20 DR. DEYO: Thank you.

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

23 Dr. Zuckerman, please.

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

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

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

14 DR. JONES: Thanks for the question.

15 I think, when we really constructed the
16 questions it was hard to figure out how to
17 evaluate differences in usual care and/or
18 placebo, compared to the interventions. So
19 what we had to do based on the available
20 evidence was actually look at specific
21 interventions compared to those things. There
22 was no clear evidence that a placebo effect
23 existed. However, we all know that in many of
24 these cases they do, we just weren't able to
25 detect that. And so along with heterogeneity,

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

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

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

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

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

1 so?

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

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

25 DR. BACH: Dr. Cuyjet.

1 DR. CUYJET: I have two questions, one
2 for Dr. Ansel, who kind of tweaked my
3 curiosity. I did not know that Italy has the
4 lowest amputation rate in the entire world, but
5 it reminded me of Ancel Keys' original
6 seven-country study from the late '40s or early
7 '50s where they plotted cardiovascular disease
8 from the Mediterranean to north of Finland and
9 came up with a saturated fat diet.

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

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

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

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

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

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

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

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

25 DR. CUYJET: Can I just ask, one of

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

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

13 DR. CUYJET: Okay.

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

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

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

25 assessment. Could you comment on his comments,

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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.

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

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

8 DR. TURCO: So what we had looked at,
9 and thank you for the question, was since the
10 AHRQ report that came out in 2013, 2012 was the
11 stop of where, the cutoff of the studies that
12 Dr. Jones and Dr. Patel looked at. There were
13 35 additional studies. Of those 35, 20 studies
14 looked at endovascular versus endovascular
15 interventional procedures, and they were
16 excluded by definition because it was not
17 comparing to, it was comparing to another
18 comparative treatment group.

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

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

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

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

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

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

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

22 claudication, so it was across the board in all
23 three categories of those patient populations.
24 DR. BACH: And actually, can I ask a
25 followup? I'm just trying to understand within

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

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

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

25 Now, the other point to consider,

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

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

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

15 DR. SALIVE: Yes.

16 DR. BACH: Okay. We can go ahead.

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

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

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

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

8 DR. SALIVE: Okay. You listed 35
9 trials or something that are ongoing, and I
10 appreciate that, and you said there are 9,000
11 patients in these trials, but most of them are
12 not trials and most of them are observational
13 studies, and one is very much driving that
14 9,000 number and I think it's one of yours, of
15 5,000 right there. So many of them are small
16 single-armed studies, not randomized trials, so
17 I'm not sure why you think that would drive
18 some of this.

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

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

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

11 DR. SALIVE: One last question.

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

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

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

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

9 DR. BACH: Thank you. Dr. Swain.

10 DR. SALIVE: I had one last
11 question --

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

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

17 going to provide some data on effectiveness of
18 the device?

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

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

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

15 DR. BACH: Thank you. My apologies,

16 Dr. Salive. Dr. Kormos is next.
17 DR. KORMOS: Thank you. I enjoyed
18 this today, this was really an eye opener, but
19 it opened my eyes to a greater problem in
20 cardiovascular disease, and my question relates
21 to the first challenge that we have in
22 asymptomatic peripheral vascular disease, and
23 I'm going to direct my question to
24 Dr. Bartholomew if he's here.
25 You gave a very impassioned plea for

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1 us to take a closer look at the fact that
2 undiagnosed peripheral vascular disease is
3 rampant, and I'm gathering that argument was
4 made because we need to look for it, and to
5 look for it, you know, ABI is probably the only
6 thing that you have right now that would do
7 that. But my question to you is, are we
8 looking at ABI as a surrogate marker for
9 cardiovascular disease in general? Because
10 what people are dying from aren't their legs
11 necessarily, but if you find something on an
12 ABI, they're dying from cardiovascular disease
13 and strokes and other things.
14 So I'm trying to put this together.

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

25 Because what I'm a little bit thinking

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

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

14 DR. BARTHOLOMEW: Well, we routinely
15 perform an ABI in our vascular medicine clinic
16 on all our patients and we, again, use it as a
17 marker for pan vascular disease. I mean, we
18 think of each individual who has an abnormal
19 ABI as likely having some cardiac problem or
20 disease, or even cardiovascular disease, or
21 even cerebrovascular disease. So, I'm not sure
22 that I'm answering that exactly how you wanted
23 it, but that's how I work with my patients with
24 abnormal ABI.
25 Now, that being said, I always go back

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

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

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

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

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

25 DR. BARTHOLOMEW: Uh-huh.

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

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

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

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

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

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1 DR. BACH: Should we get him a chair?

2 DR. SWAIN: Yeah.

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

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

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

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

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

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

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

9 DR. BARTHOLOMEW: Oh, I see. Well

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

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1 certainly I felt more reassured.

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

5 DR. SWAIN: So the question I --

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

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

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

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

8 that means you have some blockage.

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

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

14 DR. BARTHOLOMEW: I think it might.

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

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

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

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

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

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

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

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

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

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

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

4 DR. PATEL: If I might, so for the

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

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

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

1 disease severity. We've showed you other
2 observational data around disease severity but
3 in those studies, again, because of the way

4 they were characterized, there's not a
5 tremendous information on lower ABI, more
6 symptomatic patients, and let's say
7 antiplatelet agents.

8 DR. LEFEVRE: And in those studies you
9 would get, in those asymptomatic PAD patients,
10 there was a range of severity, and that makes
11 sense.

12 DR. PATEL: That's right, and so it's
13 not that we can give you such a well
14 characterized asymptomatic patient population
15 that's been described.

16 And to Dr. Carr's point, simply that,
17 again, from the secondary statin studies and
18 others, PAD is considered a CAD risk equivalent
19 so if you did identify it, you might push their
20 LDL target lower or use more of a high
21 intensity statin.

22 DR. LEFEVRE: So, my second question
23 is about the populations in key question two.
24 This relates to the studies that compared
25 exercise with interventional therapy, and my

1 question is, I mean, the guidelines for
2 interventional therapy are, obviously, that you

3 have to fail exercise first. So my question in
4 these studies, are these patients who initially
5 present with symptomatic PAD and then you
6 choose a treatment, either nonoperative or
7 operative, or are these patients who have
8 already failed exercise therapy and then are
9 randomized to either continued exercise therapy
10 or intervention? I think that would be very
11 different.

12 DR. JONES: To give you a background,
13 some of our technical expert panel is actually
14 in this room, who helped us form this question.
15 What we really wanted to look at are these
16 patients who underwent exercise and failed, and
17 therefore this treatment strategy is what we
18 were comparing. We couldn't find it. There
19 just wasn't available trial evidence or study
20 evidence to look at those specific things. And
21 so when you look at the ACC guidelines it's
22 failed to benefit from either medication or
23 exercise, or the risk-benefit ratio favored
24 revascularization. And so I would say in many
25 of these cases, we don't know if they had

1 failed exercise and then went on to

2 endovascular. All we were able to do was when
3 they actually stated their rules and stated
4 their results and methods, say that these were
5 endovascular and exercise, and this was
6 exercise, and compared those findings, or
7 endovascular versus exercise, so on and so
8 forth.

9 DR. PATEL: That's exactly right, and
10 I just might say one thing. It seems less
11 likely that they're going to be failed exercise
12 patients because we believe that investigators
13 would likely document that or describe that for
14 us. So we don't have it documented and can't
15 say either way. But if you went to the trouble
16 of ensuring the patients failed supervised
17 exercise, you would likely produce that
18 information in your journal article, because we
19 believe that would raise the impact that showed
20 you're being guideline-based.

21 And then secondly, as many people
22 mentioned, supervised exercise has not been
23 reimbursed, and so a lot of this trial evidence
24 is probably based on clinical practice.

25 DR. BACH: Dr. Lawrence, please.

1 DR. LAWRENCE: Yeah. From the
2 perspective of the public and many of our
3 specialists and specialty societies who
4 presented here, there has been a great concern
5 about the overuse of procedures, particularly
6 in patients with claudication. So I'd just
7 like to ask Dr. Carr questions related to the
8 freestanding centers that he mentioned that he
9 represents, and just a philosophy about whether
10 or not you believe that all specialists should
11 be able to treat PAD, if you were a primary
12 care physician or an interventional
13 nephrologist, or a psychiatrist. My
14 understanding is in a freestanding center that
15 there aren't the same privileging criteria as
16 there are in a hospital.

17 So first, who do you think should be
18 treating these patients, and secondly, as far
19 as practice guidelines or standards, do you
20 believe that there's a certain range of ABIs
21 that should be used as criteria as well as
22 symptoms of leg pain, to control the overuse of
23 procedures, particularly for claudication?

24 DR. J. CARR: Well, thank you for your
25 question, it's an excellent question. The

1 reason I stand here is because we care about
2 that, and we established a society to do
3 exactly that. As you know, the office space,
4 the interventional space has grown over the
5 last several years, and many like-minded
6 physicians came together to establish
7 guidelines, to establish standards and to set
8 the bar, and we feel very strongly as a society
9 at OEIS that we set the bar and match the
10 established guidelines in proof of therapy.

11 As far as other participants, certain
12 qualified physicians should be performing these
13 procedures by all means, and most of our
14 physicians are members of established societies
15 represented in this room already. We follow
16 and adopt those. We don't have a mandate yet,
17 because we're new. We have designs on creating
18 our societal standards for an office-based
19 location site of service, because we know that
20 presents unique needs and controls, and
21 insurance that the patient is safe and secure,
22 to have an effective safe outcome, so that is
23 in the works right now.

24 We have established statements of
25 quality and we have encouraged accreditation of

1 every facility that is operating. We are
2 moving toward more and more of a certification
3 process, but again, we're young, and we're
4 moving very quickly in that regard.

5 DR. LAWRENCE: So just to follow up to
6 be clear, should CMS be reimbursing someone who
7 has had no training in vascular disease
8 management or procedural endovascular? I'll
9 just use as an extreme a psychiatrist or, you
10 know, someone who we know has had absolutely no
11 training in that, does your society believe
12 that those people should have privileges or be
13 allowed to do them in a freestanding facility,
14 or should they have to join a society or
15 demonstrate expertise before getting reimbursed
16 by the federal government for endovascular
17 procedures?

18 DR. J. CARR: We firmly believe that
19 operators should all be trained, formally
20 trained in these endovascular procedures in an
21 office setting, we clearly believe in that.
22 There are established specialties that warrant
23 that and have training programs, and there are
24 certainly outliers that are entering in this
25 space that we're very careful to assess their

1 qualifications, but I believe everyone should
2 be qualified if they go through a training
3 program. We have vascular medicine folks that
4 get into an interventional program, and are we
5 going to restrict them because of the type of
6 specialty? I think you need to prove adequate
7 accredited training to do this, and I think as
8 far as reimbursement goes, I think what we hold
9 for institutions should be mandated for
10 everyone, and so I think we would like to
11 partner and educate more and more about the
12 value of this.

13 It's a preferred site of access for
14 most patients because of the ease of use. We
15 see this also as an opportunity for access. We
16 talked about the disparity of care amongst
17 different areas and by having office space at
18 local interventional facilities, we believe
19 strongly that we can assist with access. But
20 we appreciate exactly what you're saying, and
21 we're moving very quickly as a society to set
22 those standards.

23 DR. BACH: Dr. Swain, you had another
24 question?

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

24 have more and more data. The data's still
25 somewhat incomplete and I think, you know, in

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1 the PAD space we all need to realize that, you
2 know, maybe in contradistinction a little bit
3 to where we are in the coronary space, you
4 know, we're still a little bit immature.

5 And the beauty, I think, of what I
6 tried to show in that last slide of the 36
7 trials that are ongoing, nine of those 36 are
8 truly randomized control trials looking at
9 endovascular interventions that have mean
10 followup out to 3.8 years, and will follow
11 those patients anywhere between 3.8 and five
12 years, so we just probably need to be a little
13 bit patient to be able to get some of that long
14 data around the durability of some of these
15 procedures.

16 But if you take drug-eluting stents
17 for the periphery, if you take certainly bare
18 metal stent data, self-expanding bare metal
19 stent data, if you take some of the graft data
20 that we have, and now two-year data on
21 drug-coated balloons, we're starting to get
22 that longer-term data that patients want. And

23 if you look even at the 12-month data comparing
24 endovascular technologies, take a look at the
25 patency rates and the revascularization rates,

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1 if you take just our particular DCB trial at 12
2 months, you see a target lesion
3 revascularization rate that is at 2.4 percent.
4 That's hard to beat in an intermittent
5 claudication SFA population.

6 DR. SWAIN: That actually brings up a
7 good point and your slide ten I think was the
8 meat of it. You compared six different trials
9 and you've got it out to .1 percent results.

10 And unfortunately when you showed that slide,
11 and it's not your fault, the footnote was off
12 the bottom of the screen, you couldn't see the
13 footnote. The footnote says, the definitions
14 for -- these are comparing out to the .1
15 percent level. The definitions for primary
16 patency and TLR windows and analysis windows
17 were different, varied from trial to trial, and
18 data is presented for illustrative purposes
19 only.

20 What does that mean when you're
21 presenting .1 percent? And I kind of viewed

22 the presentation of the Dukies for not
23 including this so, you know, these are not data
24 that I would view as quantitative data.

25 DR. TURCO: I never criticize the

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1 Dukies except in basketball, you know, that's
2 the only time we criticize them.

3 But Dr. Swain, your pushback and
4 comments I think are valid, but realize that
5 when we try, it's like putting together a
6 meta-analysis, you know, you can only try to
7 compare apples and apples. So in the
8 consortium of folks that I stood up here today
9 to try to represent, we have industry sponsors
10 from five different companies that were running
11 five different trials. We are now trying to
12 bring uniform definitions to things like
13 patency and so forth, so that we can understand
14 them better.

15 And your point about Kaplan-Meier, is
16 Kaplan-Meier the best way to look at some of
17 these results, or should we be looking at other
18 indices for patency as opposed to looking at
19 Kaplan-Meier patency and so forth. So your
20 point of that one slide, ten I believe it was,

21 you know, where it had the eight or so
22 trials --
23 DR. SWAIN: Six.
24 DR. TURCO: Six that have very
25 significant p values, most of them going out

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1 to, you know, .001. They are comparing
2 somewhat different entities, but it was
3 illustrative of the fact that they were
4 comparing endovascular to endovascular
5 treatments, and they were very statistically
6 significant.

7 DR. SWAIN: Yeah, and unfortunately
8 none of it, you presented no data of patient-
9 centered data, you know, just TLR and patency,
10 which is, again, you know, do they live longer,
11 function better and feel better.

12 DR. TURCO: And it's, again, a valid
13 point. However, I did mention the issues of
14 quality of life, and one of the issues when we
15 look at quality of life in PAD studies is the
16 confounder of repeat reintervention, so I tried
17 to make the point, and it's hard to do
18 everything in four minutes, but I tried to make
19 the point that in the PTA group, those patients

20 who have the same level of function as the
21 drug-coated balloon or other technology group,
22 had upwards of nine times more repeat
23 vascularization than patients in the other
24 experimental arm.

25 So that's pretty significant to me

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1 because one of the points that I did try to
2 emphasize is what patients want. Patients want
3 minimally invasive procedures, they want
4 procedures that are durable with no
5 complications and without repeat
6 revascularization, and I think that's what
7 we're all trying to do with bringing these
8 newer endovascular technologies to the floor.

9 DR. SWAIN: That's very good, because
10 that's my criticism of the primary endpoint of
11 the BEST trial. The secondary endpoint should
12 be the primary endpoint because by that, what
13 you said is exactly right, because the way the
14 BEST trial is set up now, if you do surgery and
15 then redo surgery it's a failure. If you do a
16 stent of an angioplasty and then redo it every
17 single day for the rest of the patient's life
18 it's a win, so, you know, that's not what

19 patients want.

20 DR. TURCO: You didn't say a win for

21 whom.

22 (Laughter.)

23 DR. BACH: Dr. Lewis.

24 DR. LEWIS: So, I want to ask the

25 Dukies a question and this is from a little

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1 different perspective, but one of your early
2 slides identifies male gender as a risk factor,
3 and that concerns me in that if you look at
4 your absolute numbers, there are probably more
5 men in the older age groups but there are a
6 significant number of women, and
7 psychologically and through our experience with
8 coronary disease, if you say that male gender
9 is a risk factor, there can be an
10 underdiagnosis of this in women. I'm
11 particularly concerned because of the increase
12 in diabetes and the fact that this will become
13 progressively a disease of both men and women.
14 How do we deal with this perception?

15 As you have noted, they are different,
16 they have higher risks when they have the
17 disease for women. It really isn't a men's

18 disease, nor is that really a risk factor with
19 some of the complications.

