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Medicare Evidence Development & Coverage

Advisory Committee

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Centers for Medicare and Medicaid Services

7500 Security Boulevard

Baltimore, Maryland

Panelists

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Sandra J. Lewis, MD, FACC
Marcel Salive, MD, MPH
Diana Zuckerman, PhD

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Leslie Wise, JD

Guest Panel Members
Teresa L. Carman, MD
Anthony J. Comerota, MD, FACS, FACC

CMS Liaison
Lori Ashby, MA

Executive Secretary
Maria Ellis

TABLE OF CONTENTS

TABLE OF CONTENTS (Continued)

PANEL PROCEEDINGS

(The meeting was called to order at 8:10 a.m., Wednesday, July 20, 2016.)

MS. ELLIS: Good morning and welcome, committee chairperson, acting vice chairperson, members and guests. I am Maria Ellis, the executive secretary for the Medicare Evidence Development and Coverage Advisory Committee, called MedCAC. The committee is here today to discuss recommendations regarding treatment strategies for patients with lower extremity chronic venous disease.

The following announcement addresses conflicts of interest issues associated with this meeting and is made part of the record. The conflict of interest statute prohibits special government employees from participating in matters that could affect their or their employer's financial interest. Each member will be asked to disclose any financial conflicts of interest during their introduction. We ask in the interest of fairness that all persons making statements or presentations disclose if you or any member of your immediate family owns stock or has another

formal financial interest in any company, including an Internet or e-Commerce organization that develops, manufactures, distributes and/or markets consulting, evidence reviews or analyses, or other services related to treatment of patients with lower extremity chronic venous disease. This includes direct financial investments, consulting fees and significant institutional support. If you have not already received a disclosure statement, they are available on the table outside of the room.

We ask that all presenters please adhere to their time limits. We have numerous presenters to hear from today and a very tight agenda and therefore, cannot allow extra time.

There is a timer at the podium that you should follow. The light will begin -- I'm sorry, we no longer have that, I apologize. The timer is located right here on the wall behind the panel; when your time is up, it will go to zero. Please note that there is a chair for the next speaker and please proceed to that chair when it is your turn. We ask that all speakers addressing the panel please speak

directly into the mic, and state your name.

For the record, voting members present for today's meeting are Dr. Art Sedrakyan, Dr. Doug Campos-Outcalt, Dr. John Jeffrey Carr, Dr. Aloysius Cuyjet, Dr. Peter Lawrence, Dr. Roger Lewis, Dr. Sandra Lewis, Dr. Marcel Salive and Dr. Diana Zuckerman. A quorum is present and no one has been recused because of conflicts of interest. The entire panel, including nonvoting members, will participate in the voting. The voting result will be available on our website following the meeting.

I ask that all panel members please speak directly into the mics. The meeting is being webcast via CMS in addition to the transcriptionist.

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

In the spirit of the Federal Advisory

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

If you require a taxicab, there are telephone numbers to local cab companies at the desk outside of the auditorium. Please remember to discard your trash in the trash cans located outside of this room.

And lastly, all CMS guests attending today's MedCAC meeting are only permitted in the following areas of the CMS single site. That would be the main lobby, the auditorium, the lower level lobby and the cafeteria. Any persons found in any area than those mentioned will be asked to leave the conference and will

not be allowed back on CMS property again.

And now, I would like to turn the meeting over to Lori Ashby.

MS. ASHBY: Good morning. I would just like to take a moment to thank the panel for being here and giving their time. We are very excited about today's meeting and look forward to everything that comes out of it. I would like to thank also everybody else in attendance here today and in the interest of time since we do have a full agenda today, I would like to turn the meeting over to our chair, Dr. Rita Redberg. Thank you.

DR. REDBERG: Thanks very much, Lori and Maria. I'm Rita Redberg, I'm a cardiologist at UCSF Medical Center and chair of this committee. I have no conflicts to disclose.

It's a privilege and an honor to serve as chair of MedCAC when we have, as you all know, an important question here today to review the evidence on lower extremity venous disease, and so we'll hear from our evidence review as well as other presenters, and focus on what is the evidence for net benefits and

clinical outcomes in particular for Medicare beneficiaries.

As Maria mentioned, we do have a tight schedule and a lot of presenters, so my other job will be to help remind us of the time in case anyone needs reminding and I will be keeping to a strict schedule so that we can all stay on time and get everyone's remarks in today.

I think that's it, and so I will, we will just go down and introduce ourselves and state any conflicts.

DR. SEDRAKYAN: Good morning. I'm Art Sedrakyan, from Weill Cornell Medical College. I'm a professor of healthcare policy and research, leading the Medical Device and Surgical Outcomes Center at Weill Cornell.

I will be looking for some notes in my iPhone, I'm not looking at any text messages, I'm just warning you, it's just to help guide me with all the questions I have for presenters, and I will pass on to the next person.

Oh, no conflicts for me.

DR. CAMPOS-OUTCALT: I'm Doug

Campos-Outcalt with the Mercy Care Plan, which is an Arizona statewide Medicaid health plan, and part-time faculty member at the University of Arizona College of Public Health. I have no conflict.

DR. CARR: I'm Dr. John Jeffrey Carr from Vanderbilt University Department of Radiology, Biomedical Informatics and Cardiovascular Medicine. I have no conflicts.

DR. CUYJET: Al Cuyjet, I'm a medical director at HealthCare Partners and also assistant professor of clinical medicine at SUNY Stonybrook School of Medicine, and no conflicts.

DR. LAWRENCE: Peter Lawrence, I'm a vascular surgeon and chief of vascular surgery at UCLA, and director of the Gonda Vascular Center, and recently became the editor of JOVS, Journal of Vascular Surgery, and am a past president of the Society for Vascular Surgery. I have no conflicts.

DR. ROGER LEWIS: My name is Roger Lewis, I'm the chair of emergency medicine at Harbor-UCLA Medical Center in California. My primary interest is in looking at clinical

trials methodology, and I have no conflicts.

DR. SANDRA LEWIS: Sandra Lewis, I'm a cardiologist from Portland, Oregon, I'm a clinical professor at the Oregon Health and Sciences University. No conflicts.

DR. SALIVE: I'm Marcel Salive, a preventive medicine physician and medical officer at the National Institute on Aging for NIH. I'm here on my own behalf and I have no conflicts.

DR. ZUCKERMAN: I'm Diana Zuckerman, president of the National Center for Health Research, and I have stock in Johnson & Johnson.

MS. WISE: Hello. I'm Leslie Wise, I'm vice president of global healthcare economics for AngioDynamics. I am the industry representative and I do have stock in AngioDynamics.

DR. CARMAN: I'm Teresa Carman, director of vascular medicine at University Hospitals Case Medical Center in Cleveland, and have academic appointments at the Case Western Reserve University School of Medicine, and I have no conflicts.

DR. COMEROTA: Good morning. I am Anthony Comerota, a vascular surgeon and immediate past director of the Jobst Vascular Institute, adjunct professor of surgery at the University of Michigan, and past president of the American Venous Forum. My conflicts include, I'm chair of the data and safety monitoring committee for the ACCESS trial, I've received funds from the NIH for the SAT trial, and was on the protocol development committee for CTRAC, and a co-PI for the EVO trial.

DR. REDBERG: Thank you. I'll hand it over now to Dr. Jyme Schafer from CMS, to present the voting questions.

DR. SCHAFER: Hi, I am Dr. Jyme Schafer, I work in the coverage group. Good morning, I thank everyone for coming.

So, I'm here to go over the questions and just a brief introduction here. So, the purpose of the meeting is to examine the scientific evidence underpinning the benefit and risk of existing lower extremity chronic venous disease interventions, improve health outcomes in the Medicare population, and address evidence gaps.

Clinical outcomes of interest to Medicare, reduction in pain and edema; reduction in all-cause mortality; improvement in quality of life and functional capacity; improvement in wound healing; avoidance of acute and chronic venous thromboembolism; avoidance of chronic thromboembolic pulmonary hypertension; avoidance of initial venous skin ulceration and recurrent ulceration; avoidance of repeat interventions and harms from the interventions. Most of this is also contained on the Internet on the website for this MedCAC meeting, by the way.

So here we get to the voting questions. Again, these questions will be presented to the panel this afternoon.

For adults with varicose veins and/or other clinical symptoms or signs of chronic venous insufficiency, how confident are you that there is sufficient evidence for an intervention that improves, A, intermediate/near-term health outcomes in patients presenting with symptoms, in patients presenting without symptoms but with physical signs? B, long-term health outcomes in

patients presenting with symptoms, in patients presenting without symptoms but with signs? And there we give a Likert scale shown below.

And then we have discussion questions. If intermediate confidence, please identify the specific intervention or interventions that are associated with evidence-based clinical benefit and identify the associated beneficial outcomes.

And then, considering the heterogeneity of the Medicare population, discuss for which subgroups of the Medicare population the evidence demonstrates likely benefit or which subgroups are not likely to benefit from the intervention.

Number two. For adults with chronic venous thrombosis and venous obstruction, including individuals with post-thrombotic syndrome, how confident are you that there is sufficient evidence for an intervention that improves, A, intermediate/near-term health outcomes in patients presenting with symptoms, and then in patients presenting without symptoms but with signs? B, long-term health outcomes in patients presenting with symptoms,

and then in patients presenting without symptoms but with signs.

And then the discussion questions below. If intermediate confidence, please identify the specific intervention or interventions that are associated with evidence-based clinical benefit and identify the associated beneficial outcomes.

Considering the heterogeneity of the Medicare population, discuss for which subgroups of the Medicare population the evidence demonstrates likely benefit or which subgroups from the intervention, A, intermediate/near-term health outcomes, and then B, long-term health outcomes.

Additional discussion topics. Number three, discuss important venous disease evidence gaps that have not been previously or sufficiently addressed.

Four, discuss any current venous disease treatment disparities and how they may affect the health outcomes of Medicare beneficiaries.

Five, discuss any mechanisms that might be supported by CMS that would more

quickly generate an improved evidence base that would underpin improved care for the Medicare population affected by lower extremity chronic venous disease. Thank you.