20 DR. PATEL: Yeah, I think that's a
21 very good point on this slide, which maybe
22 shouldn't have been so hastily taken from
23 existing sort of dogma, guidelines, information
24 about risk factors.

25 A couple of points with respect to

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1 that. As I think everybody in this room knows
2 that there are more women alive than men right
3 now in the United States, and women live
4 probably between two and four years longer than
5 men, and for atherosclerosis not related to
6 peripheral arterial disease when they present
7 with it, they present on average five years
8 later, and maybe not with the symptoms that we
9 read in the textbook, and we've learned all
10 these different things.

11 So very much so we want to make sure
12 it's clear that women certainly get PAD, in
13 fact there are probably more women than men
14 with PAD. Women are disproportionately having
15 amputations, as you've already heard, and women
16 certainly have potentially even different sort

17 of disease burden than men because they're
18 presenting later, so I want to dispel any ideas
19 that might have been presented that women don't
20 have PAD, women don't suffer from it, and it's
21 not a risk factor. It may be the age when
22 you're evaluating the patient, perhaps you
23 haven't even thought about it before. So
24 certainly all those points are valid and we
25 should stand corrected if it was

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1 misinterpreted.

2 DR. BACH: Dr. Zuckerman, do you have
3 your tent card up?

4 DR. ZUCKERMAN: I have a question for
5 Dr. Menard. I was very interested to hear
6 about the study design and I had some questions
7 about it as it struck me as unusual, so I just
8 want to make sure I understood it correctly.
9 So I gather there is some kind of randomization
10 in the study, but that was in the randomization
11 each doctor does his or her own thing and that,
12 I think you said that can vary quite a bit and
13 it's very individualized, and I gather that
14 means it can even be off-label uses of devices
15 which have never been approved for those

16 indications or for those patients.
17 And I guess I have a couple of
18 concerns, one being that the FDA when they
19 approve devices usually don't require clinical
20 trials and so we may actually know very little
21 about the safety, and certainly not about
22 long-term effectiveness of the devices, but
23 you're putting them in a trial where you'll
24 have relatively small numbers of patients
25 getting the same kind of treatment, and that

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1 makes it very difficult, I would think, to
2 analyze in a way that would help us understand
3 which treatments are most effective for which
4 kinds of patients, men or women, people of
5 different races, people with different comorbid
6 conditions, so I just wanted to get a better
7 sense of that design.

8 DR. MENARD: Absolutely. I mean,
9 you've highlighted the challenge that we faced,
10 and anyone who's trying to design a large trial
11 faces, and there's two ways to do this. One,
12 you could do what we look on in the cardiology
13 world and envy their huge well designed trials
14 where they pick off one specific question at a

15 time, try to answer that question and get a
16 very concise answer.

17 The other way to do it is what we
18 ultimately opted to do, which is to try to be
19 all-inclusive. Clearly it's a messier way to
20 do it, the limitations are you have a much more
21 heterogeneous data set, and you struggle to
22 make very specific comparisons, which everyone
23 in the room would obviously want, so clearly
24 that was a challenge.

25 What we did not want to do was limit

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1 the treatment arm to a particular strategy or
2 particular platform ala the BASIL trial, which
3 many of us that treated patients felt was not
4 relevant to our practice by the time the trial
5 was finished, and again, it was four years ago.
6 So that was perceived as a bit of a fatal flaw
7 that supported our pragmatic design and favors
8 that design. The kind of corollary in asking
9 investigators to enter support of a trial
10 that's challenging to enroll and asking them to
11 do things differently than they typically do,
12 again, I guess is the generalizability of the
13 trial and the results, and ultimately we felt

14 that was going to be too limiting.
15 So absolutely, limitations in the way
16 we've done it. At the end of the day we felt
17 if we could achieve an appropriate power,
18 hopefully we will be able to answer the
19 questions that we wanted answered. But you're
20 absolutely right, once the patient's
21 randomized, the individual investigators can do
22 exactly what they want.
23 Just one more sort of point to that.
24 So, our effort to look at in a critical fashion
25 new technology that's come on line and decide

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1 whether it's appropriate for the trial has been
2 questioned by some, so we've looked at the data
3 for the two drug-eluting balloons that have
4 been recently FDA-approved and decided to
5 include them in the trial, so there's no data
6 on those in the CLI space over a long period of
7 time, and why is that appropriate for the
8 trial? But the counter to that is the vast
9 majority of things we do, there's no long-term
10 data for what we're trying to do, so we felt
11 rather than have a trial that at the end of the
12 day, that those patients that got treated with

13 those technologies were not allowed, we felt it
14 was better to include them.

15 DR. ZUCKERMAN: Thank you. And I'm
16 sorry, I just have a followup about the outcome
17 measures. As I recall the outcome measure, the
18 primary outcome measure was amputation-free
19 survival, and are there other outcome measures
20 that are also being looked at?

21 DR. MENARD: Yes, so, and I was going
22 to make a comment earlier on the critique of
23 the primary endpoint. A lot of thought and
24 discussion went into that. The primary
25 endpoint is not amputation-free survival,

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1 amputation-free survival is severely flawed for
2 the express point that was made earlier, if you
3 do an open endovascular intervention and then
4 there's some outcome that's other than death or
5 amputation, there's no accountability for that
6 reintervention or that secondary event.

7 MALE-free survival, yes, it's limited
8 to major events, and reintervention and
9 amputation-free survival, which is our primary
10 secondary endpoint, also includes minor
11 reinterventions. There are two clear reasons

12 why we decided not to have that be the primary
13 endpoint. There was the impact on the patient,
14 so we felt that major reinterventions have
15 significant major impacts on patients and their
16 burden was what we were hoping to focus on, and
17 so the minor interventions, yes, are very
18 important, but the overall impact on the
19 patient was less.

20 And the second point, perhaps more
21 importantly, is when we use an endovascular
22 first strategy, we presume that there will be
23 more interventions, that's an accepted reason
24 to use endovascular therapy, and it did not
25 seem fair to jeopardize or hinder the

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1 endovascular arm for that reason. So we are
2 hopefully going to have a very clear ability to
3 make comments on the burden of reinterventions,
4 we recognize the importance of that, it was
5 just not part of the primary endpoint.

6 DR. ZUCKERMAN: I'm sorry, I just
7 didn't understand. So what is the primary
8 endpoint?

9 DR. MENARD: The primary endpoint is
10 MALE-free survival, so it is not

11 amputation-free survival, and we're well
12 powered for amputation-free survival, but a
13 major adverse limb event, which was an endpoint
14 that is somewhat novel, other people are not
15 familiar with it. It came out of the SVS
16 working group on endpoints, and it includes a
17 major amputation and a major reintervention, so
18 a new bypass graft, a thrombolysis or
19 thrombectomy, any major surgical intervention
20 such as a jump graft. What it does not include
21 is balloon angioplasty, a surgical patch
22 angioplasty, quite frankly many of those are
23 date procedures and the impact of those
24 reinterventions, while very very important,
25 again, was not felt to represent a big burden

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1 to the patient.

2 DR. ZUCKERMAN: Thank you. And I'm
3 sorry, how long is the longitudinal study?

4 DR. MENARD: How long is the study?

5 DR. ZUCKERMAN: Yeah.

6 DR. MENARD: Yes, so each patient will
7 have at least two years followup, so ultimately
8 four years, possibly five years.

9 DR. ZUCKERMAN: Sorry, so the patients

10 could go up to four or five years, or that's

11 how long it will take?

12 DR. MENARD: Yes, the first patient in

13 could have over four years of followup.

14 DR. BACH: Thank you very much.

15 Dr. Lawrence, and Dr. Lefevre, do you have

16 another question? Okay. And then I would like

17 to call an end to this part of the discussion,

18 although if there are burning questions, we

19 will proceed. Go ahead.

20 DR. LAWRENCE: I had a question for

21 Mike Dake. One of the great concerns is

22 followup on my previous question about

23 appropriateness and the potential for overuse.

24 And you presented, one of the concerns is that

25 endovascular procedures, although very

232

1 successful initially, don't have the durability

2 that many, and there's been changes that I know

3 you presented, and you had some excellent

4 long-term data out to five years. But what

5 impressed me was you didn't present any

6 physiologic data, you presented TLR but didn't

7 present what we have been talking about here

8 today, which is ABI, possibly treadmill walking

9 or, post-exercise ABI.

10 So my question is, with those great
11 long-term five-year results, did you measure
12 ABI? If so, was there a physiologic
13 improvement in your study that would indicate
14 that there is durability at least, if you use a
15 drug-eluting approach, as opposed to a
16 non-drug-eluting approach? So it has to do
17 with the role of ABI as a physiologic measure,
18 which has sort of been a standard of care in
19 the field for 20 or 30 years, and why you
20 didn't present it here today?

21 DR. DAKE: Thank you, Dr. Lawrence,
22 it's a very good question, and we did measure
23 all those physiologic parameters at regular
24 intervals, yearly. One of the problems with
25 the trial design was that when someone came in

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1 symptomatic, they weren't repeated prior to the
2 intervention, and so consequently by sampling
3 only at regular interval times annually, you
4 mask any of the real benefits.

5 Now if we censor all those people who
6 basically had a reintervention, of course
7 you're going to show a benefit, but it's a

8 somewhat limitation of the trial design for
9 that particular trial that obviously all of
10 these things weren't captured prior to the
11 intervention. If that were the case, we would
12 be able to do that evaluation. Does that make
13 sense?

14 DR. LAWRENCE: Yeah. So, do you
15 believe that ABI should be a standard as a
16 physiologic test for all the interventions that
17 we're talking about today?

18 DR. DAKE: Yes.

19 DR. BACH: Dr. Lefevre.

20 DR. LEFEVRE: Yeah, my question was on
21 the evidence for key question three, it's for
22 Drs. Jones and Patel, although I think some
23 other people may want to weigh in. So, you
24 reviewed the evidence on critical limb ischemia
25 in terms of the comparative effect and efficacy

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1 of endovascular versus surgical treatment, and
2 I would have thought that was the correct
3 framing because I think you have the starting
4 point that you have to do something in those
5 situations, you can't do nothing. But then we
6 heard other evidence that came out later,

7 people pointed to the fact that amputations
8 were reduced, you know, a correlative
9 procedure, there was a correlation between
10 workup for PAD and reduced amputations.

11 So my question is, when you do your
12 evidence review, did you review evidence of
13 interventions versus no interventions for
14 critical limb ischemia, or did you think that
15 that was just not a relevant question, you
16 didn't look at it, or did you look at the
17 evidence and there wasn't any evidence?

18 DR. JONES: Thanks for the question.
19 We did review for all studies, and the way the
20 literature search was constructed was to put in
21 every intervention, every comparator, the
22 patient population and the outcomes, and
23 whatever came out within the filter would be
24 put into buckets. When they fell into these
25 buckets, however, only four looked at

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1 endovascular versus surgical or, sorry,
2 endovascular versus usual care.

3 Remember that surgery versus usual
4 care had been done but it was done before 1995,
5 which is when our study started, so it didn't

6 actually meet entry into our study. And so of
7 those four, none were good quality studies
8 because the good quality studies ended up being
9 endovascular versus usual versus care. So we
10 looked at them, we could not do a quantitative
11 meta-analysis on those studies, and that's why
12 we really chose to focus on endovascular versus
13 surgical.

14 DR. LEFEVRE: Okay. So there was no
15 evidence on intervention versus no
16 intervention. Thank you.

17 DR. PATEL: And of course all the
18 patients you saw had to be, somebody had to
19 feel comfortable that they could get
20 revascularization, and most of the guidelines
21 during this period were saying do some type of
22 revascularization.

23 DR. BACH: Any other questions?
24 Great. Okay. At this point, thank you,
25 speakers, and we're going to have an open panel

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1 discussion along these lines, and I did want,
2 Dr. Hirsch, I did cut you off earlier, and this
3 might be, if you had something you wanted to
4 say that was related to this earlier

5 conversation, we'd love to hear it. I don't
6 want to put you on the spot, though. And
7 please, also, tent cards or just interrupt each
8 other, I don't really care.

9 DR. HIRSCH: I always have something
10 to say but it's hard to know where to focus.
11 First of all, you know, to all the presenters,
12 great job. And to the panel, I'd love to
13 assist you with Medicare. I have two general
14 domains that may take three minutes, or six
15 minutes.

16 The first is, the PAD burden is
17 obviously gigantic and if I were a CMS
18 beneficiary, I'd want to look for the sweet
19 spot where the evidence overlaps with efficacy
20 and cost effectiveness, so for the moment I'm
21 going to ignore the asymptomatic population
22 where hopefully risk reduction therapy will be
23 given, and for the moment I'm going to ignore
24 the 100,000 ischemic amputations for which my
25 heart breaks every day, and look at the one to

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1 three million Americans, most of whom are
2 Medicare beneficiaries, who have claudication.

3 What I didn't hear today, I was going

4 to address this to our Duke guys, but, is
5 whether we really know that there's a
6 relationship between ankle pressure patency and
7 patient-focused symptoms, as Dr. Swain said.
8 In other words, there's a question coming. If
9 I know that medication works because there's
10 over 2,000 patients in controlled clinical
11 trials with no change in ankle pressure, and I
12 know that supervised exercise works, I think,
13 Dr. Jones, you showed that in your report, so
14 how important really is patency anyway to the
15 average Medicare beneficiary with claudication?

16 My question is, in America at the
17 current time, what fraction of beneficiaries do
18 receive a claudication medication, an exercise
19 program or an endovascular approach? I think
20 we know that; the panel and the audience might
21 want to know.

22 DR. JONES: You're asking us?

23 DR. HIRSCH: Yes.

24 DR. JONES: Since you said Duke
25 guys --

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1 DR. HIRSCH: I did.

2 DR. JONES: We prefer national

3 champion Dukies.

4 DR. HIRSCH: I love your
5 championships, Minnesotans love what you're
6 doing, it's okay.

7 DR. JONES: So, Dr. Hirsch, when we
8 look at various data sets, and you've looked at
9 them as well as we have, there are upcoming
10 areas of study with which we have all been
11 involved with today that can answer some of
12 these questions. From a CMS or Medicare
13 standpoint from what we've looked at, I would
14 say that it's unable to be determined what
15 percentage of patients get supervised exercise.
16 I would guess that it's near zero.

17 DR. HIRSCH: That's a good guess.

18 DR. JONES: Near zero. It depends on
19 how you define it so it depends on where it is.
20 Now for cilostazol and pentoxifylline,
21 specifically these modifying agents per se, it
22 looks like about 10 percent of patients get
23 those medications, sometimes surrounding a
24 vascular intervention. Does that answer your
25 question?

1 DR. HIRSCH: Manesh?

2 DR. PATEL: I guess the only other
3 question you were hinting to was the
4 relationship between hemodynamics, patency and
5 symptoms.

6 DR. HIRSCH: Yes, physiology is
7 important in understanding the results of all
8 of these trials.

9 DR. PATEL: That's right. So, there
10 are relationships in individual trials. The
11 meta-analysis and AHRQ work you saw that we
12 presented has not looked to investigate how
13 direct that relationship is. We all know from
14 several other presentations that it's not a
15 direct one-to-one relationship, there is a
16 relationship but from what we've seen it's not
17 a direct one-to-one. We did not do a
18 systematic analysis of the physiology to the
19 patency to the symptoms.

20 DR. HIRSCH: Thank you. I have a
21 follow-up question because I do care about
22 claudication, but I also care about the many
23 hundreds of thousands of ischemic amputations,
24 and I loved the speaker who said that there are
25 more amputations of PAD than there are from,

1 many ways of saying it, land mines in the
2 world, trauma, motorcycle accidents, anything.

3 There was a relationship discussed,
4 I'm not sure if we addressed this with you,
5 that amputations have decreased in the country,
6 and the implication of this is because of
7 endovascular therapy, which may very well be
8 the case. Straight line flow is important, my
9 patients get that. But I think as an
10 epidemiologist and as we think about this from
11 a CMS perspective, are there other variables
12 that could lead to the decrease, does it really
13 exist in amputation rate, like the temporal
14 decrease between 15 to 25 percent, and then
15 sort of 12 percent of current smoking, or the
16 temporal concomitant increase in use of
17 aspirin, other antithrombotic agents that has
18 about doubled over the last ten years, again in
19 the same population. Or the use of statins,
20 you know, in adults has gone from near zero to
21 nearly 60 or 70 percent.

22 So the question I guess I'm asking, do
23 we really know about the causality of the
24 temporal trends and the decrease, do these
25 temporal trends decrease all of the ischemic

1 outcomes of all the atherosclerotic diseases?

2 Anybody want to take that, Dr. Patel?

3 DR. BACH: And let me pile on. I

4 looked at some of these graphs and I saw what

5 appeared to be the slope in reduction of

6 cardiovascular mortality, which is unlikely due

7 to peripheral endovascular intervention.

8 UNIDENTIFIED PANELIST: And they

9 started before a lot of them.

10 DR. PATEL: We showed one slide, and

11 others are welcome to come in, we showed one

12 slide of just temporal trends. Of course it's

13 always tempting but there is no causality

14 information there, as you know. What we would

15 say is there are multiple confounders, as you

16 stated, other known things that affect

17 cardiovascular mortality and probably patient

18 outcomes such as risk modification, smoking,

19 statins, antiplatelet agents. The antiplatelet

20 agents, we gave you some evidence on what the

21 effectiveness of that is.

22 Second, of course, which we didn't

23 show you, is that the population's aging, the

24 burden of disease is going up, the rates of

25 diabetes are going up, so certainly the number

1 of patients in the country that are at risk for
2 any one of these may also be changing at a rate
3 that we didn't quantify, so we can't speak to
4 either, except to say that there are probably
5 confounders on both sides.

6 DR. HIRSCH: We're here to find
7 knowledge gaps and I just want to make sure the
8 gaps are well known and that non-gaps, for
9 example, the supervised exercise signal, is
10 also well known, separate the gaps from the
11 knowledge.

12 DR. BACH: Great. So, we can use this
13 time to -- oh, sorry, go ahead.

14 DR. CAMPOS-OUTCALT: So, for purposes
15 of discussion, which keep us within the FACA
16 rules, I'd like to express some discomfort I
17 have with the wording of the questions, and
18 then make sure that we're all answering the
19 same questions when we vote.

20 So for instance, for number one, for
21 adults with asymptomatic lower extremity PAD,
22 how confident are you that there is sufficient
23 evidence for an intervention that improves, A,
24 intermediate and near-term health outcomes, and
25 B, long-term health outcomes as well? If I

1 knew what health outcomes we were talking about
2 and that we agreed on, I would have a lot
3 better chance of answering that consistently
4 with everybody else here.

5 So I guess my question is, are those
6 outcomes related to the extremity or are they
7 total cardiovascular outcomes, that's question
8 number one. And then the interventions,
9 there's just a wide array of potential
10 interventions here. I mean, if I really took a
11 broad view of this question I'd say sure, yes,
12 I have high confidence because there's lots of
13 interventions that could increase lots of
14 outcomes, but that's true of everybody in
15 America, whether they have PAD or not.

16 And so I'd like to narrow the
17 questions down as a panel, if we could, and get
18 to specific outcomes, that would help a lot,
19 and then the interventions would follow.

20 DR. LEFEVRE: If I could just add to
21 the question, because I think -- first of all,
22 I just want to clarify that it says do you
23 believe that there's interventions that are
24 effective, so first of all, I mean, I assume

25 it's saying do we believe the evidence

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1 demonstrates that. I mean, you don't want us
2 to bring in our personal beliefs about exercise
3 or things like that, correct?

4 Dr. Salive: It's confidence, not
5 belief.

6 DR. LEFEVRE: I mean, I might be
7 confident that exercise works, but it might not
8 be based on this evidence. I assume we're
9 voting on this evidence, is that correct?

10 DR. BACH: I think that's an excellent
11 set of guideposts because this is an evidence
12 development coverage advisory committee, so it
13 should be, your responses should emanate from
14 interpretations of the evidence.

15 DR. LEFEVRE: Okay, and that's the
16 easy question. The harder one, I think, is the
17 comparisons and what we're comparing. And
18 again, I think the question is, when you say do
19 you have confidence for efficacy of an
20 intervention, is that efficacy an absolute term
21 or is that comparative efficacy, and I think
22 question three says that the best.

23 I mean, you might say that you're

24 confident that surgery leads to improved
25 outcomes but you're not at all confident that

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1 the comparator of surgery versus endovascular
2 has good evidence. So I think that's really a
3 sticking point for me on how we're going to
4 vote. Are we voting just in isolation for each
5 of these technologies or are we voting on
6 comparative evidence? Because most of the
7 evidence presented was related to comparative
8 effectiveness, especially for questions two and
9 three, it was mostly comparative effectiveness,
10 but then the question's not really structured
11 that way, so I'm not really sure what I'm
12 voting on.

13 DR. BACH: I think that one, I'm going
14 to do my best for that one, that one's actually
15 easier for me to answer. The issue is in
16 general terms against no intervention, even if
17 we don't have high quality evidence for it.
18 And remember, and there was some tussle over
19 this in the ACA about whether or not
20 comparative evidence could even be part of
21 coverage decisions, and I think the general
22 tenor of the law is against that, but we're not

23 here to make coverage decisions, simply to give
24 a view of the landscape.
25 So I would think even if we're looking

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1 only at, you know, head to head or intervention
2 versus intervention, the nested notion is
3 against a comparator of no intervention. The
4 question is, do we pay for X, or should the
5 government pay for X, compared to not. It's
6 not so, if you will, variable. Marcel.

7 DR. SALIVE: So, I want to comment on
8 the question about question one. I think if
9 the person is asymptomatic, their health
10 outcomes are mostly bad, so in terms of what
11 you're interested in, they have no symptoms,
12 you can't prove their symptoms, right, because
13 they have none. So all your outcomes would be,
14 then, in the area of the harms from
15 interventions to prevent death later, right?

16 I do not think that the outcomes that
17 CMS listed in their slide as to what outcomes
18 are of interest to CMS at the very beginning
19 come into play for the asymptomatic person.

20 So, a second point on this question,
21 you know, time frame, I guess for intermediate

22 versus long-term it doesn't matter, but I have
23 a general ballpark I use, but they're similar
24 points for the symptomatic or asymptomatic.
25 Finally, you know, this question is

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1 focused on asymptomatic but has peripheral
2 artery disease, so based on some criteria they
3 have peripheral artery disease. I don't want
4 to get into, for me, this question of what else
5 they might have, so they may well have a lot of
6 other things and there may be a lot of
7 lifestyle interventions that can prevent
8 disease in those people, but we're focused on
9 peripheral artery disease interventions, so to
10 me this is not as hard of a question as you
11 made it out to be, and hopefully that would
12 clarify it.

13 DR. BACH: Thank you, Dr. Salive.
14 Dr. Lystig, I'm going to get to you in a second
15 here, but I want to, actually, I want to circle
16 back.

17 Dr. Carr made a point about the AHA
18 guidelines which I wasn't immediately familiar
19 with, but I got the implication, and let me
20 restate it. Is there a way to look at this

21 first question that proposes that the discovery
22 of PAD through a series of actions which alters
23 cholesterol, actions taken against a person's
24 systemic cholesterol level, alters their
25 outcomes? So this is not treatment of the PAD,

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1 it's essentially marked PAD in the marker, and
2 I'm throwing that out there, I feel quite naive
3 in this clinical space.

4 DR. SALIVE: One last comment from me.

5 So, the coverage program in Medicare doesn't
6 deal a lot with pills, so I don't think we have
7 to focus on pills in this discussion. I mean,
8 I believe there was a Cochrane review that
9 talked about lipid lowering in PAD that was
10 very positive and it wasn't yet mentioned
11 either, but was circulated to the panel. So I
12 mean, I believe that intervention is quite good
13 for PAD patients, lipid lowering, so we can say
14 yes, we believe that's the intervention, and
15 that's another easy way to answer this
16 question, but it doesn't help the coverage
17 program too much.

18 DR. BACH: Dr. Lystig, and then

19 Dr. Hirsch.

20 DR. LYSTIG: So with the comparative
21 effectiveness issue, it also brings up the
22 related issue about using data from registries,
23 and the extent to which we should also be
24 basing our conclusions upon other types of
25 nonrandomized trial comparisons. Several

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1 speakers have pointed out the interest in what
2 might be done, for instance with the Vascular
3 Quality Initiative, but if one were to take the
4 approach that registries would be a desired
5 mechanism to get additional data, then yet in
6 the sponsored reviews that we are to see from
7 AHRQ, for example, that use available data,
8 that those questions are set up in a screening
9 process where such registry data would be
10 structurally removed from consideration as
11 valid evidence, it seems hard to say why, how
12 that could be effective.

13 We are moving towards a state where we
14 are trying to find better mechanisms to
15 synthesize evidence from a variety of sources.
16 Obviously a well-run randomized clinical trial
17 is a great source of evidence, but
18 randomization as a mechanism for treatment

19 assignment is a pretty poor proxy for overall
20 quality of the study. It's often the case that
21 there's a high quality randomized clinical
22 trial but it's not the case that only
23 randomized clinical trials can provide strong
24 evidence.

25 So if we're thinking about scenarios

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1 where we're trying to understand what real
2 evidence exists for multiple therapies to
3 inform our judgment, we should consider not
4 only how it is that we would fairly evaluate
5 the contributions from registries, but also to
6 move into saying in single-arm studies and
7 other observational mechanisms, what are
8 approaches we can take that allows us to decide
9 this evidence fairly so that we can make better
10 decisions, and I think that general concept
11 develops better use of more information that
12 will very much help in making these decisions.

13 DR. BACH: Okay. Who's next?

14 Dr. Swain, were you next?

15 DR. SWAIN: I have one quick question
16 for the center. Give me your definition of
17 long-term. Is it two years, five years? My

18 general definition, even though it's not
19 long-term, is five.
20 DR. BACH: Let me take a crack at
21 that, I certainly don't speak for the Agency,
22 correct me if I'm wrong, but I think to some
23 extent this spoke to the clinical situation,
24 and by looking at some of these overall
25 survival curves in this population, I think

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1 what we'd often think of as long-term for
2 preventive interventions is appropriate, and
3 I'd say sort of after the period where the
4 adverse, potentially adverse effects of the
5 intervention had sort of cleared. It would
6 probably be in the longer term after six months
7 for many of these trials, that that would
8 constitute maybe the beginning of a long-term
9 window, maybe a year. These looked like
10 populations of patients who had fairly brief
11 average survival, so I think looking at a
12 five-year outcome when there's serious, a large
13 number of gaps prior to that, might not be
14 appropriate.

15 DR. SWAIN: CLI, for CLI that's a for
16 sure, claudication that occurs, you know, on

17 the 17th hole when you're carrying your bags is
18 probably five years, so it's just a difficult
19 question the way it's asked.

20 And I guess the general comment for
21 today is I appreciate all the speakers, and
22 viewing all the literature as a cardiovascular
23 surgeon, you know, it's embarrassing that we
24 haven't done better. And as a former FDA
25 person it's embarrassing that more data, better

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1 data wasn't required for approving devices.

2 So we can see that the world's
3 changing now and there's great studies upcoming
4 for which we don't have any answers yet, they
5 haven't been published and able to be peer
6 reviewed or FDA committee or whatever, so I
7 think that in the future we will have data and
8 the registry I think can be important, it's
9 only a recent registry, there's only a hundred
10 thousand peripheral vascular so far, but, you
11 know, to beef up that registry, to make it
12 required, and there's incentives. Just like in
13 cardiac surgery, you don't get paid by
14 insurance companies unless you're in the STS.
15 That may well be useful in the future for

16 propensities for scoring of studies and using
17 it as a historical control like we use some of
18 the UNOS database and the InterMax database and
19 things like that.

20 So I think that, you know, we have
21 things coming, but right now the lack of data
22 is just impressive and very disappointing, but
23 I think the future and the idea that we have
24 these six randomized studies that were listed
25 by Dr. Turco, and when the PARC committee

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1 started in 2011, you've just got to have common
2 definitions and common endpoints in order to be
3 able to compare anything, and we appreciate the
4 problems our Duke friends have doing those
5 comparisons because it's where cardiac valve
6 disease was 30 years ago, you know, everybody
7 did everything differently. So I think CMS has
8 a problem right now of using evidence-based
9 medicine because there's very little good
10 evidence of not only comparison to comparison,
11 it's kind of like comparing in my family, you
12 know, we could compare who could dunk a
13 basketball best, but that doesn't really, you
14 know, we need to be able to compare in a lot of

15 these things; an intervention versus things like
16 exercise and we just don't have any of that
17 data, and I don't know that we're going to get
18 any of that data now because kind of the horse
19 is out of the barn, so I appreciate the problem
20 that CMS has had.

21 DR. BACH: I'm sure our colleagues
22 from Duke appreciate the basketball metaphor as
23 well. Dr. Hirsch, did you have a comment?

24 DR. HIRSCH: Yeah. I made a comment
25 earlier about claudication with CLI and I

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1 wanted to come back to the asymptomatic cohort.
2 This term asymptomatic is extremely
3 problematic, it probably should be discarded.
4 There is other evidence not presented today
5 that suggests, as one of our public speakers
6 said, that no one is truly asymptomatic. If
7 you have an ABI of .85 and you stop walking and
8 you don't speak English, you don't complain as
9 well, you have a functional limitation, and
10 that's what Mary McDermott of Northwestern
11 published in multiple sources. The challenge
12 is if we wait again in the post-ACA world where
13 we're not RVU-based and we're trying to keep

14 the Medicare population healthy, if we wait for
15 people to complain in the English language the
16 way we understand, we only detect one out of
17 ten, or actually one out of 20 patients with
18 PAD.

19 So when the AHA guideline was written
20 the thought was that, again, in all the trials
21 that existed, we don't really use the term
22 asymptomatic very often. If my colleague here
23 had leg intervention 20 years ago but no longer
24 complains because the intervention was
25 successful, he still has very severe PAD

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1 despite that success. If my next colleague has
2 PAD with the same ABI but, again, has stopped
3 walking, his event rate is not driven by his
4 risk factor, the question earlier, it's no
5 longer one or two percent for ten years, it's
6 now at least four to five percent, probably six
7 to eight percent of the community population.
8 So the time frame of risk is as short or
9 shorter than a patient discharged with a
10 stenting.

11 In other words, the PAD diagnosis in
12 an asymptomatic patient unmasks the functional

13 limitation, unmasks the cardiovascular risk,
14 and although we don't have a primary USPSTF A
15 grade, that's true, we don't have a prospective
16 single randomized trial, that's a knowledge
17 gap, I could probably reference five additional
18 studies, the old CAPRIE study, the current
19 PRA2P study, the previous ramipril trials, and
20 the heart protection study with statins and ACE
21 inhibitors whereby within one year those
22 coronary event rates declined by a lot, 15 to
23 20 percent, and absolute risk reduction in the
24 first year of one percent, and these drops in
25 rates are short-term, meaning the first six

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1 months to one year according to the
2 definitions, and never go away, they persist.

3 So I just want us to caution ourselves
4 that, not to be too cynical as Dr. Beckman is
5 no longer here, but there probably is no such
6 thing as asymptomatic.

7 Final one, knowledge gap. Of the
8 critical limb ischemia patients that actually
9 present in our country, fully half of the
10 presentations are first CLI, they're not stage
11 of disease. So you're asymptomatic today and

12 tomorrow your first presentation is a black
13 toe, so there is the opportunity to provide
14 surveillance for early detection if we detect,
15 quote, asymptomatic PAD. In other words, you,
16 Peter, may have a severe lung nodule but not be
17 coughing yet. We have to be careful. Unlike
18 lung cancer with microscopic lesions, here we
19 do have therapies that actually are fairly well
20 proven to change the natural history. Hope
21 that's helpful.

22 DR. BACH: Dr. Deyo.

23 DR. DEYO: I guess those comments
24 confuse me a little further actually, rather
25 than helping me. If there's no such thing as

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1 asymptomatic, then I assume that everybody in
2 this room who's had a leg symptom has
3 potentially got PAD.

4 DR. HIRSCH: Well, no. I mean, it's
5 like everybody with chest pain doesn't have
6 coronary disease. The goal is to detect the
7 ischemic symptom and accurately define it by a
8 diagnostic test.

9 DR. DEYO: I guess an underlying
10 concern that I have here is that in other areas

11 of medicine we're learning more and more that
12 screening in general populations may not have
13 the benefits that we really think it does, in
14 part because there are adverse consequences to
15 screening itself, even in non-sick patients.
16 And in the absence of a clinical trial, for
17 example, demonstrating the benefit of a
18 screening strategy, I guess I'd be reluctant to
19 endorse a screening strategy, and it seems to
20 me that's in part what underlies this question
21 about treating asymptomatic patients.

22 DR. HIRSCH: You're right on the
23 money. We have to be very careful about the
24 term screening without a prospective randomized
25 trial. The analogy is we can't have confidence

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1 of the benefits (inaudible).