DR. REDBERG: Thank you, Dr. Schafer. We can now go on to our evidence review -- pardon -- which is Dr. Jones. I'm sorry, oh, I'm sorry.

DR. ALLISON: Good morning, ladies and gentlemen, it's a pleasure to be here. These are my disclosures. This is the consulting income I get from a couple companies, none of which are related to venous disease.

So, the anatomic micropathology of the venous system is shown on this slide, showing that in the skin you have venous plexuses that ultimately will drain into two essentially different components of the venous system, the superficial and deep venous systems. The superficial system is contained within the saphenous fascia, in the lower extremities anyway, and the deep system is contained within the fascias deep within the muscle.

In the lower extremities, this illustration shows you the venous system.

Again there's a deep system which is shown on the right as the laser's pointing here, right here, and then on the left a superficial system. The deep system's composed of the femoral system, the popliteal, et cetera, down into the lower leg and the foot. And then the superficial system is comprised primarily of the saphenous system, which does branch into a couple branches on some occasions in the lower extremity below the knee. Notably, the venous system in the lower extremities is quite variable, and this is just an example of a typical presentation.

Within the veins themselves there are valves which cause unidirectional flow, or should cause unidirectional flow. As you can see on the upper illustration, the blood flows through a valve area, and then on panel B you will see that at no time during the normal situation of venous flow are these valves actually opposed against the venous wall, there's supportable flow that will keep them open and keep the blood flowing in a unidirectional pattern.

But in some cases when there's disease

of these valves or dilatation of the veins themselves you can get aberrations of this type of flow. So on the left side you see that there is unidirectional flow but on the right side you see that there's actually bidirectional flow depending on what phase of the venous cycle that the blood is flowing through.

In a normal situation when you're standing, this line here, the venous pressure in the lower extremities is about 80 millimeters of mercury, but then when you walk you have something called a calf pump mechanism which will pump blood essentially from the lower extremity up into the abdomen and into the chest and that causes the flow, I mean the pressure, to drop to about 20 or 25 millimeters of mercury.

However, in a disease state such as with venous reflux, as in tracing B, the pressure never gets back down to, say, the 20 to 25 millimeters of mercury level, it stays elevated in the 50 to 75 degree range, somewhere in there.

And those with venous obstruction,

which is shown on the line C, they're not able to lower their pressure really at all because of the obstructive disease proximally, thus causing venous, what we call intravenous hypertension.

The symptoms of venous disease are listed here, these are typical symptoms, they're not present in all patients, aching, heaviness, fullness in the legs. Some patients do report nocturnal leg cramps, itching especially, or burning especially along the site of the varicosity, the varicose vein itself. And in some cases, although in my experience it's a minority of cases, they have restless leg syndrome.

I'm now going to go through some examples of cutaneous manifestations of chronic venous insufficiency in a lower extremity. This is a spider vein or a telangiectasia. Here you can see what we refer to as reticular veins and these are in increasing severity, if you will, of the venous disease.

This is corona phlebectasia or a malleolar flare, especially seen around the ankle. This is a tortuous group varicosity

below the knee. Here you see evidence of hyperpigmentation and a certain amount of sclerosis, so essentially a fibrotic scarring of the lower extremity, if you will. This is eczemous changes of, you notice the scaling over the hyperpigmentation.

This is atrophy blanche it may be hard to see, actually it's better on your screen than on mine, but you see some white areas where the skin has become blanched, so to speak. This is more advanced with that amount of sclerosis with the contracture of the skin below the calf.

And then finally you have more the end stage of chronic venous insufficiency with hypertension, you can get venous leg ulcers, and this is an ulcer over the malleolus.

These symptoms, or not symptoms, these signs can be classified using the CEAP criteria which are shown for you here. So C0 is no visible signs of venous disease, C1 through C6, then, are those diseases that I just, and those manifestations that I just showed you on the previous slides, going from telangiectasis through varicose veins, edema, and then

hyperpigmentation and then venous leg ulcers.

When we examine the lower extremity with duplex ultrasound, we can discern the superficial from the deep venous systems, and this illustration shows you kind of the landmarks to be able to do so. So on the top of the slide you will see the skin margin and then as you go deeper you can see the saphenous vein here, right here within this saphenous fascia casing, and then deeper to that would be the muscle, and then even deeper in the muscle may be some deep venous veins.

We can interrogate these veins using duplex ultrasound and color doppler to be able to determine if there's any evidence of any reflux in those veins. So what you see along the bottom, or actually starting at the top up here, this is the area of interrogation right here with the color doppler, and then you'll see down here the tracing of the flow in this vein during the specific maneuver that is conducted.

Specifically at this point right here there's an augmentation of flow, which is usually done by grasping or squeezing the

distal part of the limb so that the blood is pushed up, if you will, through the venous system, and then in this case there is an abnormality where there is a reflux of venous blood going in the opposite direction from the augmentation response, so this is evidence of venous insufficiency.

So we've actually studied chronic venous insufficiency within the San Diego Population Study. This was a National Heart Blood and Lung Institute RO1 that was funded in 1994 to study chronic venous, or chronic peripheral vascular disease and peripheral arterial disease, but today's topic is just going to be on peripheral venous disease.

The aims of the venous disease component were to study the distribution, if you will, of chronic venous insufficiency and venous disease, and then the risk factors, symptoms and quality of life in those patients with chronic venous disease. I should note that we had a followup RO1 that was also designed by the National Heart Lung and Blood Institute to look at incidence of disease about 11 years later and about half the population.

So at baseline, we were able to enroll over 2,400 individuals, about two-thirds of which were women. The age ranged from about 30 to 91. Roughly, the ethnic distribution is listed for you there, with the majority of them being non-Hispanic whites, and then about 15 percent or so being Hispanic, African-American or Asian. They were given questionnaires on previous history of superficial vein thrombosis, and also deep venous thrombosis. They were examined by a registered venous technologist for visible venous disease which is listed for you here, so telangectasia, varicose veins and trophic skin changes, which would include the hyperpigmentation, the lymphatic dermatosclerosis or venous leg ulcers. And then they underwent a standardized duplex examination of both legs for both superficial or deep functional disease. The functional disease component could include reflux as I demonstrated on the previous slide, as well as obstructive disease where there is no flow.

So here's some of the results from this study. You can see that, this is a

distribution of visible disease and functional disease going across the top here, so visible disease and functional disease, and then the category, so to speak, for these different types of problems. And you can see that in all subjects, normal leg comprised about 18 percent of the population, so over 80 percent had some finding, abnormality, for visible venous disease. Contrary to that, though, functional disease was normal in about 71 percent.

And this was a little bit different in men versus women, such that men had less disease overall in terms of visible disease, but they have more severe disease than women when it comes to trophic skin changes, but women had more varicosities.

There's a little bit of a difference in functional disease between men and women, which is shown on the slide here. Notably, men had a little bit more deep venous disease than women did.

As you would expect, the distribution of both visible disease and functional disease increased with age and you can see that here, such that no individuals, only about eight

percent of individuals over the age of 70 didn't have any evidence of venous disease. Similarly, the prevalence of venous disease, functional disease went up with age such that about 60 percent were free of functional disease over the age of 70.

There were some small but significant differences by ethnicity such that non-Hispanic whites had the highest prevalence of visible and functional disease, but that differed a little bit, they had more deep disease and more trophic skin change, more advanced skin manifestations if you will, compared to the other groups, whereas Hispanics actually had more varicose veins and superficial disease than the other groups.

This is now kind of a cross-tabulation between functional disease and visible disease, and what you see is that there was 78 percent of the population, and this is by leg now, not by person, had normal, no evidence of functional disease. About 15 percent had superficial venous disease and six percent had deep venous reflux. The vast majority, or not vast majority, but 21 percent had no evidence

of functional disease or visible venous disease, and you can see that the prevalence of, the largest prevalence of superficial skin disease was with the trophic, or the telangectasia and spider veins.

When you look at the prevalence of edema and superficial thrombotic events and deep thrombotic events as the patients reported, here's what you see by both functional and visible disease status. So edema is largely present in those with trophic skin changes, and it's kind of irregardless of whether they have superficial functional disease or no evidence of disease, suggesting that there's obviously other reasons for edema other than reflux.

In terms of patients reporting superficially, then, and deep events, those were largest in, the largest prevalence was in those who had deep functional disease and trophic skin changes. Not really any of our participants had superficial events and were normal in terms of their functional disease status.

The risk factors for, in this case

moderate venous disease, and this includes patients with varicose veins and superficial functional disease, are shown for you here. There's three main ones that stand out, and those are age, family history of venous disease and a history of hernia surgery. It appears that the normal tendencies are actually a risk factor in this population for having moderate venous disease. There are some other risk factors here, primarily in women, such as higher weight, the more births that you have, and a higher waist circumference associated with moderate venous disease.

We then looked at severe venous disease. The risk factors are quite similar, such that age and a family history of venous disease are associated with an increased risk, or increased odds, I should say, for severe venous disease. And men, you know, laborer and current cigarette smoking was also a risk factor, where as in women as we talked about before, having a history of high levels of birth, and in this case having a flat foot was actually a risk factor for severe venous disease.

Since we believe that adiposity is related to venous disease, we actually did a study examining the relationship between adiposity-associated inflammation and different levels of venous disease by tertiles, so a tertile two would be moderate venous disease and tertile three would be severe venous disease. And what you see is that Resistin, Leptin and IL6, all measures of adiposity-associated inflammation were with the presence of severe venous disease, whereas Resistin and Leptin were only associated, were the only markers associated with more moderate venous disease, so providing some evidence that inflammation due to adiposity is associated with venous disease, and these associations were independent of body mass index, suggesting that there may be another mechanism beside the adiposity itself, the degree of adiposity itself.

So this, I mentioned before that we actually had a second RO1 to look at incidence in these diseases, and this is the only ones I have and the only study conducted so far looking at incidence of venous disease, and

what these results show, somewhat surprisingly potentially, is that an increased level of dorsiflexion of the foot, so if you're going to bend your foot back so to speak, was associated with higher odds for incidence of venous disease. There's also a borderline significant association between having a flat arch but not being protected, so this is actually contrary to what we just showed in the cross-sectional analyses, so it's going to be interesting to compare our cross-sectional and our longitudinal studies for findings, and explore reasons for many of those disparities.