2 DR. BACH: I think, and let me
3 rephrase, Dr. Hirsch, what you said. I don't
4 think Dr. Hirsch, I think he was saying
5 asymptomatic was a problematic moniker because
6 of all the stuff we assume it means about the
7 patient, but then you were listing actual
8 changes in behavior, functional status, things
9 like that, that we as clinicians may not be

10 particularly skilled at picking up or if we do
11 find them, we don't naturally reflex to logical
12 explanations like PAD.

13 I think that's what he was saying, and
14 Rick characterized it as, you know, any leg
15 symptom, but I think it's probably somewhere
16 between these two things, is what you intended
17 to say, not any leg symptom. If you stub your
18 toe, that's not an indication for screening.

19 DR. HIRSCH: You're absolutely
20 correct. I have tremendous respect for the
21 evidence-based process of USPSTF, and we don't
22 have prospective Level I data, true Level I
23 data with a control group, or with long enough
24 followup to know about the benefits versus
25 harm. However, we should have caution that we

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1 don't discard the asymptomatic group entirely
2 because there are interventions that, if you
3 were in my office and you had an abnormal pulse
4 but you felt fine, or your ABI was .5 and you
5 felt fine, you could be maintained in health
6 with Medicare-based medical interventions that
7 are known to be effective.

8 DR. CAMPOS-OUTCALT: Yeah. I just

9 have to correct an implication that the USPSTF
10 only accepts randomized control trials as high
11 level evidence, that's entirely not true. They
12 have a process where they do look at
13 observational studies, observational studies
14 can be upgraded because of quality, consistency
15 of results, magnitude of effect and so forth.
16 It does not require a randomized control trial
17 to get an A or B from USPSTF. And the rating
18 when it comes to screening using ABI for
19 peripheral artery disease is an I, which is
20 insufficient evidence, which is where I think
21 we're at, so I don't think we really have a
22 disagreement with USPSTF on this particular
23 point.

24 DR. SALIVE: And I think their review
25 that was provided to us was positive on the ABI

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1 for detection. It did reflect that the
2 intervention needed to be proved to be
3 beneficial after that, so there was a path
4 forward to something that might be useful, so I
5 don't think we need to endorse or disendorse
6 that, I think it's a reasonable approach to
7 take, and hopefully there will be some

8 interventions eventually.

9 DR. BACH: Dr. Cuyjet.

10 DR. CUYJET: I'm going back to not so
11 much a question but just a comment really to
12 the evidence. Most people don't just have one
13 risk factor or two risk factors for PAD or CVD,
14 and there's some evidence in trials going back
15 to if you know that you have one risk factor,
16 or two risk factors, or three risk factors, for
17 diabetes, for example, and this is basically
18 what economics means: if you're going to
19 invest the time and energy to manage your
20 diabetes, you're not going to ignore your
21 hypertension or your smoking or your other
22 stuff, so it's not really an answer, but we
23 mentioned that we're going from an RVU to an
24 outcome-based medical encounter.

25 My comments don't really help us

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1 answer these particular questions, but it's
2 just a general framework about how patients
3 will modify and invest, even older patients
4 with a marginal return on investment in terms
5 of health outcomes will be less than 30 years
6 before, but it's not a factor that should be

7 underestimated in what patients do to commit to
8 maintain a good outcome.

9 DR. BACH: Dr. Kormos.

10 DR. KORMOS: So, I may unmask my
11 naivete, but in my world there are very few
12 devices, everything is a clinical trial. I'm
13 trying to understand, and I guess as we decide
14 about whether interventions make a difference,
15 the word I heard in a lot of the presentations
16 today was heterogeneity, there's a lot of
17 heterogeneity both in the disease, the
18 presentations, the patient populations, and
19 today I heard that in fact how these devices
20 are used are very heterogeneous, there's all
21 sorts of different methodologies and strategies
22 per implication, and that's where I get a
23 little bit fuzzy about how definite I can be
24 and how I'm going to try to answer these
25 questions.

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1 Because, you know, is one 510(k)
2 device the same as the other? You know, when
3 was the predicate device laid down, how long
4 ago? How much are we following the same path
5 but the devices have really changed now, so at

6 what point do you say okay, it's really time to
7 do a full clinical trial? I don't know.

8 And so when you ask me to, you know,
9 what's the evidence that any -- I mean, some of
10 these I think I've got a handle on,
11 interventions that clearly help. But as I get
12 into the more esoteric device area, then I'm
13 having a little more trouble understanding how
14 to make that interpretation given the variety
15 of devices, how they're used, and the variety
16 of the disease states, so that's where I'm
17 struggling, and I don't think there's an
18 answer, it's just a comment.

19 DR. BACH: Dr. Lefevre.

20 DR. LEFEVRE: I just want to make a
21 comment about the issue of RCTs and registries
22 because I think there's a lot of comments made
23 here, and I'm certainly in favor of registries,
24 and I think the presentation by Dr. Cronenwett
25 was very good in terms of what registries can

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1 do and what they can't do, but I think
2 sometimes we go beyond what registries can do
3 and we expect to be able to get treatment
4 effect information from registries. And I

5 think there's only very few situations where
6 you actually can get treatment efficacy or
7 comparative effectiveness of treatments from
8 registries, and those are when you have
9 relatively unconfounded interventions and a
10 homogeneous population.

11 Here we have very much the opposite.
12 We have heterogeneous populations with very
13 highly confounded outcomes, and then we have
14 cardiovascular disease with very highly
15 confounded outcomes. So I think we absolutely
16 need to insist on RCTs for the primary
17 questions. For the issues of intervention
18 versus medical therapy, for example, we need to
19 insist on RCTs for those questions. And if we
20 try to get by with lesser data, registry data,
21 we'll end up ten years or 20 years in the same
22 situation we are now, we won't know, we won't
23 be able to answer the question. We'll have
24 some suggestive data, we won't be able to
25 answer it.

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1 So I think we need to be very clear
2 about what kind of studies we need, where we
3 need RCTs, and what registries can do, but not

4 to mix those, and be very clear where the RCTs
5 are needed and what questions cannot be
6 answered by registries.

7 DR. BACH: Thank you. Dr. Lystig, did
8 you have something else?

9 DR. LYSTIG: Yes, but it actually
10 comes back to this most recent comment again
11 with respect to the registries issue. So first
12 off to the prior comment, I agree that there
13 are mechanisms out there that exist, primarily
14 in many journals, about how you can view
15 observational studies as being equivalent to,
16 or at least the same level as a randomized
17 trial.

18 My point that I was trying to make
19 earlier was that if there is interest from CMS
20 in the use of registry data to make informed
21 decisions in a panel such as this, then there
22 seems to be a problem between having a
23 commission review that has as part of its
24 requirements that the data to be summarized has
25 to be a randomized clinical trial, so you're

1 structurally throwing away that information
2 from saying that, okay, how can we learn from

3 the registries?

4 And to this most recent point about
5 what we can learn from the registries, again, I
6 think there are many endpoints that we are
7 interested in, and for things such as quality
8 of life, that sometimes can be something that
9 is easier to get out of a registry framework,
10 provided that the analysis plan is done
11 appropriately and steps are taken to find
12 subsets of the population where you can find
13 homogeneity and you can get rid of some of that
14 underlying heterogeneity. So there are
15 scenarios where it is almost a requirement to
16 have randomized clinical trials, I'm not saying
17 that. I'm just saying that if we want to make
18 the most use of information that is being
19 generated, we should consider avenues that
20 would allow that nonrandomized trial
21 information into the committee's deliberations.

22 DR. BACH: Thank you. Dr. Lefevre,
23 your card is still up, and Dr. Kormos, your
24 card is still up. I don't know if you have
25 more to say. This is very stimulating

1 discussion and I appreciate the panel members

2 pushing each other to be clear on their points.
3 We're going to take a break, but before we do
4 that, when we come back from the break I'm
5 going to ask you to vote, so I would actually
6 like the panel to take a moment before we break
7 and think carefully if you feel like you have
8 the bounds of the questions adequately defined
9 or whatever, so that we can go through a voting
10 process and the discussion around our
11 questions. And if not -- Dr. Carr.

12 DR. J.J. CARR: Just a point of
13 information. So on question one, long-term
14 health outcomes, those would be cardiovascular
15 death, coronary heart disease death,
16 cerebrovascular events, those would be the
17 long-term health outcomes we would be voting
18 on?

19 DR. BACH: So on the voting sheet,
20 there's a list of the clinical outcomes of
21 interest, it's the second half of the third
22 paragraph in your packet, and it lists a set of
23 outcomes which includes the ones you just
24 listed as well as a number of others. I can
25 just read them, reduction in pain, avoidance of

1 amputation, improvement in quality of life
2 and/or functional capacity including walking
3 distance, wound healing, avoidance of
4 cardiovascular events -- these are the ones you
5 listed, MI, stroke, cardiovascular death and
6 all-cause mortality, and avoidance of harm from
7 the interventions. So that's the sort of
8 market basket of outcomes.

9 DR. J.J. CARR: I mean, there was some
10 discussion among us to limit the scope of that
11 question to just peripheral vascular disease
12 outcomes, but our mandate clearly includes
13 cardiovascular events, death, cerebrovascular
14 accident. So when I'm voting, I'm voting
15 according to the instructions on the sheet, and
16 we really presented very little to no evidence
17 on prevention of those outcomes for
18 asymptomatic people, but there is a robust
19 literature in that area that would indicate
20 that peripheral arterial disease is a CVD
21 equivalent much akin to diabetes, and that we
22 have prevention strategies that are highly
23 effective.

24 DR. BACH: Right, so I understand the
25 question, and I'm just doing the best I can as

1 well, but the first level question allows for a
2 range of responses which, my read of it would
3 be you would express the level of confidence
4 you have for the highest effective intervention
5 on the highest outcome, because the subsidiary
6 questions, the follow-on discussion allows us
7 to then bifurcate or trifurcate the space with
8 the discussion.

9 If intermediate confidence, on all
10 these interventions in your head, please
11 discuss the specific interventions and
12 associated outcomes. So that gives you the
13 discussion around each of those questions, one,
14 two and three, which allows you to segregate,
15 okay, I'm talking about CV events, cardiac
16 events or peripheral events, these are the
17 events I'm talking about. I hope that helps.

18 And then beneath that there's a
19 question in each of the, there's a
20 sub-discussion in each of the questions saying,
21 considering the heterogeneity of the Medicare
22 population, discuss which subgroups of the
23 population are likely to benefit or likely to
24 not benefit from that intervention.

25 DR. J.J. CARR: So I mean, just point

1 of information, we really have six voting
2 questions as I look at the green sheet, right,
3 so we're going to rate for questions one, two
4 and three, an A and B on each question, that's
5 just a point of information, are we?

6 DR. BACH: Yes, that's right. I
7 believe we're voting six times, one immediate
8 and near-term, and then long-term.

9 DR. J.J. CARR: And each of those have
10 the outcomes that are in the instructions.

11 DR. BACH: That's right, and then
12 after each one there's a discussion, about
13 which outcomes, okay, which interventions. I
14 hope that helps.

15 DR. J.J. CARR: Right. I'm just
16 making sure that we didn't change the
17 instructions when we vote when we come back.

18 DR. BACH: Right, the only thing we
19 cannot change is this piece of paper.

20 DR. J.J. CARR: Okay.

21 DR. BACH: Please.

22 DR. ZUCKERMAN: It seemed that there's
23 some differences of opinion about long-term
24 data and what that means, and also obviously
25 that long-term is different for the different

1 groups, and certainly I was not comfortable
2 with the idea of looking at just long-term data
3 regarding what happens immediately after the
4 intervention, because there are a lot, because
5 if the intervention is successful for a short
6 period of time and then not successful, that's
7 important too. So, I don't know if that can be
8 clarified by CMS, or if you don't want to
9 clarify it, but I'm just trying to get a better
10 sense of what we're talking about.

11 DR. BACH: What I would propose, I
12 don't think it's particularly productive if
13 each of you voting has a different definition.
14 I don't know if we could easily converge on one
15 but I propose we try right now to try and
16 separate those two questions for us
17 collectively, and then CMS will take, within
18 the context of the definition we arrive at, the
19 answers we give. So, the floor is open to the
20 difficult distinction for short- and long-term
21 outcomes.

22 DR. LEWIS: I think for number three,
23 the short-term outcome being wound healing,
24 with knowing that sometimes these things can

25 fail at eight months or 12 months, that would

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1 be long-term, and if the wound had healed in
2 the interim, that still might be a short-term
3 outcome.

4 DR. BACH: So, can you put a time
5 frame around that?

6 DR. LEWIS: I guess six months for
7 wound healing.

8 DR. BACH: I'm totally comfortable
9 with choosing a different breakpoint for each
10 of the three questions also, I mean, I think
11 within reason, does that solve our problem?
12 I'm just trying to get to a structure before we
13 vote.

14 DR. LEWIS: That's why I started with
15 three, it seems like it would be very different
16 than one.

17 DR. BACH: And it's easier than one.

18 DR. LEWIS: Well, one seems almost
19 easy in its own way too, because long-term
20 outcomes would be the cardiovascular events
21 that would start in maybe two to five years.

22 DR. BACH: Okay. So I think the
23 proposal on the table very loosely is a

24 six-month cutoff for critical limb ischemia

25 between short and intermediate versus

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1 long-term. Are people comfortable with that?

2 DR. LEWIS: I mean, I was just giving

3 a number. People could choose a different

4 number.

5 DR. BACH: In the critical limb

6 ischemia, question number three, we're going to

7 use six months as the breakpoint between --

8 DR. HIRSCH: It's hard to know, Peter,

9 you know, what time frame is appropriate. Let

10 me just give an alternate perspective, but I

11 don't know the answer. If we were the patient,

12 not the trialist, not the company, not me, you

13 know, when I get an intervention in a doctor's

14 office, I'd like it to work, I'm just going to

15 say out loud for at least a year, I don't want

16 to be coming back every three to six months.

17 And if I were thinking long-term, what I'd want

18 my wife or my best friend to have, it would be

19 five years.

20 Of course the reality for PAD is we

21 don't have any outcomes generally beyond one

22 year or two years for almost anything, but we

23 could take all three questions and, I hate to
24 say it, but kind of merge them, since all we
25 really have is one year for almost everything.

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1 For question three, even for wounds
2 even if they heal at three or six months, we
3 all know they recycle and reopen, and then
4 reclose and reopen, so in our trials it's very
5 hard to pick a time point that makes sense. So
6 for the panel, you could choose one and three,
7 one and five, but be careful if it's anything
8 much shorter, because I don't think patients
9 necessarily value that.

10 DR. LEWIS: Months?

11 DR. HIRSCH: Years. Durability is
12 important, so I'm advocating for longer time
13 frames.

14 DR. BACH: So the counterproposal, I'm
15 just trying to triangulate on something here,
16 the counterproposal is a one-year, short-term
17 outcomes mean outcomes out to a year, and then
18 there's a separate thing which I think is
19 largely constrained by trial design and
20 followup, which is five years arbitrarily,
21 meaning gives us a view into the long-term

22 durability.

23 Are people comfortable with that?

24 That's across all three questions now.

25 DR. SWAIN: But I think it's just so

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1 different. In group one you may be talking
2 about a 40-year-old with an ABI of .9 or
3 something, you know, so aspirin is an
4 intervention, you'd really want to know five-
5 to ten-year data.

6 Whereas in the second one,
7 intermittent claudication, which could be,
8 again, not able to walk across this room,
9 versus the other end of the spectrum is
10 claudication when you're carrying your bag of
11 golf clubs on the 17th hole, so you've got a
12 huge thing, so I would throw out five years for
13 that as long-term, if you're going to study
14 device or drugs or whatever.

15 And then for the horrible limbs, the
16 CLI, you know, one to two years is long-term,
17 and then intermediate may be six months to a
18 year, and acute is less than that.

19 DR. BACH: Does anyone have a view on
20 that? I think the first decision we're making

21 now is are we going to use a common standard
22 for all three questions, or if we want it to be
23 sort of a moving cutpoint, and I'm not hearing
24 a clear consensus.

25 UNIDENTIFIED PANELIST: There's three

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1 different populations so I think there should
2 be a different cutpoint for each.

3 UNIDENTIFIED PANELIST: I agree.

4 DR. BACH: I'm seeing nodding heads.

5 We're not going to vote on this. Is there some
6 articulate difference of opinion around that or
7 are we going to use a moving cutpoint?

8 DR. LEFEVRE: I think question three
9 is different, but on questions one and two I
10 would agree with Dr. Hirsch. Like less than
11 one year short, one to five years intermediate,
12 and greater than five years long, I think
13 that's a general standard. But I think here we
14 should just make it simple and say one year and
15 less, or greater than one year, because we say
16 immediate and near-term and then long-term, so
17 we don't really have an intermediate step, so I
18 would just make it simple, one year and over
19 one year.

20 DR. BACH: So the proposal on the
21 table for question one is up to one year, up to
22 five years, for the immediate/near-term versus
23 long-term. Are there objections to that? One
24 year and five years.

25 We haven't talked about intermediate

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1 claudication, so let's go to question three and
2 resolve that. Are we comfortable with one year
3 and five years, or do we want to talk about six
4 months and two years?

5 DR. LEWIS: I guess I'm uncomfortable
6 with the one year, because the data don't
7 support that people even live much longer than
8 that. If they have pain control immediately,
9 that would be a good outcome for many people,
10 so is it what I want, no, but it is what
11 happens.

12 DR. BACH: I think the important
13 dichotomy is actually separating the research
14 into its appropriate buckets as well as sort of
15 the clinical experience of patients. I'm
16 throwing out a number here, I don't have a
17 preference, six months and two years for
18 question three? Okay, six months and two years

19 for question three.

20 And then for the one that's between,
21 the intermittent claudication group, is this
22 also one-year and five-year, or is there some
23 other? Dr. Lystig.

24 DR. LYSTIG: The proposal I heard
25 before sounded like it was saying that we

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1 should consider this not in terms of an average
2 of one-year or average of five-year with a one
3 to five split, but things less than one-year
4 and things greater than one-year, so I'm
5 confused.

6 DR. BACH: That's for question one and
7 two.

8 DR. LYSTIG: Yes, that makes more
9 sense to me.

10 DR. BACH: Okay. So, can you
11 rearticulate that in a statistical sense so
12 that we can all know what you're saying, or
13 what the distinction is?

14 DR. LYSTIG: Less than or equal to 12
15 months, versus greater than 12 months, and have
16 that be short-term versus long-term, because
17 you're just splitting the space up into two

18 adjacent areas, rather than targeting things
19 just at one area versus targeting things just
20 at five years. So there's two spaces, and the
21 questions are set up in terms of essentially an
22 endpoint for a therapy for which you have the
23 most evidence, and it's just where that time
24 point falls in within that dichotomy.

25 DR. BACH: So those are outcomes, so,

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1 I'm trying to make sure I have this distinction
2 clear. So we're not talking about
3 experiencing, for example, outcome improvement
4 through one year as the short-term, you know,
5 by continuing to experience that outcome up to
6 365 days, versus up to five years. You're
7 talking about experiencing improvement in
8 outcome within the zero to one time interval,
9 but that could decay and it would still qualify
10 as a short-term health benefit, but then having
11 the continued experience between one year and
12 five years would count as the long-term.

13 DR. LYSTIG: That being said, for many
14 of the outcomes that are like survival
15 analysis, so you're effectively making your
16 inference based upon 12 months, which is a

17 function of what had happened up until 12
18 months.

19 DR. BACH: Agreed.

20 DR. LYSTIG: So effectively, just
21 saying the information available within the
22 first 365 days, versus the information
23 available after that time point.

24 DR. BACH: Okay. Is there comfort on
25 the panel about that?

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1 DR. ZUCKERMAN: No. I mean, I just
2 want to say, we certainly don't want a study
3 that's two days long. I understand that not
4 every study's going to be up to a year, but I
5 don't think we can just say anything up to a
6 year is a short-term benefit, because a
7 one-week study is, I think, too weak to be --

8 UNIDENTIFIED PANELIST: But we're not
9 talking about a one-week study for any of this.

10 DR. BACH: Okay. So the distinction
11 on the table, speaking just about the
12 short-term outcomes here, is the distinction
13 between, is a short-term benefit, can it occur
14 before the end of a year and for example
15 disappear and it still counts, or

16 alternatively, does it have to be durable to
17 365 days to count? I think, Ted, is that the
18 distinction you're making? I think it is.

19 DR. LYSTIG: My distinction had to do
20 with just trying to split the time scale into
21 two adjacent regions, right, so things
22 happening up to a year, things happening after
23 a year. Again, the way I'm reading the
24 question, and maybe I'm reading it incorrectly,
25 is how confident are you that there exists, A,

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1 therapy for which there's sufficient evidence
2 for immediate or near-term health outcomes? So
3 it's the best evidence for some therapy in one
4 of these three areas in a particular time
5 interval. So it's not to say on average across
6 all therapies for all outcomes, it's what's the
7 outcome with the best evidence.

8 DR. SWAIN: I mean, again, you're
9 comparing the third question to the first
10 question, and the idea that a 13-month,
11 evidence of something for 13 months in an
12 asymptomatic patient doesn't, I could never use
13 the term long-term for that. So I don't know
14 what the solution to this one is, other than we

15 qualitatively define it when we vote on it,
16 what we mean by it, and CMS can look at the
17 transcript, which we know you'll do.

18 DR. ZUCKERMAN: Yeah. I don't know
19 why it has to be adjacent, I don't see the
20 benefit. I also just want to say even if you
21 have a five-year study and not everybody lives
22 to five years, that doesn't mean it's not worth
23 looking for as long as you can look, for those
24 patients who live longer.

25 DR. BACH: We've done a more

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1 sophisticated interpretation of the document in
2 front of us, and short-term is the, we're going
3 to go, if this works for you and everyone, with
4 Dr. Lystig's definition, which is during the
5 time interval up to, for example, a year, there
6 is an intervention that alters health outcomes.

7 But the second question, long-term has
8 a reasonable time point of durability, call it
9 three years, four years, five years, something
10 like that. We're limited by data on that, so
11 if you're sort of, the cartoon version of this
12 is if you have an intervention, at 364 days
13 you're doing fabulous, that's short-term. If

14 you're doing fabulous at day 367 and 368,
15 you're not, you haven't satisfied the long-term
16 benefit, you have to be at five years, or, I
17 think we acknowledge that data run out before
18 we would like, so, you know, in the projection
19 across the time horizon.

20 Does that work with everyone, that
21 distinction? So if you will, there's a large
22 doughnut hole between those two endpoints.

23 DR. LAWRENCE: Just so I understand,
24 so if it's 366 days for an intervention, that
25 would be a successful short-term?

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1 DR. BACH: That's right.

2 DR. LAWRENCE: It seems short to me
3 for surgery, it doesn't for medication, but for
4 surgery and interventions that seems like a
5 very short period of time. And as was pointed
6 out, from a patient perspective I don't think
7 they would consider a success to be if they
8 went one day over 365, I think maybe two years.

9 DR. BACH: Let me say it again. First
10 of all we get to answer both, right, but my
11 understanding is, if you will, over that time
12 period if you get a blip of benefit in the

13 short-term, we're counting that, and there's
14 obviously the discussion, but that is a
15 benefit. And then if it's a question of
16 durability, and let's imagine that we had
17 perfect follow-up data past five years, to get
18 an outcome benefit that is long-term you have
19 to see that benefit at five years, that's what
20 we're going to go with, all right, or three or
21 four years, a long period.

22 I would like to take, I promised
23 everyone a ten-minute break, I would like to
24 stick with ten minutes, and then we are going
25 to vote.

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1 (Afternoon break.)

2 DR. BACH: Okay, thank you all. Can I
3 ask you to either take your seats or have your
4 conversations in the hall, please? This is the
5 moment everyone has been waiting for.

6 One more clarification. In thinking
7 about this issue about question one, the issue
8 of asymptomatic, I'm going to try as best I can
9 to remap this onto a regulatory framework with
10 Dr. Hirsch's comments very much in my mind.

11 I think what is intended, in fact I'm

12 confident that what is intended from the
13 question regarding asymptomatic patients is
14 patients whose PAD is discovered through
15 screening. So whether it is a narrow view of
16 the symptoms that trigger the doctor, or the
17 evaluation, or a broader view such as happening
18 to catch a history of reduced walking distance
19 or something, that would be off the table. It
20 is sort of systematic screening of patients
21 without symptoms of the disease, if that's the
22 trigger, that's the bucket, so it's essentially
23 the chain of event following screening that's
24 the question.

25 Go ahead, Dr. Hirsch.

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1 DR. HIRSCH: Just to be clear, that's
2 excluding the fact that five years ago I had a
3 right ilial angioplasty and I'd been feeling
4 just fine, seeing my primary care doctor.
5 We're not dealing with that beneficiary, all
6 right?

7 UNIDENTIFIED PANELIST: That's not an
8 intervention at all.

9 DR. BACH: I would think that's a
10 documented prior history of PAD, assuming that

11 was an intervention for PAD, right?

12 DR. HIRSCH: Yes.

13 DR. BACH: I would think that

14 documented PAD puts you into a different

15 category. Go ahead, Rick. I'm doing the best

16 I can here.

17 Dr. Deyo: Let me just press you a

18 little bit. It seems to me you've reframed the

19 question from whether there are benefits for

20 asymptomatic patients to the advisability of a

21 screening program.

22 DR. BACH: No, Rick. What I believe

23 is, I'm trying to define the cohort, not the

24 question of screening itself, right? So if we

25 were going to conduct a study, I think the

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1 entry criteria would probably be screening, but

2 then it could have different interventions, but

3 I'm just trying to narrow the cohort into

4 those, but I think those two things are related

5 ideas. I'm open to other definitions. We just

6 need to be able to give Medicare some guidance

7 regarding the cascade of events that could

8 occur after a screening test is done.

9 DR. HIRSCH: So, Peter, I don't know

10 the best answer, these are very tough
11 questions. But I'm going to, again, take a
12 patient centric CMS perspective. If in the
13 United States of America fully half of the
14 population, more or less, has no identifiable
15 chief complaint but has PAD with both
16 functional impairment and high event rate, that
17 means our meeting and our panel is really
18 excluding a huge population of beneficiaries.
19 In contrast, a member of the USPSTF screening
20 population really hasn't been studied, so we're
21 taking the first question and truncating it to
22 a tiny fraction of the actual PAD cohort, and
23 I'm just asking myself, or CMS, is that wise.
24 DR. BACH: We're going to take the
25 questions I believe as written, and I take your

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1 point, of course, but I think it's perfectly
2 okay, quite commonplace for the discussions to
3 focus on narrow populations, and there's lots
4 of people with lots of conditions who are not
5 being considered, and it's sort of the best --
6 I don't know how else to constrain this so
7 we're voting on the same thing.
8 MS. ELLIS: All voting panel members,

9 you should have your keypads. When it's time
10 to vote, please press your vote of choice hard
11 so that it will register. Also, when it's time
12 to vote, we will need you to state your name
13 and your vote for the transcriptionist and for
14 those individuals on the webcast. So again,
15 please speak into the mic, state your name and
16 your vote, and we can begin.

17 DR. BACH: Okay. So I'm going to read
18 the questions. The first question is, for
19 adults with -- and remember, we're voting twice
20 here. For adults with asymptomatic lower
21 extremity PAD, how confident are you that there
22 is sufficient evidence for an intervention that
23 improves immediate/near-term health outcomes,
24 which we as a panel decided constituted
25 outcomes occurring within the first year after

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1 identification?

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

4 MS. ELLIS: We're waiting on three,
5 two, one. If you're not sure, would you just
6 push your button again.

7 MS. JENSEN: And just as a reminder,

8 every panel member should vote.

9 DR. BACH: Okay. The mean is 1.4, you
10 can see it on this screen. I don't know if we
11 can fix this screen up here which doesn't show
12 the bottom. Oh, there we go. The mean value
13 is 1.4, and that's with all ten panel members
14 voting.

15 So, I'm going to ask on the second
16 question, which is essentially 1(b), let me
17 read that. The same question, for adults with
18 asymptomatic lower extremity PAD, how confident
19 are you that there is sufficient evidence for
20 an intervention that improves long-term health
21 outcomes, which we agreed as a panel is
22 outcomes that were assessable up to five years,
23 or I should say at five years, given the
24 constraints of the data.

25 (The panel voted and votes were

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1 recorded by staff.)

2 DR. BACH: Okay, the mean was 2.8
3 there. Hold on a second. I apologize, I've
4 missed a process step which I knew, and I
5 apologize. Hopefully we can regenerate this.
6 I actually have to poll you now for your

7 responses, so if we could return to 1(a), you
8 don't have to vote again but hopefully everyone
9 remembers what they voted 15 seconds ago. On
10 question 1(a) on the asymptomatic near-term
11 health outcomes, Dr. Campos-Outcalt, will you
12 tell us how you voted?

13 DR. CAMPOS-OUTCALT: I voted one.

14 DR. BACH: Dr. Carr? You can identify
15 yourself, or I can identify you.

16 DR. J.J. CARR: Three.

17 DR. BACH: Dr. Carr. Dr. Cuyjet?

18 DR. CUYJET: One.

19 DR. BACH: Dr. Deyo.

20 DR. DEYO: Two.

21 DR. BACH: Dr. Lawrence.

22 DR. LAWRENCE: One.

23 DR. LEFEVRE: Two.

24 DR. BACH: That's Dr. Lefevre.

25 Dr. Lewis?

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1 DR. LEWIS: One.

2 DR. BACH: Dr. Salive?

3 DR. SALIVE: One.

4 DR. BACH: Dr. Swain?

5 DR. SWAIN: One.

6 DR. BACH: Dr. Zuckerman.
7 DR. ZUCKERMAN: One.
8 DR. BACH: Okay, and what are we doing
9 now?

10 MS. ELLIS: Go ahead, Dr. Kormos.

11 DR. KORMOS: One.

12 DR. BACH: That's Dr. Kormos.

13 Dr. Lystig.

14 DR. LYSTIG: One.

15 DR. BACH: Dr. Hirsch?

16 DR. HIRSCH: The outlier, three.

17 DR. BACH: Okay. And I would like to
18 do the same for 1(b), and actually, can I ask
19 you to identify yourselves so I don't have to
20 do that?

21 DR. CAMPOS-OUTCALT: Campos-Outcalt,
22 two.

23 DR. J.J. CARR: Jeff Carr, four.

24 DR. CUYJET: Al Cuyjet, two.

25 DR. DEYO: Richard Deyo, four.

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1 DR. LAWRENCE: Peter Lawrence, four.

2 DR. LEFEVRE: Frank Lefevre, two.

3 DR. LEWIS: Sandra Lewis, four.

4 DR. SALIVE: Salive, two.

5 DR. SWAIN: Swain, two.

6 DR. ZUCKERMAN: Zuckerman, two.

7 DR. KORMOS: Kormos, two.

8 DR. LYSTIG: Lystig, two.

9 DR. HIRSCH: Hirsch, four.

10 DR. BACH: All right. My preference
11 is we're going to do the other voting and then
12 we will return to the discussion of each topic,
13 okay, so we're on to question two. For adults
14 with lower extremity intermittent claudication,
15 how confident are you that there is sufficient
16 evidence for an intervention that improves
17 immediate/near-term health outcomes?

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

20 MS. ELLIS: We're waiting on one vote.

21 There we go.

22 DR. BACH: 3.2. Can I poll you?

23 DR. CAMPOS-OUTCALT: Campos-Outcalt,
24 three.

25 DR. J.J. CARR: Jeff Carr, two.

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1 DR. CUYJET: Al Cuyjet, three.

2 DR. DEYO: Deyo, four.

3 DR. LAWRENCE: Peter Lawrence, three.

4 DR. LEFEVRE: Frank Lefevre, three.

5 DR. LEWIS: Sandra Lewis, three.

6 DR. SALIVE: Salive, four.

7 DR. SWAIN: Swain, four, and we're not
8 copying each other.

9 DR. ZUCKERMAN: Zuckerman, three.

10 DR. KORMOS: Kormos, three.

11 DR. LYSTIG: Lystig, four.

12 DR. HIRSCH: Fascinating. Hirsch,
13 five.

14 DR. BACH: All right. And for 2(b),
15 for adults with lower extremity intermittent
16 claudication, how confident are you that there
17 is sufficient evidence for an intervention that
18 improves long-term health outcomes?

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

21 MS. ELLIS: We're waiting on one vote.

22 DR. BACH: Okay. Doug, go ahead.

23 DR. CAMPOS-OUTCALT: Campos-Outcalt,
24 two.

25 DR. J.J. CARR: Jeff Carr, three.

1 DR. CUYJET: Al Cuyjet, three.

2 DR. DEYO: Deyo, four.

3 DR. LAWRENCE: Peter Lawrence, five.
4 DR. LEFEVRE: Frank Lefevre, two.
5 DR. LEWIS: Sandra Lewis, four.
6 DR. SALIVE: Salive, four.
7 DR. SWAIN: Swain, four.
8 DR. ZUCKERMAN: Zuckerman, two.
9 DR. KORMOS: Kormos, four.
10 DR. LYSTIG: Lystig, four.
11 DR. HIRSCH: Hirsch, five.
12 DR. BACH: Okay, and on to question
13 3(a). For adults with lower extremity critical
14 limb ischemia, how confident are you that there
15 is sufficient evidence for an intervention that
16 improves immediate/near-term health outcomes?
17 And remember, in this case we decided
18 that these were health outcomes experienced
19 within the first six months.
20 (The panel voted and votes were
21 recorded by staff.)
22 MS. ELLIS: We're waiting on two
23 votes, now one. We need one more vote, just
24 one. Can everyone just press your button one
25 more time? There we go.