One nice thing that we were able to do was conduct analyses using blood samples for genetic analyses, so to speak, so this is a paper that Christine Wassel published a few years ago looking at the genetic risk scores that were derived from a thromboembolism, so a single genotype polymorphism or a variation of the genetic structure, so to speak, and how that can be used to actually look at risks for moderate plus severe venous disease. And so these risk scores, both based on 33 SNPs and five SNPs, were both seen to be associated with

the presence of moderate and severe venous disease, I think a little bit more so, more robust for those with the five-SNP genetic risk score than the 33-SNP, but they were both significant.

So just in summary, chronic venous disease increases with age, it's more common in non-Hispanic whites than Hispanics, African-Americans or Asian-Americans, although Hispanics tend to have more superficial functional disease and have varicosities.

Telangectasia and spider veins, varicose veins and superficial functional disease were more common in women, whereas more extensive disease was more common in men.

Visible and functional disease were highly concordant, such that 92 percent of legs had some form of functional and visible disease, meaning that eight percent were discordant, but importantly, 25 percent of the limbs with trophic skin changes had no functional disease that we were able to detect.

Superficial venous thrombosis, deep venous thrombosis and edema increased dramatically with trophic skin changes and deep

functional disease, but it did in some cases occur in their absence.

When we did multivariable modeling for risk factors for venous disease, both moderate and severe venous disease were related to age and family history in both sexes.

In both sexes, moderate venous disease was related to previous hernia surgery and normotension, although normotension actually increased your risk for some reason we're not sure of, and I mentioned before, severe venous disease is related to waist circumference and flat feet.

I think in the interest of time since I don't know where I'm at time-wise, you can read the rest of this, this is just a summary of what we had, and it's also in the reading materials, so I think I'll stop there. Thank you.

(Applause.)

DR. REDBERG: Thank you very much, Dr. Allison. So, we'll go on, we'll take questions later, and we'll go on now to the next speaker, Dr. Jones, who is the lead clinical investigator for the technology

assessment, and I believe he will be joined by Dr. Vemulapalli.

DR. JONES: Thank you for having us. My name is Schuyler Jones, and on behalf of our coauthors and colleagues at the Duke Evidence-Based Practice Center, it is my pleasure to present our systematic review which is titled Treatment Strategies for Patients with Lower Extremity Chronic Venous Disease. As you'll see over the next 50 minutes, we'll present work from the last ten months.

The technology assessment was actually posted this week last year as we presented the PAD systematic review, so we've done a fair bit of work over that time. The report is publicly posted, it's about a 250-page Word file, I'd like for each of you to go home and read that tonight.

Sreek and I are both academic cardiologists; we see patients with venous disease, we do not do procedures on patients with venous disease. We have disclosures for both of us that are mainly research grants. None of these, with the exception of the AHRQ grant for this systematic review applies to

venous disease. Additionally, none of our coauthors have disclosures. The key informant and technical expert panel that we've utilized for this review have adhered to the AHRQ policies.

As you've heard, venous disease is a heterogeneous condition; as you can see, Dr. Allison did a very nice job talking about the different presentations of patients. We'll go through some of the general concepts of that, but then we'll really focus the next 45 minutes or so on the systematic review results.

I'd like to start by telling you what we did. I told you how long it took. We broke our questions down and we called them key questions, or clinical research questions, into three questions, and these were requested by AHRQ and Medicare, but they really followed the questions that the panel will be voting on today.

The first one is a narrative description, actually not a question at all, it's a narrative description of the diagnostic tests used for chronic venous disease. We'll go through that literature first, but before

that we'll talk about the second key question, which is the treatment strategies or treatments available for patients with lower extremity varicose veins and/or lower extremity chronic venous insufficiency, incompetence or reflux, and we'll refer to it as lower extremity chronic venous insufficiency in the coming slides.

We broke these down into comparative effectiveness of the treatment modalities, the diagnostic methods and criteria used, the modifiers of effectiveness, and then the comparative safety concerns of each treatment comparison.

Our key question number three involves patients with lower extremity chronic venous thrombosis and obstructions, and that includes patients with postthrombotic syndrome, and the same criteria of comparative effectiveness, the diagnostic methods used, as well as modifiers and effectiveness and safety were addressed, and we tried to report that and we'll describe that today.

As you heard, the additional considerations for today's panel include

evidence gaps, treatment disparities and how to generate an improved evidence base, and we'll have conclusions at the end of this talk with some suggestions.

As we thought broadly about chronic venous disease in our population that we were studying, you can see that the conceptual framework moving from the left of this slide which includes the patients to the treatments, which Medicare and all of you are interested in, really centered on what the outcomes were, and some of these outcomes were intermediate or near term and some of them were long term, and we'll describe that.

On the lower panels you'll see that we've looked at individual characteristics that we thought were important for venous disease patients, as well as adverse events or complications of treatment. So this is our conceptual framework, it is a little difficult to see on this slide; it is publicly posted as well.

Our review started, like I said, about ten months ago. We decided to review all abstracts starting in January of 2000 up until

the time that we pulled the data in December of 2015, so a 15-year period. We identified over 10,000 abstracts; many of them were duplicates but we still ended up reviewing 10,201 abstracts over this time.

We separated these into the specific key questions: Number one, the diagnostic narrative; number two, chronic venous insufficiency and varicose veins; and number three, chronic venous thrombosis and obstruction. In this panel you can see how these articles fell into these categories.

A total of 103 studies were included. As we proceed and in the report we tried to do a good job in determining what the indication for treatment was in each study, the diagnostic modalities and criteria used, the clinical outcomes and timing of this outcome, as well as the strength of evidence.

We used the AHRQ Methods Guide to help guide us for strength of evidence. There are five categories that we used to help grade that evidence. They then fell into four categories, from high strength of evidence, so it's unlikely that more research will change the

opinion or change the outcome; moderate, further research may change the result; low, meaning that further research is likely to change the result of the systematic review; and then insufficient evidence, evidence that's either unavailable or does not permit an estimation of effect, and we'll talk about effect size and confidence intervals throughout this talk.

All right. As we move into the results section I'll start with key question one, which revolved around the diagnostic testing of patients with lower extremity chronic venous disease. I think Dr. Allison did a nice job talking about some of the tests that were done. In the interest of time I'll go through this relatively quickly, because I think the meat of this MedCAC is to make sure that we talk about treatments associated with lower extremity venous disease.

Before we move there, we'll just remind you of the definitions and terms used that were posted on the CMS website, and I know many of you are familiar with venous obstruction, venous reflux, venous thrombosis,

chronic venous insufficiency, and then postthrombotic syndrome are the terms that will be used. I think Dr. Allison did a nice job talking about some of these.

Like he said, it's very important to have a complete medical history and physical examination. The adjuncts to diagnosis that are often used include plethysmography, duplex ultrasonography, MRV or magnetic resonance venography, CTV or computed tomography venography, and then invasive venography and its adjuncts.

Like I said, a high index of suspicion for chronic venous disease is really critical. Thorough investigation like they did in the San Diego cohort study of looking at prior trauma, prior DVT, and then family history is important, and then a complete physical examination.

I will move through these quickly. These have grades of evidence from the SVS, American Venous Forum guidelines for duplex ultrasonography as well as ambulatory plethysmography, MRV, CTV, invasive venography and then adjuncts like IVS, intravascular

ultrasound use. These slides are available for anyone that would like to have further discussion, including the panel, but in the interest of time I'll move on to the results of the systematic review for diagnostic testing.

So we ended up looking at each of the diagnostic testing modalities to see if there is comparative effectiveness data from 2000 to 2015 to see if one was better than the other. You can see in the coming slides that very few comparative effectiveness studies exist in the contemporary literature. Those studies published before 2000 were not included in our review.

In the review there is an extreme heterogeneity of patients, comparisons and outcomes for diagnostic testing strategies, and we would conclude that there was insufficient evidence to suggest that one was better than the other, but mainly because the evidence really wasn't there.

These were small studies, I'll give you just a snippet of each one of these. So sometimes patients would undergo each of these tests, they would look for sensitivity and

specificity and other diagnostic characteristics. Most of the time it was compared to duplex ultrasound, but all of these studies were under 100 patients and had a heterogeneous group of both patients and outcomes assessed.

Looking at more extensive technologies like CTV and MRV, there was a comparative study on both, but only a single one. You can see that doppler sonography was the gold standard in the CTV study and it performed pretty well, as well as invasive sonography, the gold standard for MRV, and it performed well as well, but very small studies and single studies.

When we looked at duplex ultrasound in many of the earlier studies, the top three rows compared it to venography as it was being established, these were early 2000 studies. Again, small groups of patients, but it did perform very well in these populations of patients with chronic venous insufficiency, varicosities, and in some cases chronic venous thrombosis.

So for conclusions for the first key

question, which was diagnostic methods and criteria, because of the relatively sparse comparative data for these studies, we found the strength of evidence to be insufficient to suggest one diagnostic test of choice, or to consider that there's a best test prior to the planned invasive treatment.

There were also no studies that had modifiers of effectiveness and therefore, the strength of evidence for this is also insufficient.

I put this slide in here to suggest to everyone that the guidelines from the SVS and AVF are published, and it is relatively thorough. Their grading of evidence was slightly different than ours, and it relies on expert opinion more than our review did.

As we moved into the treatment comparisons, we thought it was important to make sure people knew how patients were diagnosed in these treatment comparison studies. In these studies, KQ2 being varicose veins and chronic venous insufficiency, most of these patients were diagnosed with duplex ultrasound or a combination of clinical

assessment and duplex ultrasound.

In only eight studies of the 88 total, was it unclear how these patients were diagnosed and then therefore entered into the study.

For KQ3, which is the chronic venous thrombosis and obstruction group of studies, there was a fairly disparate group of diagnostic methods and criteria used, including clinical assessments, duplex ultrasonography as well as sonography only, and other modalities like MRV and CTV. So you can see fairly complex, as well as different studies that are being included in this KQ1. Hopefully for the other KQs, you will have a little bit more, or a little bit better idea of what was studied and how it was studied.

I'm going to turn it over to Dr. Vemulapalli, who's going to go through the KQ2, which is a fairly dense group of studies.

DR. VEMULAPALLI: Thanks, Schuyler. So just as a reminder to everybody of what KQ2 is, this is looking at comparative effectiveness primarily of varicosities and chronic venous insufficiencies, again looking

at what were the diagnostic methods used, what were the modifiers of effectiveness, and the comparative safety concerns.

So as an overview, what are the treatment options for chronic venous insufficiency and varicosity? Well, they include exercise training, medical therapy, lifestyle modifications, and then invasive therapies which would probably break down into endovenous intervention and surgical intervention.

So before we go into the details, we would like to talk a little bit about what the populations were that were assessed in those studies. So, we found 73 studies looking at a symptomatic population and four studies looking at an asymptomatic population, but perhaps most importantly 15 studies, including 14 RCTs and one observational study, with an unclear patient population.

And then if you look in terms of varicose veins, they represented 66 of the studies, and then lower extremity chronic venous disease, 74 studies. And again, two studies, one RCT and one observational, where

it was unclear what the disease process was.

So, Schuyler showed you earlier the outcomes assessed and I won't run through all of them, but will point out that these outcomes largely overlap with the ones that CMS presented this morning as being of interest within the Medicare population, including lower extremity edema, lower extremity pain, wound healing, quality of life, and procedural complications.

So, study quality overview. We used the AHRQ Methods Guide as our guide for assessing study quality, and we found 24 studies all of which were RCTs, to be of good quality; 47 studies, the majority, to be of fair quality; and 17 studies, including 14 RCTs, to be of poor quality.

This is a relational diagram to help understand what some of the comparisons actually looked at, and I'll just use this to point out a couple things. We have a number of studies looking at within-group comparisons here within surgical and endovascular procedures, and the majority of the other studies were compared to either mechanical

compression or placebo/control.

So let's start with interventions versus placebo or usual care. So starting with compression versus placebo, we'll point out 11 studies, five of which were good quality studies comprising about 1,500 patients, and although these studies explored a variety of different compression therapy strategies, it does appear that compression was effective relative to no compression for a variety of clinical outcomes, but the strength of evidence rating here is insufficient.

So moving forward to endovenous interventions versus placebo, again I'll point out three studies total, two of which were good quality, 540 patients, with a strength of evidence of moderate. There was a significant effect on VCSS, elimination of reflux and quality of life, which favored foam sclerotherapy over placebo.

Endovenous interventions versus medical therapy, again, three studies, no good quality studies, only 150 patients. Therefore, strength of evidence was insufficient. It did look like for venous ulcer patients, laser

ablation was associated with significant improvement in ulcer healing and reduction in recurrence of ulcer, as compared to compression stockings.

How about surgical interventions versus medical therapy? Seven studies, two of which were good quality, 1,244 total patients. And I'll point out here in the red, we have mostly insufficient and low strength of evidence ratings, with no difference in ulceration healing rate, no difference in quality of life or venous hemodynamics. There was a significant improvement in pain scores favoring surgery which generally was high ligation and stripping, but that's balanced by rates of surgical infection.

So in summary in terms of interventions as compared to placebo or usual care, for endovenous versus medical or placebo, there was a significant effect on VCSS, elimination of reflux, quality of life, which favored in this particular instance foam sclerotherapy over placebo, with a strength of evidence of moderate.

For venous ulcer patients, laser

ablation was associated with significant improvement in ulcer healing and in reduction and recurrence of ulceration, but again, strength of evidence was insufficient.

For surgery versus medical therapy, no difference in ulceration healing rate, quality of life or venous hemodynamics and again, I'll point out an insufficient strength of evidence. And then there was an improvement in pain scores and reduced ulcer recurrence, but again, strength of evidence was low.

For compression versus no compression or placebo, it did appear that compression was effective relative to no compression or placebo for a variety of clinical outcomes but the strength of evidence was insufficient.

So, remember our relational diagram, I said there were a number of within-treatment strategy comparisons, and we'll move to those next.

So breaking that down further, you can see a lot of different comparisons. The point to take from this here is that many of the comparisons were against laser ablation and there were a number between radiofrequency

ablation and laser ablation, okay?

So laser ablation versus sclerotherapy, three studies, two good quality, about 1,400 patients with reflux and varicosities, and no significant difference between those two treatment strategies in terms of efficacy for long-term quality of life or standard symptom scores, and again, the strength of evidence was low.

In terms of intermediate time points, there was an improvement in quality of life which favored laser ablation, but again, strength of evidence was low.

And then post-procedure lower extremity pain, sclerotherapy was favored versus laser ablation in two studies, but the strength of evidence was low.

How about laser versus RFA? Five studies, two good quality studies, 543 patients, and again, no significant difference in efficacy between laser ablation and RFA, with a low strength of evidence in terms of venous hemodynamics and in terms of intermediate symptom scores, and again, low strength of evidence.

In terms of long-term improvement in symptom score, that actually favored laser ablation, again with a low strength of evidence.

Short-term improvement seemed to favor RFA in terms of two good quality studies, but again, low strength of evidence.

And in terms of short-term bruising or procedural complications with hematoma, this also seemed to favor RFA with two studies, and again, low strength of evidence.

So, moving to surgical versus surgical comparisons, generally most of the comparisons were against high ligation and stripping, plus or minus phlebectomy, and you can see here from the slide there are a number of different comparisons but again, low number of studies, one good quality study, one good quality study, no good quality study, 700, not quite 12,000, and 900 patients. You can see in this top one, this is high ligation and stripping versus high ligation and cryostripping plus or minus phlebectomy.

And again, before going into these details, I'll just point out to you because of the numbers of studies here and the quality of

the studies, our strength of evidence for these findings are insufficient. So in terms of high ligation and stripping versus high ligation and cryostripping, no difference in post-op pain, quality of life or greater saphenous vein recanalization, and there was very heterogeneous data regarding perioperative complications.

High ligation and stripping versus CHIVA, CHIVA was associated with higher varicosity recurrence. Again, one study, and no difference in perioperative complications, one study.

And then high ligation versus stab evulsion, again, insufficient data really to evaluate.

So in summary for our within interventions comparisons, in terms of endovenous versus endovenous, again, low strength of evidence, but laser ablation versus sclerotherapy, there was no significant difference in the efficacy between the two in terms of long-term quality of life or standard symptom scores, and no significant difference between the two in terms of venous hemodynamics

and intermediate symptom scores.

For surgical versus surgical, I would leave the summary as very few studies overall all within our study period, and fewer good quality studies, and really no demonstrated difference in terms of post-op pain, quality of life or GSV recanalization, and this is primarily high ligation and stripping versus high ligation and cryostripping.

So, comparison of hybrid techniques, this is a very busy slide but I'll break this down for you a little bit. The comparison was generally against high ligation and stripping and then you can see a hybrid technique such as high ligation and laser, high ligation and foam, high ligation and sclerotherapy, and high ligation and endovenous microwave therapy. But again, the take-home points, one study, one study, two, one, no good quality studies, several hundred up to a thousand patients, and suffice it to say based on this, the strength of evidence is insufficient, and I won't go into these details here.

How about between treatment strategy comparisons, surgical versus endovenous

interventions? So again, a relational map, and the standard to which most of these were compared was high ligation and stripping. And remember, I gave you a list earlier of all the outcomes that we looked at and you'll see that list again here, but in terms of RFA versus high ligation and stripping, the only ones that we could actually significantly evaluate were reflux recurrence rate and periprocedural complications, the rest of these grade out for insufficient data.

So, we were able to actually meta-analyze these, and one of our requirements was having at least three studies to do this, so this is for an endpoint of reflux recurrence at one to two years, RFA versus high ligation and stripping, you'll see here from the forest plot that the summary estimate crosses one in terms of the confidence interval, and there's an insufficient strength of evidence, so no demonstrable difference between RFA and high ligation plus stripping for reflux recurrence at one to two years.

RFA versus high ligation plus stripping and now the endpoint is adverse

events, and again, three studies with an even wider confidence interval this time, and again summary estimate crosses one, and as you can imagine, the strength of evidence is insufficient here.

So that was RFA versus high ligation and stripping. How about laser ablation versus high ligation and stripping? And here we have more outcomes that we were potentially able to meta-analyze. So looking at long-term VCSS, again, the summary's specific, just about right at crossing the unity. Long-term CEAP, again, crossing unity, so really no significant difference between laser ablation and high ligation and stripping in terms of symptom scores, here represented by VCSS and CEAP. The strength of evidence for VCSS was low, whereas for CEAP it was moderate.

Laser ablation again versus stripping, this time looking at reflux or incompetence at two years, so five studies here and the confidence interval summary estimate just, again, crosses one, so again, no difference in terms of taking into account the confidence interval between the two treatment strategies,

and the strength of evidence here is low.

So laser ablation versus ligation and stripping, this time looking at changes in quality of life as measured by AVVQ at two years, six studies here, and again, the summary estimate is at unity with a strength of evidence of moderate.

So same comparison, now we're talking about reduction in pain score, four studies, wide confidence interval, again crossing unity, with a low strength of evidence.

Looking at periprocedural complications, ecchymosis and bruising, three studies, and in this case there was actually a statistically significant benefit for laser ablation versus surgery, and the specific endpoint was bleeding risk as measured by ecchymosis and bruising, and the strength of evidence was moderate.

So that was laser ablation. Moving through to sclerotherapy versus high ligation stripping, and again, three endpoints here that we were able to meta-analyze. So starting with long-term recurrence rates, again, the summary estimate crossing unity and the strength of

evidence is low, so no significant difference that we could demonstrate between sclerotherapy and high ligation and stripping for long-term recurrence rates.

Same comparison now looking at quality of life at two years, and here the confidence intervals are much much smaller but again, right at unity, so no significant difference between the treatment strategies, but a much higher strength of evidence here.

So, that was a lot of data in a short period of time, but I'd like to sum it up a little bit for you. So first, there's really limited evidence to support the use of endovenous and/or surgical intervention over compression therapy or conservative therapy, or over each other. And perhaps most importantly, both endovenous and surgical interventions seem to be associated with improvements in symptom scores and QoL scores when you compare baseline to post treatment overall. And there's limited evidence, really, to support the use of one treatment modality versus another.