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1 DR. BACH: Doug?

2 DR. CAMPOS-OUTCALT: Campos-Outcalt,
3 four.

4 DR. J.J. CARR: Jeff Carr, three.

5 DR. CUYJET: Al Cuyjet, five.

6 DR. DEYO: Deyo, three.

7 DR. LAWRENCE: Peter Lawrence, five.

8 DR. LEFEVRE: Lefevre, three.

9 DR. LEWIS: Lewis, five.

10 DR. SALIVE: Salive, two.

11 DR. SWAIN: Swain, four.

12 DR. ZUCKERMAN: Zuckerman, two.

13 DR. KORMOS: Kormos, four.

14 DR. LYSTIG: Lystig, three.

15 DR. HIRSCH: Hirsch, five.

16 DR. BACH: Hold on a second. Okay,
17 great. The last question, which people are
18 already answering, it's 3(b). For adults with
19 lower extremity critical limb ischemia, how
20 confident are you that there is sufficient
21 evidence for an intervention that improves
22 long-term health outcomes?

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

25 DR. BACH: Okay, go ahead.

1 DR. CAMPOS-OUTCALT: Campos-Outcalt,
2 two.

3 DR. J.J. CARR: Carr, two.

4 DR. CUYJET: Al Cuyjet, three.

5 DR. DEYO: Deyo, four. Or,
6 correction, three.

7 DR. LAWRENCE: Peter Lawrence, five.

8 DR. LEFEVRE: Lefevre, two.

9 DR. LEWIS: Lewis, five.

10 DR. SALIVE: Salive, two.

11 DR. SWAIN: Swain, four.

12 DR. ZUCKERMAN: Zuckerman, two.

13 DR. KORMOS: Kormos, three.

14 DR. LYSTIG: Lystig, three.

15 DR. HIRSCH: Hirsch, three.

16 DR. BACH: Thank you very much. We're
17 going to now cycle back to the discussion on
18 each of the questions, and in the context of
19 these questions, the discussions have
20 thresholds so if the vote is below, I can't
21 remember if it's less than or equal. Yeah. So
22 a vote, an average vote less than 2.5 means
23 that we will not further discuss the particular
24 intervention, so in this context, 1(a) referred
25 to near-term outcomes of asymptomatic patients,

1 that received a score below the cutoff, I
2 believe it was 2.2 or something like that,
3 so -- right, 1(a), the mean was 1.4, which
4 means we won't now discuss the questions
5 related to it.

6 But the next one, 1(b), the long-term
7 health outcomes with asymptomatic disease was
8 over the threshold, it was 2.8, so the question
9 to the panel, this, if you will, allows you to
10 flesh out the question and the discussion and
11 things like that, so, please identify the
12 specific interventions and associated outcomes
13 in terms of long-term outcomes in asymptomatic
14 PAD. And the floor is open.

15 One of the, I don't want to call it a
16 shortcut, but one approach that we all can
17 take, or some of you can take, is you can
18 actually point to some of the literature,
19 reviews and other presentations that we've
20 heard today, if you don't feel that cataloging
21 every single thing is an efficient use of time.
22 But the floor is open, and we're talking about
23 long-term outcomes for asymptomatic patients.
24 Go ahead.

25 DR. J.J. CARR: I would just say

1 current guidelines for both primary and
2 secondary prevention have significant benefit
3 on cardiovascular, heart and -- cardiovascular
4 mortality, anywhere from 20 to 40 percent, and
5 that was the intervention I was thinking of,
6 basically lifestyle, control of risk factors,
7 and medical intervention where appropriate.

8 DR. BACH: Thank you very much. So
9 systemic interventions aimed at non-peripheral
10 limb outcomes. I won't -- I in no way want to
11 curtail the conversation, but I would take the
12 view that that's a consistent theme we've heard
13 throughout the morning. If there's a
14 difference of opinion over these things then
15 let's continue to pursue it. I would rather
16 now put that to the side, again, with any
17 objections I won't do that, I'm just trying to
18 keep the process going.

19 With that off to the side, I would
20 turn the question to both directed
21 interventions and peripheral outcomes, given
22 that you've just, I think, covered the
23 waterfront of systemic interventions and
24 non-peripheral outcomes. I'm looking for
25 interventions in the peripheral space amongst

1 asymptomatic patients, evidence supporting
2 those.

3 DR. HIRSCH: Just because there's
4 silence, I mean, I think we heard from every
5 speaker and from our Dukies that there is no
6 role in space for that if we're saying, again,
7 as you defined this, this is a truly ischemic
8 limb population, then there is nothing to do.

9 DR. BACH: Dr. Swain.

10 DR. SWAIN: With the exceptions of
11 popliteal aneurysms and the AHA exceptions.

12 DR. BACH: Okay, understood. Thank
13 you for pointing to it, and we know exactly
14 where to look for the AHA exception as it
15 relates to peripheral disease. Dr. Lefevre.

16 DR. LEFEVRE: I do agree with the
17 first commenter, we expect there is efficacy
18 for antiplatelet and other interventions for
19 patients with vascular disease. However, I
20 think the reasons why I would rate this lower
21 is I don't think we know what populations this
22 is directed at. We say asymptomatic lower
23 extremity PAD; I think we've heard here that's
24 a very nebulous population, I think we heard

25 the studies include a whole range of patients

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1 with all kinds of risks, so I don't think we
2 can say who needs to be treated, so I rated it
3 lower because of that, because of the
4 populations being ill defined.

5 DR. BACH: Okay. Dr. Deyo.

6 DR. DEYO: Just to add slightly to
7 that, I agree with the argument about systemic
8 therapy, I think there's little question in my
9 mind that that is effective and will have some
10 benefit for these patients, but I have real
11 reservations about recommending a screening
12 program specifically for PAD, as opposed to
13 screening for risk factors in general.

14 DR. BACH: Point taken, and, you know,
15 the point of this discussion, we do not need to
16 reach conclusion, if you will, during the
17 discussion, but I want very much to get the
18 impressions and conclusions aired for the
19 purpose of the transcript and for the purpose
20 of aiding CMS in the future.

21 DR. HIRSCH: So maybe for the purpose
22 of the transcript, there's qualitative data
23 unpublished, probably about one-fourth of

24 current CMS beneficiaries have an ABI done, or
25 any PAD diagnosis, or at high risk. So even

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1 though we're not advocating screening, Peter,
2 and we don't know its role and there's no
3 randomized trial, we unfortunately live in that
4 world, as Dr. Beckman said, between marked
5 profound under diagnosis and the disease that
6 becomes evident. So I'm just putting it out
7 there for the record.

8 DR. BACH: Okay, large reservoir of
9 undiagnosed --

10 DR. HIRSCH: Just that it's having
11 real cost and real effects.

12 DR. BACH: In bifurcating this
13 discussion, I want to make sure that I have not
14 shortchanged the possibility that some of the
15 systemic therapies have peripheral benefits. I
16 didn't hear that brought up, I didn't hear it
17 in the evidence, but I don't want to -- that is
18 a version of the two-by-two table that I should
19 at least explicitly bring up and ask members of
20 the panel if they feel the evidence supports
21 peripheral benefits in the asymptomatic
22 population of systemic therapy per se. I

23 focused on, if you will, cardiovascular and
24 cerebrovascular outcomes in the way I separated
25 things. So that's the question to you also.

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1 Do you have a --

2 DR. J.J. CARR: I agree with what you
3 said. I was just going to, for the record,
4 there are prospective data comparing Framingham
5 risk score, family history, ankle-brachial
6 index, carotid IMT and coronary calcium in the
7 NHLBI multiethnic study of atherosclerosis, a
8 cohort of 7,000 people, Yeboah, published in
9 JAMA, 2012, that could be used to evaluate the
10 efficacy of a primary intervention with those
11 tools.

12 DR. BACH: That was Dr. Carr speaking.
13 Dr. Cuyjet.

14 DR. CUYJET: I would just add the
15 comment, there was one slide that correlated
16 GFR with outcomes, and we know that if your
17 blood pressure and diabetes are well managed,
18 renal insufficiency disease declines, so I
19 would add that to systemic interventions.

20 DR. BACH: Thank you, Dr. Cuyjet.

21 Okay. Go ahead, Dr. Salive.

22 DR. SALIVE: I didn't hear any direct
23 evidence and so I'm kind of the opposing view
24 on that.

25 DR. BACH: Could you speak closer to

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1 the microphone, please?

2 DR. SALIVE: Sorry. I didn't hear any
3 direct evidence that was positive on this. I
4 felt that this was negative, and although the
5 evaluation was, the average met our criteria,
6 and I think that would be valid for a screening
7 test, but I think this was negative. The
8 presenters showed two aspirin trials that were
9 both negative after screening for
10 ankle-brachial index, and then there was some
11 discussion about lipid lowering, which I
12 believe was, you know, maybe in the high risk
13 people, but lipid lowering is now widely
14 recommended anyway, so I don't see why high
15 risk would need to be identified through the
16 ankle-brachial index.

17 DR. BACH: Okay. So Dr. Salive, when
18 you said this, you're talking about the
19 long-term outcomes with systemic therapy.

20 DR. SALIVE: Yes.

21 DR. BACH: Okay. Does anyone want to
22 pick up on this point, because that differs
23 from what I think Dr. Carr concluded, so is
24 there a way to fill this in with evidence?

25 DR. HIRSCH: Well, if we're here to

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1 highlight evidence gaps because, again, I've
2 been very careful in saying what we know and
3 then say what we don't know, so CMS, AHRQ and
4 the investigators can fill in the gaps, we
5 hardly reviewed the totality of evidence in
6 this data-focused meeting today and there's no
7 way we could have done that.

8 So there are at least two prospective
9 trials, 4S was the one simvastatin trial, I
10 can't remember the other lipid trial, where
11 asymptomatic patients did not develop incident
12 claudication, a robust pre-hoc defined
13 endpoint. It's never been repeated, it's not
14 been the focus of care, but there is some
15 evidence out there, it's an evidence gap. Just
16 because we don't know doesn't mean it might not
17 be effective. And in the current Vorapaxar
18 power one antagonist antiplatelet domain, there
19 is initial evidence, a Bonaca paper in

20 Circulation a year and a half ago suggesting,
21 again, that limb events actually are decreased
22 by that particular antithrombotic agent.

23 But we haven't gotten that granular
24 today, so these are evidence gaps that could be
25 filled in.

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1 DR. BACH: Okay, I appreciate it. I'd
2 like to move on to question 2(a), which had a
3 3.2 mean score which, again, asks for, or leads
4 to a discussion about which interventions and
5 which outcomes in the context of immediate or
6 near-term health outcomes for patients with
7 intermittent claudication.

8 And let me actually propose, and we'll
9 further curtail it within the limb, the
10 peripheral outcomes, they need not be
11 peripheral interventions but peripheral
12 outcomes, as opposed to this kind of global set
13 of cardiovascular and cerebrovascular outcomes.
14 Dr. Swain.

15 DR. SWAIN: I think the exercise
16 results are very reasonable for the short-term
17 and I'll make my comment for the next question,
18 for the long-term too, so I think exercise for

19 sure.

20 And then there's the question of
21 whether endovascular revascularization does,
22 and I think I agree with the Dukies, that
23 that's an intermediate level of evidence for
24 that.

25 DR. BACH: Do you want to distinguish

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1 between supervised and home-based exercise?

2 DR. SWAIN: Oh, supervised, yeah. I
3 know the results of this is whether CMS will
4 cover that, and I think CMS should cover
5 supervised exercise for all these reasons.

6 DR. BACH: Other -- Dr. Zuckerman?

7 DR. ZUCKERMAN: I'm just happy to
8 agree with that.

9 DR. BACH: Oh, great, I love these
10 comments. Dr. Lawrence.

11 DR. LAWRENCE: Yeah, I gave it a
12 three, and the reason I did was because it
13 really to me is dependent on the level of
14 disease. So in intermittent claudication, the
15 more proximal, the more the intervention is
16 likely to be successful initially, so a
17 claudicator with iliac disease will do

18 dramatically well and have a very long survival
19 with a procedure. In fact, a juxtarenal aortic
20 occlusion can benefit greatly from an
21 aortofemoral bypass, immediate benefit.

22 But as the disease moves more
23 distally, as in SFA or infrapopliteal, then
24 claudication becomes to me a much less
25 compelling indication for doing either a bypass

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1 or intervention. So it's sort of in the middle
2 where to me if it's distal, then it's a medical
3 problem and it fits in with Dr. Swain about
4 exercise and maybe cilostazol, whereas if it's
5 proximal, you have a 90 percent success with
6 any of the open or any of the endovascular
7 approaches, so level of disease becomes
8 critical to me in claudication.

9 DR. BACH: Other comments?

10 Dr. Lefevre.

11 DR. LEFEVRE: I just want to say, I
12 don't think it's quite right to say supervised
13 versus unsupervised are different
14 interventions. I think it's better to say, you
15 know, exercise improves walking distance and
16 supervised exercise more than unsupervised

17 exercise, indicating like a dose-response
18 effect, it's a more intensive exercise
19 intervention. So I don't think we should just
20 say supervised is effective and unsupervised is
21 not, we should just say exercise is effective
22 and the greater the intensity of the
23 intervention, the greater outcome benefits you
24 get.

25 DR. BACH: Okay. And same question,

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1 then, for long-term health outcomes for
2 intermittent claudication.

3 DR. HIRSCH: Well, actually I'll speak
4 up and --

5 DR. BACH: And actually you need not
6 if -- no, no, no, Dr. Hirsch, I did not mean
7 you need not speak up. What I was about to --
8 although that would be fine. No. I was about
9 to say it may actually help for everyone else
10 here who doesn't have a list of how everyone
11 voted to say what your vote is. And you need
12 not do that if you'd rather just speak, but it
13 might help everyone to anchor your comments.
14 So go ahead, Dr. Hirsch, I'm sorry for cutting
15 you off.

16 DR. HIRSCH: I'm not sure I exactly
17 followed that. Just to push the panel to have
18 an open discussion, again for CMS and the
19 audience, I was surprised at the relative
20 downgrading of all of the interventions for
21 claudication, and so just to provoke you all to
22 speak up, whether it was the Duke presentation
23 or the primary information offered, we have
24 been presented evidence that pharmacotherapy
25 that supervised exercise, yes, based on a

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1 dose-response, endovascular and surgical
2 intervention all work and they have been
3 studied, each of these at least one year back
4 to the bimodal TED distribution. So why is the
5 level of evidence and confidence not higher?
6 I'm confused.

7 DR. BACH: Also, that's a great way of
8 asking a question that will also help answer
9 some of the other discussion points, so I
10 actually open the floor up to answer
11 Dr. Hirsch's question. Dr. Lawrence.

12 DR. LAWRENCE: I would say the answer
13 is because the superficial femoral artery is
14 the key of a lot of the discussions here, and

15 the perception is that it's not durable so that
16 it may get immediate success but there's a lack
17 of durability. So it has to do, with me,
18 again, the level of disease, not that it can't
19 be initially successful, but that the
20 durability is a major question with both open
21 and endovascular approaches.

22 DR. HIRSCH: Peter makes a very good
23 point, and for the audience that's not endo
24 focused, it is true that from mid thigh down
25 our patencies are not quite what we want them

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1 to be, although they have certainly markedly
2 improved.

3 But this gets to, our questions are
4 difficult because we have three interventions,
5 right? We have exercise, we have
6 pharmacotherapy, and we have a range of
7 anatomic possibilities, and yet we're asked to
8 vote on all of them on one vote. What's
9 challenging, if I were reading the transcript
10 as a CMS officer later, I might be quite dour
11 about the confidence that we can approve claudication
12 interventions for Medicare beneficiaries when my
13 level of confidence might be very high overall.

14 DR. BACH: Dr. Campos.

15 DR. CAMPOS-OUTCALT: Yeah. I voted
16 three and two. That's because the evidence
17 report showed a moderate level of confidence,
18 moderate level of evidence, and it didn't go
19 past a couple years, so I voted a three and two
20 for that reason.

21 DR. LEFEVRE: I would agree. They
22 were also very small studies, there were no
23 large scale studies, and I think the effect
24 size wasn't great, the walking distance
25 improvement was not that great.