DR. JONES: All right. We're going to flip back to me, I'm a year or two ahead of

Sreek at Duke, so I gave him the very dense, very difficult topic, and I'm coming back to the third key question which is on chronic venous thrombosis and obstruction and, as you remember, comparative effectiveness, diagnostic methods, modifiers of effectiveness and then comparative safety were our focus.

The treatment options for this are similar but slightly different than for KQ2. We looked at exercise training; medical therapy, specifically anticoagulation; lifestyle modification including weight reduction; and invasive therapy including endovenous interventions, which are slightly different. We'll talk about some of them, as well as surgical interventions.

The KQ3 treatment paradigm is a little different, it's a little bit less complex because there are only eight studies. As you can see, we looked at compression studies versus control or placebo, we looked at exercise versus control. There were a number of studies that included endovenous stenting that we'll describe here, but there's a fairly heterogeneous population of studies and

treatment modalities here, and only eight of them.

We'll go through them here. The first study was an exercise training study versus a routine care patient education study. It was actually a good quality RCT; there were only 43 patients, however, and the exercise intervention was strengthening, stretching and aerobic components, and the outcomes that were assessed were at six months. As you can see, there was a statistical difference in a quality of life measure but the Villalta score was not different, and therefore we graded this as insufficient based on a single study.

When we looked at compression therapy versus usual care control, there were two studies. However, one was in patients with postthrombotic syndrome and the other had venous leg ulcer patients, so a heterogeneous population. One study had long-term outcomes and one had intermediate-term outcomes but either way, no significant difference in quality of life or postthrombotic syndrome severity were observed, and therefore we concluded that the strength of evidence for

this treatment comparison was insufficient.

Additionally, compression therapy versus endovenous intervention, there's a single retrospective study, it was 216 patients all with a Villalta score of greater then 10, so a postthrombotic syndrome cohort. The outcome was recurrence-free ulceration, and it was significantly higher and it favored endovenous stenting. However, given the single retrospective study and the very moderate differences between the pre and post group pain score and edema score, we considered this insufficient evidence.

Finally when we look at the hodgepodge of endovenous interventions for chronic venous thrombosis or obstruction, you can see that there are three retrospective studies looking at 419 patients with chronic venous obstruction, May-Thurner in this case, so the comparisons were very different, endovenous stenting alone versus stenting plus thrombolysis, laser ablation alone versus laser ablation plus endovenous stenting, and then stenting alone versus stenting and greater saphenous ablation, very very different groups

of treatments. To make that matter worse, the outcomes were very heterogeneous and the time points of those outcome assessments were very disparate. Therefore, we concluded that for this treatment comparison, the strength of evidence was insufficient.

We're saying insufficient a lot. We would be happy to talk about our methods as we go forward for the panel and for the group, but to conclude with KQ3, there was insufficient evidence to demonstrate a benefit of one therapy over another and I want to stress that, one therapy over another, not one therapy in general, for the treatment of lower extremity chronic venous thrombosis and obstruction.

There's also something that we were very interested in, insufficient evidence, no critical studies that showed a benefit of different forms of anticoagulation or duration of anticoagulation in patients who had true chronic lower extremity chronic venous thrombosis or obstruction.

All right. As we begin to conclude the evidence review today, I'd like to start with KQ1. As you see, or as you've heard,

there are very few comparative studies that exist in the contemporary literature. I would say we did not go back before 2000 and that's one of the limitations I'll mention later.

There's insufficient evidence to support or refute the use of duplex ultrasound as a first line test to confirm the diagnosis of lower extremity chronic venous disease or to plan an invasive treatment.

For KQ2, which involves patients with long-term chronic venous insufficiency/ incompetence/reflux you can see that patients, and I think Sreek said it nicely at his conclusion, that patients who underwent surgical or endovenous interventions had significant improvements in symptom scores and hemodynamics when compared to their baseline state.

Whether directly compared to each other or amongst the groups, there was no significant differences in CEAP classification or VCSS clinical severity score. Quality of life, additionally, was not different, or there was no significant difference, and that was between the surgical and endovenous

interventions. So we concluded that there is insufficient evidence to support the use of any one treatment modality over another based on our findings.

For the key question three which involved patients with lower extremity chronic venous thrombosis and obstruction, we thought that with very few studies assessing medical therapy, lifestyle modification or skin or wound care, there was insufficient evidence to suggest the use of any treatment modality over another in this population as well.

Now, I'm sure many of you are thinking there are multiple limitations and gaps that have been uncovered by this evidence review and report, and I'd like to talk about some of them now. We started with English-only studies because of 10,000 studies that we started with, it was hard enough to get through those in the English language.

Few treatment strategy studies actually exist, so if I tried treatment X first and then used Y if it didn't work, very few of those treatment strategy studies existed.

We were unable to stratify results by

disease severity, for instance by only patients with varicose veins or only patients based on a certain CEAP classification, because data wasn't there for patient-specific and disease-specific outcome reporting.

Again, there were numerous and heterogeneous endpoints, and many of these endpoints were reported at disparate time points, so early time points, intermediate time points and long-term outcome endpoints. With that, it's very difficult to lump intermediate or long-term or near-term outcomes together and therefore we did, I think, a very nice job of trying to put them into each category, but that limited our ability to do quantitative analysis on them.

Finally for KQ2, you saw the bulk of these studies. So there were 84 randomized control trials that we uncovered, and as we began doing our analysis we noted that there were a handful more observational studies, and it was going to be difficult to complete all of that work for this MedCAC. We decided with AHRQ guidance to include observational studies with greater than 500 patients in addition to

randomized control trials. We have planned sensitivity analyses for these analyses and will look at these observational studies as well, but that is a limitation of our evidence base. And that was only for KQ2, not for 1 or 3.

When we look at challenges for patients with lower extremity venous disease, I think the biggest challenge was the population differences that exist in the literature now. I told you a little bit about endpoint differences. Not only did some people use one classification, others used their own quality of life measures, differed between publications, the timing of outcomes, very dramatically across studies. But as you all know, the evolution of endovenous techniques has changed the landscape of this field and it was very difficult to account for that in the evidence review.

And then finally, the studies that we looked at, the descriptive characteristics of the patients in terms of disease severity as well as demographic characteristics were pretty limited.

When we were asked to identify research gaps within each key question, we broke them down based on each key question and I'll give them to you here.

As you can see, in key question one we thought a research gap was which patients should undergo additional testing and should that be duplex testing after the clinical diagnosis. Another question was which patients should undergo other testing like anatomic testing for obstructive disease or other entities prior to invasive treatments, and the literature is very scant on both of these topics.

When we look at KQ2, chronic venous insufficiency patients, we thought that additional studies were needed to determine which patients benefit the most from invasive treatments, so we need really a lot better studies that are stratified by CEAP classification, VCSS score, and then anatomy, deep and superficial, et cetera.

We also concluded that more studies of treatment strategy are needed, so invasive therapy plus weight reduction versus

compression therapy and invasive treatment.

Finally, this is a call for standardization of endpoints, it's occurred in a lot of other disease states. We need more uniform definitions as well as a more uniform use of allocation concealment and blinding in these studies.

Finally for KQ3, gaps that we identified and questions that remain, should patients with lower extremity chronic venous thrombosis and obstruction be treated with oral anticoagulation and if so, for how long and in which patients.

And then, should treatment be different in these patients who have chronic venous obstruction or thrombosis when compared with patients who have an uncomplicated deep vein thrombosis. Those were unanswered questions in our review.

There's a lot left to discuss. I think there are a number of people coming up that are going to talk about current studies, registry studies and randomized trials. We look forward to that.

This is just a publication we put out

for about four or five years from now just looking at clinicaltrials.gov. The pipeline is relatively sparse for patients with vascular disease in general and venous disease specifically.

So with that, I would like to conclude, and thank the audience and the panel for allowing us to present.

(Applause.)

DR. REDBERG: Thanks very much, and we will take questions later, but I just want, am just going to mention two technical kind of questions that you can answer now or later, because -- and thank you, that was a great summary of clearly a very complex literature, and I think you really did an excellent job of trying to summarize everything.

Obviously we're talking about Medicare beneficiaries, and I'm interested if you will be able to tell us later what was the percentage of over 65 in the studies that you looked at.

And also, you used the term short, intermediate and long-term outcomes. If you could define the time period for short and

long-term outcomes, we'll save the more complex questions for later.

DR. JONES: We would be happy to.

DR. REDBERG: Okay, great. Thank you very much.

Next we have Dr. Thomas Wakefield, who is the Stanley Professor of Surgery in the Section of Vascular Surgery at the University of Michigan, and you have 20 minutes, Dr. Wakefield.

DR. WAKEFIELD: Thank you very much. So, I'm going to be presenting on behalf of the Vascular Quality Initiative, the first ten months data from the VQI Varicose Vein Registry on behalf of the committee that put this registry together.

I have no disclosures myself for this talk. I do have a VIA contract from the NIH in conjunction with industry developing new antithrombotics, but no disclosures related to the registry.

So as you've heard, varicose veins are a very common clinical problem, ten to 15 percent of all men and 20 to 30 percent of women are afflicted with this chronic

condition. Varicose veins can cause a number of symptoms, from pruritis, leg heaviness and aching, to thrombophlebitis and occasionally eczema, lipodermatosclerosis, and even venous ulceration.

The annual incidence of development has been estimated at two percent per year associated with a number of circumstances, some of which include multiple pregnancies, obesity, family history, and increasing age. Varicose veins are a part of the health continuum of chronic venous insufficiency that can lead to eventually in some patients venous ulceration, and for chronic venous insufficiency that incidence has been suggested, or prevalence has been suggested to be between .06 percent and two percent, and estimates of overall annual cost of chronic venous insufficiency treatment is in the billions of dollars, and this has been estimated to be one to two percent of the total health care budget in some of our European countries.

So, this is the outline of what I'm going to be talking about, and you'll see we'll start with talking a little bit about how the

data was compiled, kind of break it up into truncal reflux-specific data, perforator data, and cluster-specific data for those varicose bumps that the patients present with, and then talk about outcomes, and then at the end I'll say a couple words about PRO and age.

So, the purpose of the VQI Varicose Vein Registry is to analyze procedural and followup data, to benchmark outcomes regionally and nationally for continuous improvement, to improve outcomes by developing best practices, to help meet IAC certification requirements for vein centers.

The data collection included procedural and followup data, so followup out to 90 days and then out to one year. And the data on ablation treatments includes thermal radiofrequency ablation including ClosureFast, thermal laser ablation, mechanochemical ablation, chemical ablation including Varithena and foam sclerotherapy, embolic adhesive therapy including VenaSeal, and surgical ablation including high ligation, stripping, and phlebectomy.

The Varicose Vein Registry is a

followup to the registry that was established in the American Venous Forum that started in 2009. That lasted to about 2013 and had two reports out of it. The Varicose Vein Registry, the VQI was established about a year and a half ago.

The inclusion criteria included percutaneous or closed and/or cut-down or open procedures to ablate or remove superficial truncal veins, perforating veins or varicose vein clusters in the lower extremities, thus C2 disease or greater.

Exclusion criteria included any treatment of deep veins of the lower extremity, interventions done for trauma, and treatment for C0 or C1 disease.

The objective is to provide a real world view of trends in treatment and outcomes associated with varicose vein therapy. For this report we performed univariate statistical analysis.

Just a word about the VQI. The VQI was started in 2011. The Varicose Vein Registry is one module of the VQI. The VQI right now has 379 centers in 46 states and in

Ontario. There are 17 regional quality groups associated with the VQI in order to try to bring the data to a more local level for data evaluation and quality improvement.

You can see that as of June 1st of this year, there were almost 300,000 procedures in the overall VQI. We had close to 5,000 procedures in the Varicose Vein Registry, which was a good start for the registry only a year and a half in.

So, compiled data on all procedures. We had for the first ten months 1,406 individual patients aged 55, 71.5 percent were female. The BMI was 29 plus or minus seven. 78.3 percent Caucasian, seven percent African-American. Previous varicose vein treatment in 31 percent of the patients. There was a history of DVT in seven percent of the patients, and eight percent of the patients were on anticoagulation at the time of their procedure.

There were 2,661 veins treated on 1,803 limbs with 1,751 procedures, performed usually in the office or in the operating room. You'll see that the laterality was essentially

equivalent, 48 percent right, 49 percent left, three percent bilateral.

When we looked at the CEAP classification of these patients, you will see that the highest CEAP group was C3, second C2, and the third highest group was C4a, so this suggests that patients undergoing varicose vein treatment are not just patients who have varicose veins only, but also present with other manifestations of chronic venous insufficiency.

When we look at the anatomy of reflux overall, 75 percent of the patients, whether you're talking about the right or the left, had great saphenous vein insufficiency in the thigh, almost 50 percent had great saphenous vein insufficiency of the calf, a third of the patients had small saphenous vein insufficiency, ten percent had insufficiency of the anterior accessory branch, and a third of the patients also had underlying deep vein insufficiency at the time that they were assessed.

As far as the anesthesia for the patients overall, you will see that only 18

percent got general anesthesia, so most of the patients had some combination of tumescent, local and sedation. And you'll see that essentially 98 percent of the patients post procedure had some sort of compression, pretty much even between stockings and bandages.

Now specifically looking at truncal reflux specific data, you'll see that 55.8 percent of patients had great saphenous reflux of the thigh, 15.5 percent of the calf, so over 70 percent had reflux of the great saphenous vein. About ten percent the anterior accessory branch, small saphenous around 17 percent, and the largest vein diameter treated was 7.74 millimeters, the length of the saphenous treated was 35 centimeters, suggesting that most of the time the reflux being treated starts right about at the knee.

55 percent radiofrequency ablation, 34 percent endovenous laser ablation, eight percent were treated with an open procedure, one percent with foam, and less than one percent with mechanical treatment.

When we look at postoperative compression in these patients with truncal

reflex, again, half and half between bandages and stockings, and the type of bandage was predominated by multilayer long stretch.

For perforator-specific data, we had 43 patients who had perforators treated, 28 of the 43 were previously treated, they had been recanalized. 70 percent of the perforations were located in the calf. The largest diameter was a mean of 3.85 millimeters. All but two patients were treated with compression post procedure. Most perforators were treated in a hospital outpatient center. The most common treatment was open ligation.

Regarding cluster-specific data, we had 640 patients who were treated for clusters, 66 in the thigh and 574 in the calf. 76 percent of the patients who had clusters treated also were treated with an ablation of their refluxing truncal vein at the same time. The largest vein diameter was 4.54 centimeters. The most common location of treatment was in the office, 78 percent. The remainder of the cluster treatments were performed in the hospital outpatient, 19 percent, or in the ambulatory surgery center at three percent.

Open surgery was most common, involving 434 stab phlebectomy and 78 patients who had trivex or powered phlebectomy.

All patients except three underwent post procedure compression, and here you'll see that after cluster treatment, bandages were much more common than stockings. Again, long stretch bandage was the most common, probably because most people don't want to put the stocking on if there are multiple small incisions initially.

Now looking at outcomes, we have, because it's only ten months into the registry we don't have followup on everyone. Time to followup mean was 44.6 days, number of lost work days was 2.2.

Local complications were small, 714 limbs were able to be looked at for local complications, 1.3 percent pigmentation, one percent superficial phlebitis, less than one percent for proximal thrombus extension, DVT, wound infection or skin blistering.

We had very few systemic complications. We had three unplanned admissions, two allergic reactions, and the

other unspecified systemic complications.

When we looked at change in the C score, you'll see that there was a mean change of .71. Now you really can't do a number with the C score, it's more a change in categories, and you'll see that going from pre-op in blue to postoperative in red, with postoperative we had many more patients who were C1 after the procedure, and patients who were less, for example C3, suggesting that we are moving the disease process back to a more early stage with treatment.

When you look at changes in the VCSS score, you'll see that there was a statistically significant improvement in VCSS by minus 4.68 points.

And we have in the registry patient reported outcomes, which is an extension of the VVSymQ which I'll talk about in a second. And we have pre and post procedure data available for 670 patients and you'll see that for each one of these seven categories including heaviness, achiness, swelling, throbbing, itching, appearance and work impact, there is a significant improvement from pre to post

procedure, and the total improvement if you add them all together was a minus 10.74 points.

I mentioned that this is a takeoff of the VVSymQ. The VVSymQ is the first PRO specifically designed in accordance with the FDA guidance for PROs to evaluate varicose vein treatments from the patient's perspective in clinical trials. The VVSymQ essentially has five of our seven components, and for each component a score of zero to five is assessed, and the patients are asked questions regarding that score.

This is a study that was published on the VVSymQ regarding foam sclerotherapy so I'm using this to talk about a PRO. In this study there were 112 patients in the placebo group and 283 patients who underwent foam sclerotherapy. You'll see the age, sex, race, the weight and BMI listed on the slide for these groups.

In this dense slide, if you look for example at the overall VVSymQ score between baseline and the change, you'll see that those patients who were treated had a higher change in their VVSymQ compared to placebo in overall

and in each one of these categories. And when they looked and asked something called the patient's global impression of change, which was asking the patient the question, are you improved or not, you will see that patients who were significantly improved, or much improved, had a VVSymQ change of between 6.2 and 6.7 points. When we went back on our data and just looked at the five components that were used in this study, our change was around 8.04, suggesting that in the registry we are seeing patients who are much improved by their treatment.

This is also an interesting slide from this paper, suggesting that if you compare the VVSymQ to another patient-reported outcome, the VEINES Quality of Life score, there is a significant correlation. On the other hand, if you compare it to VCSS or changes in duplex, the correlation is not as strong, suggesting that PROs do measure something different than what is usually determined by a physician or provider-oriented measure and/or measuring just laboratory changes.

Just a comment about patients by age.

We went back and looked at the entire group just to see how many patients were in the 65 age range or greater, and you can see that about 15 to 20 percent of the patients were in fact in that age range. And although I don't have the analysis done yet, I can tell you that just looking at PROs and looking at VCSS, there certainly is no decrement to the improvement in the patients who are age 65 or greater, they seem to actually get as good a result as those who are younger.

So in summary, modern day varicose vein treatment is characterized by largely office-based and outpatient hospital-based treatment, endovenous treatment of axial reflux, open surgery for perforators and clusters, nearly universal postoperative or post procedure compression, improvements in C score, VCSS and patient-reported outcomes.

The VQI VVR provides a complete assessment of varicose vein interventions. The VQI VVR is particularly useful for monitoring changes after treatment, and future studies should utilize this database to identify best practices and continue to improve outcomes in

varicose vein patients.

And finally I would like to ask, what are some of the potential questions that the VVR could answer, or that registries could answer in general, so here would be some of my thoughts. The efficacy of combined procedures, ablation plus phlebectomy versus multiple single procedures. The efficacy of tumescent-less, MOCA or glue, versus thermal, versus foam sclerotherapy for saphenous vein ablations. The role of perforator interruption in patients with C2 to C4 disease. The progression of C2 disease to higher levels of disease. The relationship of age to treatment outcomes, including quality of life assessments. Variation in indications being used for treatment of superficial venous disease across centers. And finally, modern day complication rates. Thank you very much.

(Applause.)

DR. REDBERG: Thanks, Dr. Wakefield, for your presentation and your work in putting together this registry.

Next is Dr. Fedor Lurie, who's the president of the American Venous Forum

Foundation and associate director of the Jobst Vascular Institute, also at the University of Michigan, and you have ten minutes.

DR. LURIE: Thank you. I am here as the president of the American Venous Forum Foundation, and I thank CMS for giving us the opportunity to share our approach to evidence generation analysis and synthesis.

Here are my disclosures.

My objective for this talk is to describe the integrated systematic process developed by the forum to address the issues of gaps in identification, to support the generation of evidence that addresses those gaps, and to synthesize them into practice guidelines.