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1 MS. JENSEN: Can you identify yourself
2 for the record, please?

3 DR. BACH: That was Dr. Lefevre, I'm
4 sorry. Dr. Swain.

5 DR. SWAIN: I voted four but it was,
6 again, the heterogeneity on durability because,
7 again, if it's a minimal claudication, I think
8 durability should be defined out to five years,
9 that's how I define long term. If it were
10 somebody that couldn't walk, you know, 20 feet,
11 that's a whole different patient. So the
12 heterogeneity in this question makes it almost

13 impossible to answer, but we don't have good
14 durability for endovascular or open surgical
15 interventions, and I don't believe we have good
16 five-year durability for things like exercise.

17 DR. HIRSCH: So Julie, I think you're
18 making a very good point. What the group is
19 saying is they want longer outcome studies for
20 all interventions, and you're right, even for
21 CLEVER it was 18 months only. Although if you
22 had angina or if you had some other symptoms
23 that migrate, my guess is you got 18 months of
24 relief, my guess is you would be happy.

25 DR. SWAIN: That was my original --

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1 DR. HIRSCH: Let's not minimize what
2 18 months means.

3 UNIDENTIFIED PANELIST: And also --

4 DR. BACH: Wait. I don't think
5 anyone's minimizing it, but they have been
6 separated into different categories.

7 Dr. Lawrence, or, I'm sorry, go ahead,
8 Dr. Lefevre.

9 DR. LEFEVRE: I think another way to
10 look at the outcomes would be if they defined
11 the minimal clinically important improvement in

12 walking distance and then we have a response
13 rate, that would be much more meaningful to me
14 than just an average.

15 DR. SWAIN: And we saw no MCIDs or
16 anything.

17 DR. BACH: Dr. Lawrence?

18 DR. LAWRENCE: Yeah. Without a quote
19 because this is from memory, but within the
20 last year there has been a paper, I believe it
21 was in JAC, that looked at patients and
22 interventions, and I think it was exclusively
23 in claudicators. In the United States there
24 are almost as many procedures done for
25 reintervention in less than two years than

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1 there are the initial procedure. So in other
2 words, we've almost reached a point where the
3 initial procedures are occurring at about the
4 same rate as reinterventions, and that
5 addresses the issue of durability.

6 DR. BACH: Great, thank you. Other
7 comments? No. Dr. Zuckerman, you still have
8 your card up, I think. Go ahead.

9 DR. ZUCKERMAN: I just wanted to say,
10 I think for many of these, and this was one, it

11 was a conflict between what seems logically
12 likely and what the data show, and the data
13 just aren't very good. And so even though it
14 seems like if people exercise or have some kind
15 of successful short-term benefit that would
16 help them in the long-term, but we just don't
17 have the data to show it.

18 DR. BACH: Okay, thank you. On to
19 question three, the issue is critical limb
20 ischemia in terms of interventions and outcomes
21 affecting immediate and near-term health
22 outcomes interventions and again, separating
23 out those things that are systemic and
24 targeting other parts of the body other than
25 peripheral.

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1 DR. SWAIN: Julie Swain. Again, you
2 know, as I think it was AHA or ACC, you know,
3 more blood flow. I think that's established,
4 more blood flow will heal wounds, so for
5 short-term into the heal wounds, get rid of
6 pain, I think the evidence is fairly good that
7 that occurs, I voted a four on that one.

8 DR. BACH: Let me ask you a point of
9 clarification, and again, this is not my area

10 of expertise. What I heard was that there were
11 no comparative studies that were at least a
12 high enough level of evidence to get into the
13 Duke review or they predated the Duke review,
14 where usual care or nonintervention was the
15 control?

16 DR. SWAIN: Yeah. Nowadays really,
17 the standard of care is to intervene, I mean,
18 that's the standard of care. So the idea that
19 you're going to have a comparative study to do
20 nothing and let them sit there and have a
21 stinking wound before you amputate, or do
22 something, and, you know, on this particular
23 subset I think it's the provide more blood
24 flow, we have good short-term healing, and
25 we've seen it from the practitioners and all of

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1 us who do vascular surgery, heal and get rid of
2 pain and make the patient more comfortable.

3 And long-term wise, most of them are
4 going to die pretty soon anyhow, so if we say
5 long-term is seven months or eight months, then
6 make them more comfortable, as part of the
7 interventions and the outcomes that you all are
8 looking for.

9 DR. BACH: Thank you.

10 Dr. Campos-Outcalt.

11 DR. CAMPOS-OUTCALT: Yeah. I think
12 this is the classic example where observational
13 data can be upgraded, because the magnitude of
14 effect of doing nothing versus doing this is
15 quite large, and so you don't have great
16 studies but you could upgrade them because of
17 the observational magnitude of effect. So
18 that's why I gave it a four, even though I
19 don't think the studies are particularly
20 robust.

21 DR. SWAIN: Yeah, and I have a big
22 problem with the graphs we saw on several
23 slides of length of life for vascular
24 intervention or those that were amputated, and
25 people may have a shorter lifetime. I mean,

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1 there is no comparability between those two
2 groups of patients, and I saw no propensity for
3 analysis studies done for that, so I think
4 those are just, the idea of having another
5 MedCAC panel on amputations, I don't see the
6 reason for that.

7 DR. BACH: Dr. Lewis.

8 DR. LEWIS: One of the evidence gaps
9 with the compression devices and hyperbaric
10 treatment may be in the patients who are not
11 candidates for that intervention.

12 DR. BACH: Yeah, we didn't hear much
13 evidence of that, although we did see some
14 dramatic pictures. Dr. Lefevre, did you want
15 to say something?

16 DR. LEFEVRE: Yeah, I just wanted to
17 comment. I gave it a three. I do agree that
18 this is an issue where we could accept a lower
19 level of evidence, we don't necessarily need an
20 RCT. If you have a patient population that
21 truly has no other alternative and is heading
22 for a limb loss, then certainly these are
23 improved outcomes. The reason I only gave it a
24 three and not higher is because I think that's
25 a slippery slope at selecting the patients, and

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1 it's very easy to think, you know, it's not
2 easy to select just the patients who are going
3 to lose their limb, it's going to be hard, you
4 know, and you might end up selecting patients
5 with less disease and end up potentially even
6 doing harm.

7 So I think that kind of threshold of
8 where to intervene and could we truly define a
9 population that has no other alternatives than
10 to lose their leg, I think is questionable, so
11 that's why I gave it a three.

12 DR. BACH: Dr. Carr.

13 DR. J.J. CARR: My thinking on this
14 question, and I voted a three and two, is that
15 an ounce of prevention is worth a pound of
16 cure, that there's tremendous investment in
17 resources here at the end, and I think the
18 speakers and the public speakers did a good job
19 indicating that there's a huge reservoir of PAD
20 out in the community that is undiagnosed, and I
21 would urge CMS to develop strategies to uncover
22 clinical disease that's simply not manifest,
23 and encourage trials that would allow us to
24 better risk stratify these people with disease
25 and develop strategies, rather than continually

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1 going from simply asymptomatic to symptomatic
2 in critical limb ischemia.

3 I think there's a lot of opportunity
4 to target, you know, identify through
5 biomarkers, through genomics, through risk

6 factors, not necessarily imaging or diagnostic
7 testing, but there are probably ways that could
8 more effectively risk stratify and identify
9 at-risk women and minorities that have evidence
10 of peripheral arterial disease, as well as
11 treatments that could be more effective.

12 DR. BACH: Dr. Salive.

13 DR. SALIVE: Yeah, I guess I
14 downgraded it because there was only the one
15 trial, but I did actually appreciate that there
16 was quite a lot of observational evidence
17 presented in the TA, and so it was helpful but
18 it didn't sway me further. I just think that
19 it is too weak, and other speakers have
20 commented that some of these can be studied
21 observationally and stronger evidence could be
22 provided that way, so that's what I was
23 thinking.

24 I think the trial that's underway that
25 was presented was helpful as well, in terms of

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1 answering this question farther down the road.

2 DR. BACH: Dr. Lawrence.

3 DR. LAWRENCE: I think the reason that
4 there are not prospective randomized trials is

5 because it would be unconscionable to not treat
6 patients who have critical limb ischemia
7 lesions. So I mean, this is evidence that's 40
8 and 50 years old, and it would be like saying
9 we need a new randomized trial to justify the
10 use of Heparin and warfarin for PE. It's not
11 going to happen because it would literally be
12 negligent to have the patient with an arterial
13 lesion and true critical limb ischemia.

14 Now, rest pain is always a little
15 questionable because that can go either way and
16 sometimes patients can sit with that, but if
17 you truly have an ischemic ulcer, gangrene, and
18 don't treat the patient, I can't see any
19 rationale or justification as long as they have
20 a treatable lesion.

21 So to me, this has to go to both early
22 results and long-term, they need to be a five.
23 This is the only option for these patients, and
24 it's just a question of what kind of treatment
25 they're going to get, not whether they get

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1 treatment of not.

2 DR. BACH: Okay, thank you. Marcel,
3 did you have something else? Let me move on to

4 (b) then, which scored slightly lower than the
5 immediate and near-term outcomes. The
6 long-term health outcomes for critical limb
7 ischemia, and using the rule that we
8 established this is outcomes durable to two
9 years amongst these interventions.

10 So again, it's a limited number of
11 interventions that have come up and I guess the
12 question is, you know, discussion around those
13 interventions and outcomes, is there more
14 detail or texture that we can give CMS around
15 these outcomes or interventions? Great, I
16 managed to pose a question where I silenced
17 everyone, which of course is my goal.

18 (Laughter.)

19 All right. And I'm going to circle
20 back one more time here through the three
21 questions, there is another discussion point
22 that we need to bring up, and I grouped these
23 because I think to some extent they go
24 together, but the second bullet reads
25 considering, and this is for each of the three

1 questions, considering the heterogeneity of the
2 Medicare population, discuss which subgroups of

3 the Medicare population the evidence shows are
4 likely to benefit or likely not to benefit from
5 intervention.

6 And so I'll take these in order
7 beginning with the asymptomatic population, but
8 then again, disagree with me as you like, I
9 believe these are, the answers to these will
10 generalize across the three questions, but
11 again, correct me if I'm wrong. Dr. Carr, you
12 still have your tent card up. Dr. Swain.

13 DR. SWAIN: I just don't think we have
14 enough data for subset analysis, that's the
15 problem, and the biggest subset I see is
16 diabetes or no diabetes. It may be that doing,
17 let's say an open surgical or endovascular
18 intervention in diabetics may well give you
19 better long-term results or it may well have a
20 blended long-term effect depending on the
21 control of the diabetes and all that. So
22 again, the data is just, if there's not enough
23 data for the aggregate, there's certainly not
24 enough data for subset analysis in different
25 Medicare populations.

1 DR. BACH: And would your view of that

2 cut across all three categories, all three
3 questions?

4 DR. SWAIN: Pretty much so.

5 DR. BACH: Okay, fair enough.

6 DR. SWAIN: I don't know about
7 critical limb ischemia, again, I do think you'd
8 supply blood, but the other two for sure.

9 DR. BACH: Fair enough. Dr. Carr.

10 DR. J.J. CARR: For question one in
11 the asymptomatic, there's a fair amount of
12 large scale data that subclinical
13 atherosclerosis in people with peripheral
14 arterial disease predicts cardiovascular
15 morbidity and death, especially in women and
16 minorities in an untreated group, and so I
17 think that there are data that could be
18 reviewed that would justify more aggressive
19 prevention in the at-risk populations and
20 reduce morbidity later in Medicare-aged
21 beneficiaries.

22 DR. BACH: More on that point, or
23 something else. Dr. Cuyjet.

24 DR. CUYJET: I'd just make a general
25 comment. I mean, the literature regarding

1 depression as a comorbidity and its impact on
2 coronary heart disease is irrefutable, and
3 there's been not much discussion, we had one
4 case presented of a gentleman who continued to
5 smoke and did all this other stuff, but I did
6 hear the word depression come up in the
7 presentation. So when we talk about general
8 care of the total patient, I think depression
9 screening is indicated and recommended for it
10 to be a general part of the evaluation of
11 patients with suspected PAD.

12 DR. BACH: Thank you. Dr. Salive.

13 DR. SALIVE: Yeah, so I think to
14 generalize maybe the last couple comments, I
15 think it is the multiple chronic condition
16 people in the Medicare population who benefit
17 greatly, so yes, it might be the diabetic, it
18 might be depression, and there's many other
19 chronic diseases. And I think there was a nice
20 slide from someone about kind of the overlap of
21 coronary artery disease, cerebrovascular
22 disease and PAD, but I would just say it
23 extends to a variety of chronic diseases and,
24 you know, we don't know much, it would be nice
25 to know more, so the studies need to kind of

1 ascertain the chronic deceases, the comorbid
2 diseases that are accompanying this so that it
3 can be understood a little bit better and, you
4 know, this is really a very high risk group
5 with the PAD group.

6 DR. BACH: Yes, please.

7 DR. KORMOS: So just following up on
8 what Dr. Swain said, I also saw a fair amount
9 of data, getting back to the issue that there's
10 a differential in presentation, especially in
11 intermittent claudication based on gender,
12 race, age, we mentioned diabetes, and there
13 were a few others in there as well that if
14 trials are going to be designed in the future,
15 then they probably need to adjust for some of
16 these differences and it goes with some of
17 these things.

18 And it actually gets to the point
19 that, I think that Dr. Hirsch meant, that we
20 talked about asymptomatics, but those
21 asymptomatics could include people with
22 previous peripheral vascular disease, and
23 that's a subset that doesn't really get
24 addressed in any of this.

25 DR. BACH: Thank you. Okay. Moving

1 on, then, that's the end of the discussion of
2 the questions and the voting and the subsidiary
3 discussions around those.

4 I do want to leave, the floor is open
5 and if we in the next discussion come back to
6 some of those things, that's fine. This is
7 supposed to be a free ranging discussion.

8 But we do have some additional
9 discussion topics that I think we've already,
10 some of the comments have sort of bled into
11 this area already. They are to discuss the
12 important evidence gaps that have not been
13 previously or sufficiently addressed by the
14 literature, and to discuss any apparent lower
15 extremity PAD treatment disparities and how
16 they may affect the health outcomes of Medicare
17 beneficiaries.

18 I'll start. I'm not providing the
19 answers, I'm just going to repeat some of the
20 things I've heard during the course of the
21 discussion in terms of evidence gaps. I've
22 heard very consistently today that there are
23 important subsets, of course this is not my
24 disease area, but diabetics, nondiabetics;
25 gender or, pardon me, sex difference; race,

1 particularly African Americans; location of the
2 lesion. These are all themes that I've heard
3 from multiple people over the course of the day
4 as important ways of thinking about this
5 condition.

6 And then interplay between other types
7 of vascular disease, nonvascular disease such
8 as depression is another evidence gap that has
9 come up, and then the issue that really has
10 revolved initially around the questions, but
11 very much around the discussion around clinical
12 trials design, the tightness of the definition
13 of the cohort, the tightness of the definition
14 of the outcome, and in the middle of there is
15 the tightness or looseness of the interventions
16 given a rapidly changing, particularly on the
17 device side, rapidly changing landscape of
18 devices. So I have already heard all those
19 things; if you want to take any of those off
20 the list, let me know. If you want to add
21 things to the list, please have at it. Dr.
22 Lawrence.

23 DR. LAWRENCE: Yeah, there are two
24 that I would just suggest you consider adding,

25 although you touched on them. One is the

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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

24 interesting and important. Peripheral vascular
25 disease and diabetes together is a bad

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1 combination, and I just think that there's
2 going to be differences in treatment that need
3 to be fleshed out.

4 Secondly, the disparities, we've
5 documented disparities but I'm not sure we've
6 got a lot of research on why the disparities
7 exist.

8 DR. BACH: We're going to get to that.
9 We're not on that question.

10 DR. CAMPOS-OUTCALT: Okay, so I'll
11 hold that one. I think the research on better
12 ways to find symptoms, which has been
13 discussed, is probably another one I would add,
14 and then the obvious one is comparative
15 effectiveness. We just don't have very good
16 comparative effectiveness data.

17 DR. BACH: Thank you. Dr. Deyo.

18 DR. DEYO: Yeah. In terms of subsets
19 that I think need more attention, we tend to
20 think of everybody in the Medicare population
21 as old, but I think there's an important
22 difference between young old and old old, and

23 the risk/benefit equation may change with
24 increasing age, and I'd like to see more
25 studies that segregate out the old old

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1 population and help inform us better about that
2 group.

3 DR. BACH: Fair enough, and I assume
4 for all of us that cutpoint moves up about a
5 year every year. No, the point is taken. I'm
6 sorry, I don't mean to be silly. Dr. Carr?