The American Venous Forum was created to address the needs to improve venous health in the populations of the United States by creating an academic environment and infrastructure that supports generation of appropriate evidence and then promotes those evidence to support the practices. Today it is an organization that is focused on venous disease, it is open to any society,

collaborates with many societies but is free from interest of any specific society.

In order to operate, we have identified important gaps in knowledge. The expertise was defined as a combination of in-depth standard methodology, successful evidence generation, and sufficient understanding of (unintelligible). A deficiency of any in these three dimensions can hamper this process, so it's important to combine all three.

A methodology was developed by the forum that minimizes the bias in the investigation of gaps while keeping the input from all important stakeholders. The first attempt to implement this technology was here in the forum, Pacific Vascular Symposia, that realized that at that time no sufficient evidence existed that can be meaningfully analyzed because of the disparity in methodology and the classification and assessment of venous disease.

Addressing this need, this gap, the forum developed the CEAP classification and the venous severity score. This instrument became

the gold standard of venous practices today around the globe. More importantly, they allowed for generation of new analyzable evidence. A decade later the forum implemented the same methodology and concluded that sufficient evidence exists to summarize them in a practice guideline, and under the leadership of Dr. Peter Gloviczki and with collaboration of the Society for Vascular Surgery, those guidelines were written and published soon after that meeting.

Three years later our forum looked at the issue of venous ulcers. Many patients with this condition are Medicare beneficiaries. It was identified that we are lacking the meaningful epidemiological data for specifically the United States populations at that time. This was important because it allows us to monitor the progress we can make in decreasing the prevalence of this population, and this is why the project headed by Dr. Michael Gloviczki is so important. Not only we know about now the prevalence and incidence of venous ulceration in the United States population, we can re-sample that at any

time to measure our success.

Addressing the second high priority, with the collaboration of the Society for Vascular Surgery, we developed guidelines that specifically addressed the issue of venous ulcerations.

You might see now the point I'm trying to make. Having all the elements of this process integrated under one umbrella organization allows us to continue to indeed improve the evidence base for venous practice. It makes possible to minimize bias by implementing quite a sophisticated process as depicted in this slide and published in the Journal for Vascular Surgery. I would like to emphasize that evidence grading is consistent through the entire process from identification of gaps to funding, to summarizing them in synthesis in the practical guidelines.

The most recent knowledge gaps and priorities were identified just five months ago and again, that was a collaboration between basic scientists, clinical researchers, practitioners, developers of new technologies, peers, and government agencies like NIH. CMS

was invited but decided not to participate, and I'm glad that in just a few months they realized the importance of this issue.

Before I move forward, there's a variety of tools to facilitate the generation of evidence to address the priority gaps, one of which is the first American Venous Forum registry that now is the Vascular Quality Initiative, presented by Dr. Wakefield just before this talk. I submit to you that these two guidelines are unique in their quality and practicality. Again, the methodological approach is consistent with gaps and identification and funding, and that's not about, those guidelines don't just summarize the evidence available at that time but actually reach to the future allowing the process to continue to generate new meaningful evidence.

The GRADE system is familiar to all of you. What's rarely discussed is it allows for grading, making strong recommendations based on weak evidence, and making weak recommendations despite the presence of strong evidence. This is where our three-dimensional definition of

expertise comes into play. Some recommendations should be made based on the best practice when the supporting evidence is lacking or impossible to generate. It is always important to realize that while the highest standard of evidence is essential in accepting a new treatment option, it is unrealistic to expect the large studies producing the highest level of evidence for a treatment that existed for decades and centuries, and is widely accepted as effective by the medical community. The compression therapy is a good example of such treatment.

Consistency of findings with established clinical expertise and whether or not the results are replicated is also important to consider, especially when you're making practical or qualitative recommendations. We're all aware that less than half of the best highly thought of randomized trials were ever replicated, and the rest of them were challenged and refuted over time. Not infrequently, methodologically superb studies also do not translate in important improvement in clinical outcomes.

That is why I think it's very important to go beyond just the methodological purity of studies, especially when you're making recommendations for policy and practice.

In the nearly 30-year history of forum groups, their integrated approach to evidence from identification of gaps to the synthesis is an effective way to improve the evidence base for venous practice. The major barrier for this process is the discrepancy between the guidelines that are generated by a systematic approach and the policies, including Medicare. Those discrepancies on one hand open the door for some practices that might be questionable but on the other hand may limit the access of patients to more appropriate treatment. More importantly, those discrepancies impede that systematic process by broadening the gap between the best available evidence, whatever the level of it is, and the real world practice that's directed by, in part by the reimbursement policies.

I would like to conclude by asking the panel to consider our approach to evidence analysis, and especially when it comes to the

policy recommendations, to look beyond the methodological purity of the studies, to differentiate the standards between the new treatment and the existed for a long time options, especially when the other options are not available, and to recommend to align the policies with our guidelines. Thank you very much for your attention.

(Applause.)

DR. REDBERG: Thank you, Dr. Lurie. We will now take a ten-minute break so, I have 9:54, we'll return at 10:05, and then we'll have scheduled public comments.

(Recess.)

DR. REDBERG: I would like to welcome everyone back, so let's get started. Dr. Oscar Alvarez.

DR. ALVAREZ: Good morning. My name is Oscar Alvarez, I'm the director of the University Wound Healing Centers and on the faculty at New York Medical College. These are my disclosures relevant to this talk.

I want to speak to you about a study that we published that I'm sure fell through the gaps because it was less than 500 people,

and the quality is retrospective in regard, but with these venous patients you get anything you can get in terms of science, and they're not easy studies to do.

So this is Improvement in Clinical Outcomes, Physical Function and Body Pain Following a 12-Week Course of Intermittent Pneumatic Compression. I just want to tell you that compression is the cornerstone of managing venous disease, and if any of you had a venous ulcer, you would want compression treatment first.

So this was a review of clinical record of 94 chronic venous ulcer patients treated at two independent specialty centers, and it was included in a longitudinal retrospective analysis. Both clinical centers employed the VCSS score to monitor outcomes. IPC application was with a four-chamber gradient pump, both centers used the same pump, and they were both identical treatments. IPC was applied on top of standard compression bandages so, this is just to point out that the pneumatic compression was also added to standard compression therapy alone that is

static. All patients were seen weekly for standard evaluations and patient record analysis was for 12 consecutive weeks.

I'm going to skip the statistic section just because of time.

The demographics and clinical characteristics overall are shown here. You can see the mean age was of Medicare age. The sex was about the same. Ulcer duration in months was about nine or ten months so these are recalcitrant ulcers, and remember, these people cannot get the IPC prescribed unless they have six months of non-healing. The baseline ulcer size was as you can see there, and similar, and there were no ambulatory patients at my site but the percentage was 11.7, so most were ambulatory, and the mean BMI was 31.

So, the pooled VCSS scores at baseline prior to treatment with IPC and week 12 are shown here, and you can see that at almost every level there was a statistically significant difference when IPC was used for a 12-week period.

In conclusion, the incidence of ulcer

healing was 80 percent after 12 weeks of IPC therapy, obviously in conjunction with static compression. Symptomatic improvement was noted in every category of VCSS. In the category of pain, there was a significant difference in the number of patients reporting severe pain before and after IPC therapy. Also, the number of patients reporting no pain before and after IPC therapy increased by 67 percent. In the category of edema, significant improvement was noted after 12 weeks of IPC therapy in patients that had severe edema at baseline, that was statistically significant, and also in the number of patients where edema was resolved, also statistically significant. Severe inflammation was significantly reduced in all study patients and completely resolved in 60 of the 94 patients. Thank you very much for your attention.

(Applause.)

DR. REDBERG: Thank you, Dr. Alvarez. Maybe you can hold your applause to the end, because we have 23 speakers.

So, Dr. Marlin Schul is the next speaker. He's the owner of Indiana Vascular

Associates.

DR. SCHUL: Good morning, everyone, it's actually an honor to be here, and my role today is to represent the American College of Pathology's Patient Reported Outcomes Vein Registry.

When considering questions about evidence gaps, treatment disparities, outcomes, and if you will, building the evidence for Medicare beneficiaries, the most effective way to do that is through sophisticated registries.

I've tried to simplify this slide but I think this is a very important slide. When you look at the top area those are medical records; in legacy data and legacy registries people are doing manual data entry. Sophisticated registries actually take the routine documentation that a provider is doing in their electronic medical record, and it flows seamlessly to the registry.

The bottom part cannot be possibly overemphasized, and that's where your culturally related quality of life data comes in. If patients can complete simple queries that are disease-specific and/or generic, or

both is preferable, and you combine that with the routine documentation of an encounter, all of a sudden you've got very powerful data.

You can see that there are many stakeholders involved, and it not only can help us with identifying outcomes, but it can also put a face on the patients that have this disease process.

If we look at the registry realities, there's a dilemma. If we look at the second column, one registry of a scientific meeting in February reported 20 percent of their patients used general anesthesia or had general anesthesia with thermal ablation as well as phlebectomy, but little to no chemical ablation was employed. Right after that, Registry B reported widespread chemical ablation and thermal ablation for patients but no general anesthesia.

What this represents is selection bias. Here we have three registries trying to capture outcomes from patients, and you've got a different set of providers with each registry and you've got different procedures being used. So in order to get a true real world

assessment, data warehousing needs to be considered.

This is a table of the existing registries, each is sponsored by a society. You can see each has a venous focus of varying degree. The ACP PRO Venous Registry is largely CVI focused and management focused. One of the reasons our registry has grown so quickly with over 40,000 encounters is because we have two EMRs that are already connected and a third publicly traded organization that is in the process of building a patch so that these providers can easily enter their data.

The data focus is either procedural or epidemiology and procedural. We're unique in the standpoint that we capture two different queries, both a generic and a disease-specific query. An SF6D, as you know, is a short form quality of life form, it's generic, it takes very little time to complete. Patients do that by filling it out on an iPad or they can do it through a patient portal. These do not disrupt work flow. Each registry is able to benchmark, each is recognized by regulatory bodies.

And at this stage, when you consider

the three registries are all about a year and a half in their development, you have well over 20,000 now unique patients that have been captured in these registries. Using conservative estimates alone, it's easy to see where over 150 to 200,000 unique patients will be captured over the next two years, so --

DR. REDBERG: 30 seconds.