7 DR. J.J. CARR: Just for the record, I
8 was going to point out that, and this may be
9 obvious, but atherosclerosis is the disease,
10 and within atherosclerosis there are
11 manifestations within different vascular beds,
12 renovascular, peripheral arterial, coronary
13 disease, cerebrovascular. And then I would
14 just for the record say that there are large
15 and medium arteries that could be involved with
16 the disease, and small vessel disease in the
17 kidneys or in the distal legs, and that as CMS
18 thinks about this, just like they would lung
19 cancer, realize that it's one disease that may
20 have multiple manifestations based on where the
21 disease metastasized to or the organ system

22 involved.
23 That complexity confounds a lot of
24 this discussion, but an understanding of that
25 pathobiology will be very helpful as we move to

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1 precision medicine where we look at genetics,
2 we look at evolving treatments that are near to
3 being available to the Medicare population that
4 will have multiple organ system effects across
5 the vascular system.

6 So, I think thinking of peripheral
7 arterial disease in isolation from these other
8 manifestations of atherosclerosis will not give
9 us a comprehensive picture of how we can best
10 manage it in the Medicare population.

11 DR. BACH: Thank you, Dr. Carr.
12 Dr. Deyo, is it your card or are you done?
13 Dr. Lefevre.

14 DR. LEFEVRE: One more subpopulation I
15 think would be by severity of the PAD. I
16 didn't see any studies that restricted or
17 stratified patients by mild, moderate or severe
18 level of disease, and I think I'd like to see
19 studies segregated by either ABI or maybe even
20 better, functional status, in terms of

21 interventions directed at different stages of
22 disease.

23 DR. BACH: Thank you. Dr. Salive, I
24 guess you don't have a question. Dr. Swain.

25 DR. SWAIN: A subpopulation of those

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1 who are having a second intervention, because
2 that's a specific one, and I disagree again
3 with the BEST trial that, you know, an
4 intervention that can lead to death or limb
5 loss, which is endovascular, surgery or
6 anything, that it is not a minor procedure. So
7 we have that particular subset of
8 reintervention, which apparently is very
9 common.

10 DR. BACH: Dr. Zuckerman. Thank you.

11 DR. ZUCKERMAN: I don't think it was
12 part of this discussion so much, but to
13 emphasize what someone else said before about
14 the importance of having better data earlier in
15 the process, so that when they're more likely
16 to be short- and long-term benefits and just
17 having better data on, we have to figure out
18 how to do screening that works and that leads
19 to interventions that work, and I don't think

20 we have research that shows that. Maybe there
21 is no way to do it, but maybe there is and we
22 just haven't gotten the research done yet.

23 DR. BACH: Okay, thank you.

24 Dr. Lawrence.

25 DR. LAWRENCE: Just a brief comment.

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1 It's interesting to me that in all of the
2 discussion today, I haven't heard the word stem
3 cell mentioned once, and yet there have been
4 like five or six trials of stem cells, and many
5 people in the cardiovascular community think of
6 the lower extremity as the place where the role
7 of stem cells will be investigated. So not
8 that it should be thought of now as a therapy,
9 but when you're talking about gaps in
10 knowledge, I think that approaches, that's why
11 I mentioned unreconstructible disease and
12 restenosis, the patient has multiple
13 procedures, is that stem cell may have a role
14 there, and that's certainly something we can
15 encourage CMS to support, and there will, I
16 think there will be research, and that may be
17 all that we're talking about at a conference
18 like this, is the role of stem cells in PAD.

19 DR. BACH: Okay. Well, that goes into
20 the, if you will, to categorize it, that's sort
21 of, let me call it new technologies, or not
22 well understood.

23 I actually wanted to ask a question
24 about that, which is the compression devices.
25 We've heard a fair amount about it. It's not

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1 an area that I know much about. Is there an
2 evidence gap there, or was it that our reviews
3 didn't take in what we should have taken in?
4 Dr. Hirsch.

5 DR. HIRSCH: Yes, there's an evidence
6 gap. Clearly we were presented with a number
7 of trials that demonstrated some initial
8 efficacy but the sample sizes are small, the
9 descriptive populations are not necessarily
10 representative, but there is at least a
11 biological reason to presume there might be
12 efficacy, so there is a research gap.

13 DR. BACH: And again, apologies for
14 the naivete. Is it possible that could be side
15 by side with other interventions for critical
16 limb ischemia, or does it only have to, is it
17 your expectation this will only be for

18 nonoperable patients?

19 DR. HIRSCH: Once again, this may come
20 off Peter's comment. For all the things we
21 study, when we tend to combine different
22 syndromes, CLI and claudication, asymptomatic
23 and claudication, we tend to learn very little,
24 because already the panel doesn't like the
25 sample sizes, so it's always wise to have a

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1 relatively well described single population. A
2 CLI compression trial would likely be distinct
3 from a claudication compression trial.

4 Peter, your comment about cell
5 therapy, you know, the National Heart Lung and
6 Blood Institute sponsors the CCT-based trial,
7 I'm the national co-PI looking at claudication
8 cell therapy, but there's only 80 patients, and
9 if you didn't like CLEVER and you didn't like
10 the other studies of a hundred, you're not
11 going to like this either. So I think what
12 we're maybe saying to ourselves back to CMS is
13 since it's been very, very, very, very, very,
14 how many very's, hard to get people to be
15 actually aware of the trials and to be
16 randomized. Again, like other new therapies,

17 if there isn't a reason to incentivize research
18 participation to have adequate enrollment and
19 adequate sample sizes, this field will never
20 move.

21 DR. BACH: Point made, thank you.

22 Dr. Swain.

23 DR. SWAIN: I'd like to second that

24 for virtually all the trials. You know, I

25 think CMS was, one of the first ones to require

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1 payment be, that you be in a trial was lung
2 volume reduction surgery, and I think for a
3 whole lot of these devices and trials that they
4 should go on, and the way to incentivize if
5 you're going to pay for it is you be in the
6 trial. And that works well, because the
7 off-label use and everything is impossible.

8 DR. HIRSCH: But Julie, if you're
9 going to ask for that, I'm going to ask for
10 parity, it's not just device trials, my device
11 maven, but it's equal for pharmacotherapy and
12 behavioral therapies. Thank you.

13 DR. SWAIN: Very good.

14 DR. BACH: Dr. Zuckerman, do you have
15 another comment?

16 DR. ZUCKERMAN: No, I'm sorry.

17 DR. BACH: That's all right, thank

18 you.

19 So along the lines I have heard a call
20 for coverage under evidence development, is the
21 technical term for that. There were also
22 discussions about registries and quality
23 improvement in the context of registries. We
24 heard about a large registry going. Is it
25 reasonable to argue that there would be subset

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1 differences in outcomes based on institutions
2 participating in those registries or not? I'm
3 seeing head nods, which is one of the things we
4 can't record in this meeting.

5 DR. SWAIN: Swain says yes.

6 DR. BACH: Dr. Lewis.

7 DR. LEWIS: Well, we certainly saw
8 differences in rates of such things as
9 amputation, et cetera. I don't know why we
10 would think that there would be homogeneity
11 across the country in these things, so I think
12 looking at heterogeneity of site is very
13 reasonable.

14 DR. BACH: Dr. Salive.

15 DR. SALIVE: So yeah, I think one
16 thing to incentivize also is the pragmatic
17 trial, and I think we heard a pretty good
18 example of one, although I didn't hear enough
19 details today about that trial. But I think
20 that the reason to do it is to allow for wider
21 strategies for treating these problems and, you
22 know, have some ability to compare them and
23 enroll a variety of different specialties, I
24 think as we heard, to do the procedures and
25 treat the patients.

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1 So I think, you know, that pragmatic
2 trial idea, it didn't sound like it was fully
3 pragmatic, and I know it's a spectrum of
4 pragmaticness, but to me also, I think this
5 gets to the idea that people were mentioning of
6 personalized medicine but, you know, an
7 individualized approach that involves the
8 patient is needed, I think, in this, that I
9 don't think we heard too much about, because
10 what are their priorities? And older people
11 have different priorities, they don't all have
12 the same priorities, and it's not related to
13 the diameter of a certain vessel in their leg,

14 so it may be related to their functional
15 status, and I think that was reasonably
16 examined here.

17 So I think the studies of patient
18 preference are also a gap that we should try to
19 get, encourage some work there.

20 DR. BACH: Okay, thank you.

21 Dr. Lystig.

22 DR. LYSTIG: So, you'd asked the
23 question about the registries and about seeing
24 heterogeneity by sites, so I think in the
25 presentation we've seen from the registry

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1 result I did not see what would deem to be
2 sufficient accounting for the possible
3 differences in the patient populations by
4 sites, so I'm less interested in seeing that
5 sites have differential performance than seeing
6 after having made appropriate adjustments to
7 see a comparable patient population between
8 those sites, you might then have differential
9 performance. So when we are looking at these
10 observational data sources, we have to take
11 appropriate steps so we can draw the
12 appropriate inferences from it and make fair

13 comparisons.

14 But then I'd also just point out too
15 that within the context of registries, there is
16 a difference between doing a census and doing a
17 sample. If you do the samples right, within
18 stratified sampling, for example, you can make
19 very good inferences about targeted subgroups.
20 It is not necessarily a requirement that in
21 order to have effective findings from a
22 registry it needs to be a census of everyone
23 with a particular condition, it's appropriate
24 not to conflate those two issues.

25 DR. BACH: Agreed. Dr. Hirsch.

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1 DR. HIRSCH: I was going to add one
2 more positive comment to get us out of our
3 depressive rut.

4 No, but seriously, I'm worried a
5 little bit today about disparities and to
6 answer questions that focus on what we don't
7 know, we don't know, we don't know. And for
8 those who presented, there's an awful lot of
9 consensus out there that is well grounded, I'm
10 conservative in the scientific base, and gosh,
11 I don't have quite the date right, but PAD

12 performance measures, these six to seven things
13 that every vascular site thought were
14 appropriate exist and have been published and
15 peer reviewed, there's no controversy.

16 It was simple things, as you've said
17 before, like statins, appropriate antiplatelet
18 therapy, appropriate ABI use, appropriate graft
19 surveillance once you've had your bypass graft,
20 and these disparities that exist within
21 registries and practices are a problem, aren't
22 they? Because even if we know what, you know,
23 a CMS beneficiary should do if there's this
24 huge disparity, we already know scientifically
25 with dissemination research it's easy to

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1 abolish disparity by measuring these and then
2 having appropriate pay interventions.

3 So I just want to put on the record
4 that the performance measures that exists for
5 CMS is an excellent guidepost to a bare minimum
6 of what we know.

7 DR. BACH: Okay, thank you.

8 Dr. Swain, do you have another comment?

9 DR. SWAIN: This is totally different
10 than the others, but is there a possibility

11 that CMS with their big bucket of money that
12 they have, to support, help support the
13 registry? Because the biggest lack I see in
14 the SVS compared to the STS is on-site audit.
15 Once you start doing some, it doesn't matter
16 how many you do, it's amazing how the data get
17 changed when you're at risk of having an audit,
18 not just a statistical audit, that's certainly
19 important, but on-site audits, and then a
20 requirement to enter data in the registry for
21 payment, I think would go a long way in
22 helping. And audits are the most expensive
23 part of any of these, is having help pay for at
24 least some number or percentage of sites'
25 audits.

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1 DR. BACH: Let me move on to the
2 last -- I can answer that question, which is I
3 think it's unlikely to have a mechanism in
4 place. But, you know, as a condition of
5 coverage, there are other financial incentives
6 for institutions to do it.

7 The last question is, discuss any
8 apparent lower extremity PAD treatment
9 disparities and how they may affect the health

10 outcomes of Medicare beneficiaries.

11 Dr. Cuyjet.

12 DR. CUYJET: Al Cuyjet. Obviously
13 we've seen disparities in outcomes among
14 different populations and given the evidence
15 gaps, it begs the question as to how we're
16 expected as primary care providers to assess
17 and manage these patients. You can look at
18 the, New York's just in its seventh month of
19 the Nurse Practitioner Modernization Act, I
20 think we're the 17th or 18th state.

21 And so the point is, it brings me back
22 to 2002 with the ALL HAT trial and we all got
23 carted off down to Texas for dissemination
24 training, and I think a big piece of this needs
25 to be, when we have the evidence, it's fine

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1 that we know it, but it needs to be
2 disseminated and diffused into the practice
3 population so when patients do show up, they're
4 assessed and managed accordingly, and I think
5 CMS can play a big part in that.

6 DR. BACH: Okay. Thank you for that
7 comment. So you skipped over the answer to the
8 question so let me fill it in, which is that

9 there are, appear to be at least outcome
10 disparities and large treatment disparities in
11 terms of amputation rates at least by race,
12 this is what I saw on the slides, correct me if
13 I'm wrong, and that very large effects due to
14 income as well, or at least using ecologic
15 metrics of income as well, such as income or
16 ZIP code or something like that. And I think
17 you went further and said okay, given that,
18 what should we start thinking doing about it;
19 is that right?

20 DR. CUYJET: I can tell you just as a
21 simple example, I mean thiazides are the
22 cheapest way to treat hypertension. The
23 prescription rate was tracked actually with an
24 implementation dissemination product and the
25 curve kind of went like this, it had been going

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1 like that for some time. So it's an effective
2 intervention that does work and it does improve
3 control rates, depending on what your target
4 is.

5 DR. BACH: Other comments about
6 disparities? There was an earlier comment that
7 suggested that subsets of patients, probably

8 the ones showing high rates of amputation, for
9 example African Americans, might be evaluated
10 differently, that maybe, I think what I was at
11 least reading between the lines, that the
12 approach in African Americans, maybe the
13 screening approach should be more aggressive or
14 started earlier, or that the triggers for
15 evaluation of vascular disease might be set at
16 a different threshold in populations at higher
17 risk of these very bad outcomes. If I didn't
18 hear that, then please correct me.

19 DR. HIRSCH: You heard correctly. So,
20 the general global epidemiologically accurate
21 disparities is African Americans, Hispanics,
22 Native Americans, yes, the extreme elderly who
23 are still viable, smokers, diabetics, and
24 people with Stage III and Stage IV CKD all have
25 the highest CLI and amputation disparity rates.

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1 But the disparity has at least four
2 components which could all be solved. One is
3 access to research again; it's true that women
4 are underrepresented, there's almost no
5 minorities in our current research portfolio,
6 it's unbelievably adverse. Access to

7 diagnostic interventions, a simple ABI or
8 duplex. The third is access, again, to
9 treatments; the thiazide motif is true, more
10 potent antiplatelet agents are better, and
11 they're not used as well in the lower
12 socioeconomic groups. And then lastly, again,
13 obviously rehab and outcomes.

14 All these disparities exist. As my
15 colleague Dr. Beckman says, PAD by itself is
16 the disparity. It doesn't matter if you're
17 white, black, you live in downtown Minneapolis
18 or Rochester, you're not going to do very well,
19 but yes, we could serve to focus on those high
20 risk groups very very easily.

21 DR. BACH: Further comments?

22 Dr. Cuyjet, did you have another comment?

23 Okay, great.

24 I want to thank the audience for
25 putting up with us, I want to thank the panel

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1 for putting up with me, and for Medicare for
2 giving us the opportunity to have this
3 discussion, and for the presenters for what is
4 obviously hundreds of hours preparing for this
5 combined, for a very, if you will, very long

6 runs for very short jumps in some cases, but
7 thank you very much for the broad perspective
8 and for the academic discussion.

9 We have, we are going to essentially
10 wrap up. That is essentially my closing
11 remarks. The purpose of this committee and of
12 FACA type activities is to have an open public
13 dialogue around issues that hopefully will do a
14 number of things, not only to help the Agency
15 contemplate important problems, but also drive
16 a research agenda, and this room is full of
17 people who are thinking about research agendas,
18 and hopefully eventually drive policy, although
19 Medicare would never say that is true. You
20 know, when you hear calls for supporting
21 registries, hopefully the folk a few miles
22 south of here are hearing that as well. So
23 thank you again, all of you, for your time, and
24 I want to give the microphone to Tamara.

25 MS. JENSEN: Thank you, Dr. Bach,

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1 thank you for being the chair today. It was a
2 great panel, it was a great day, very
3 impressive presentations, a very impressive
4 panel. So let me reiterate what Dr. Bach said,

5 and thank you very much for everything you've
6 done today, it's been very helpful. We have a
7 lot to take back and we will be looking at this
8 over the next six to eight months to see what
9 we will be doing next. So, again, thank you
10 very much.

11 DR. BACH: We are adjourned.

12 (Whereupon, the committee adjourned at
13 3:53 p.m.)

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