DR. SCHUL: -- it's going to be something where Medicare beneficiaries are going to be a large part of that.

In summary, no registry is perfect, each has merit. CMS would do wonderful to support additional quality of life capture and support data warehousing. Thank you for your time.

DR. REDBERG: Thank you, Dr. Schul. Next is Dr. Francis Lee, who's the founder and medical director of Advanced Vein Care Center.

DR. LEE: Good morning, panel members and ladies and gentlemen. My name is Francis Lee, I come from western Massachusetts, I'm a general surgeon, and I have no industry affiliation. My office is the kind of office where American health care takes place all

across the country, especially with a vein practice.

I brought a lot of data with me but today I'm going to change what I'm going to say based on the data that were presented by the gentlemen from Duke. In my practice I probably treat more patients in a year than most of those studies. My experience, the endovenous treatment, it improves symptoms in the vast majority if not up to 85 to 95 percent of patients, so why is there that disparity?

In my experience and many other vein specialists across the country, and the data that are in the literature, well, there are many reasons, I think. Number one, these are the data, they do not include the kind of end outcome, for example CEAP and VCSS, they do not really adequately address what the patient cares about. What the patient cares about is my pain, how is my pain improved. I'm a waitress, I'm a single mother, I have to quit my job because I can't stand on my feet. CEAP and VCSS does not measure that, okay? That's number one.

Number two, it is very difficult to

conduct randomized clinical trials at multi-sites, and in this industry the last ten to 15 years, those kind of data just have not been there mainly because of lack of funding for research and opportunities. And so while most data are in the moderate range in terms of level, which is for most individual randomized clinical trials, we do not have yet the multi-site, the kind of trials that we need or that we're used to seeing for drug companies for drugs and large scale cardiology medications for example, in this industry we simply don't have that yet. And a lot of that is not because of our not wanting to provide it, but those opportunities just have not been there because of funding.

Three, a lot of this data talks about alternatives to an endovenous laser or RF treatment. Compression stockings is one. The studies that have been mentioned, they do not take into account the real life practical issue. For example I would submit, of the Medicare beneficiaries which you're charged to serve, for those patient populations, I would say between half to two-thirds of those

patients cannot even put those on in the morning, it's not an option.

Foam sclerotherapy has a closure rate of 80 percent, but it's highly dependent on the operator, it's more like 60 percent in some instances.

And lastly, taking anybody to the operating room for phlebectomy or doing an endovenous treatment is simply, it's just not practical nor cost effective anymore.

So those are the realities. In addition, there has been an evolution in the technology in this industry for the last ten or 15 years, so it's kind of daring to see the technology back from ten years ago compared to today, and it's vastly different.

So in conclusion, what I would like to say to the panel members is please take into consideration that sometimes in surgery, which is my background, data and evidence follows real life experience. If we had ignored that, we would not have made the strides that we have made in laparoscopic cholecystectomy --

DR. REDBERG: Thank you, Dr. Lee.

DR. LEE: -- nor in other areas.

Thank you.

DR. REDBERG: Next is Dr. Morrison, who is the president of the International Union of Phlebology, and he is representing the United States Compression Alliance.

DR. MORRISON: Thank you very much. I'm going to talk about compression for venous and lymphatic disorders. That is my disclosure slide.

As far as the first question, is there intermediate and near-term health outcomes for patient with symptoms, there are various modes of compression, everyone knows there's graduated compression hose, compression multilayer bandaging, and then the inelastic devices from Unna's boot all the way up to the pneumatic compression devices. It really is the cornerstone treatment for venous and lymphatic medicine disorders and remains an important intervention, even in this time of technological advancement and there is some evidence base for this.

This is a consensus document, this was very well developed over course of time, started by Hugo Partsch, and these are all of

the things that have good evidence that they are improved with treatment using compression.

This is from the Mayo Clinic using stronger compression for more advanced disease and lymphedema and less compression for the mild disease.

This is a meta-analysis of randomized control trials, so they looked at 11 RCTs. Compression with ten to 20 millimeters of mercury had a clear effect on edema and symptoms, as compared to placebo stockings, and the meta-analysis suggested that leg compression with ten to 20 millimeters of mercury is an effective treatment CVD.

This is from the excellent Bonn Vein Study, indicating that patients with, symptomatic patients had improvement of all of these symptoms you can see on the right side, all of these symptoms with treatment with compression hose.

And then a systematic review of compression hosiery for uncomplicated varicose veins. Compression hose is used widely but there are still some gaps and we heard a lot about those gaps earlier on. So in this

analysis the RCTs were looked at and where they weren't available, evidence was used, where compression improved the symptom management but there was no consensus found regarding the class of compression. The evidence for benefit of compression hose for varicose veins was equivocal, as we heard earlier, and where a compression to slow the progress or prevent the reoccurrence of varicose veins could not be supported by the currently published evidence.

Bonn Vein Study in fact does show progression of venous disease, but no data regarding compression retarding the advancement of that disease.

As far as the long-term health outcomes, registry I think is the key, and we have a number of registries that you heard about so I won't go into those.

I thought what might be helpful for those who don't see these patients all the time to have a case study, simple case study. This is a 42-year-old woman with a 20-year history of venous ulcers in the left leg. A duplex exam showed the entire DV system to be normal but reflux was identified in the great

saphenous vein and its tributaries. Patient underwent sharp debridement, phlebectomy for the varicosities, foam sclerotherapy for the truncal insufficiencies, followed by compression bandages and eventually compression hose over the long term. That's on the 13th of August, the patient underwent debridement. That's four days later, the wound is starting to granulate. This is three days after that, the wound is beginning to heal, and that's the patient two months following that treatment, with compression over that two-month period, complete healing of those ulcers, so it does work. Thank you very much.

DR. REDBERG: Thank you, Dr. Morrison. Next is Dr. Peter Gloviczki, the Joe M. and Ruth Roberts Professor of Surgery and the Chair Emeritus at the Gonda Vascular Center, Mayo Clinic.

DR. GLOVICZKI: Thank you very much. It's a privilege to present on the evidence of intermediate and near-term outcomes of interventions available for chronic venous disease. These are my disclosures.

Together with the next five speakers I

represent the SVS, the world's largest vascular surgery society, and the AVF, the world's most respected academic vein society.

Venous disease management has been an integral part of the practice of many vascular surgeons. The two societies developed joint guidelines on chronic venous disease, and during the past 20 years the Handbook of the American Venous Forum defines management of venous disorders in this country and abroad.

The benefit of surgery for varicose veins compared to conservative treatment in the REACTIV trial, quality of life, complications, symptom improvement and the anatomical extent of varicosity endpoints. Quality of life improved significantly after surgery versus conservative treatment, symptomatic improvement was significantly better at one year, and anatomical extent of varicosity did not change at all after compression therapy.

Three major society guidelines recommend against compression therapy as the primary treatment if the patient is a candidate for saphenous vein ablation, a strong recommendation with adequate evidence of

moderate quality.

Minimally invasive techniques compared to surgery, 13 randomized control trials that included 3,000 patients in a recent Cochrane review. In this review foam sclerotherapy, laser and radio frequency were as effective as surgery.

In this analysis of 28 RCTs show significant early benefit of endovenous ablation, they saw less hematoma, pain, wound infection, and earlier return to normal activities than surgery.

Rasmussen and colleagues randomized 500 patients to four different treatments and at one year all the treatments were efficacious, with similar improvements in disease-specific quality of life. Time to resume normal activity and return to work was shortest after radiofrequency and foam, while the VCSS was significantly improved in all the groups.

Today all of the major guidelines recommend endovenous thermal ablation over high ligation and stripping, a strong recommendation based on moderate quality of evidence.

This review of four major RCTs concluded that all endovenous treatments are safe with low complication rate and morbidity, that interventions resulted in significant and clinically important improvement in symptoms and signs, and that all interventions result in significant improvement in quality of life. So we are very confident, a high to intermediate level of four, that interventions for symptomatic chronic venous disease improve immediate and near-term health outcomes.

We have a classic study where Neglen observed 100 percent secondary patency with stents placed in patients with symptomatic primary iliac reconstruction. Evidence from 16 studies supporting stenting for venous obstructions is still weak. However, stenting is safe, promising, and should be considered acceptable treatment for iliac reconstruction while the evidence base is improving.

Our enthusiasm rating is high, but because of the evidence our confidence level is low, settling on two, that stenting improves immediate and near-term outcomes. Thank you for the opportunity to present this data.

DR. REDBERG: Thank you, Doctor. Next is Dr. Cynthia Shortell, who is a professor of surgery at Duke University.

DR. SHORTELL: I'm honored to discuss the long-term outcomes of interventions for chronic venous disease. My disclosures.

Specifically, for adults with varicose veins and/or other clinical symptoms or signs of chronic venous insufficiency, how confident are you that there is sufficient evidence for an intervention that improves long-term health outcomes in patients presenting with symptoms?

You were introduced to this study comparing laser, RFA, foam sclerotherapy, and surgical stripping by Dr. Gloviczki. The vast majority of patients in all groups had excellent and sustained reduction in VCSS scores at three years. However, foam sclerotherapy patients required more secondary interventions.

In another RCT, the same investigators compared laser to surgical stripping at five years. Both modalities showed sustained equivalent improvement in VCSS scores.

In 2011 the SVS published these

guidelines for the care of patients with varicose veins and associated venous diseases, recommending endovenous ablation over surgery for the treatment of venous incompetence, compression only for patients unsuitable for intervention, and abolition of the three-month trial compression prior to ablation, and that sclerotherapy be reserved for small vein telangectasia.

In a subsequent set of guidelines the SVS and AVF recommended endovenous ablation of incompetent saphenous and perforator veins to improve healing and prevent ulcer recurrence of patients with deep or C6 disease.

The REACTIV trial was a randomized control trial comparing surgery with conservative treatment in patients with varicose veins. At two years, quality of life, symptoms, and anatomic measures were superior in the surgical group.

In 2013, the same REACTIV trial group also performed a systematic review of 34 RCTs designed to evaluate the effectiveness and cost effectiveness of modalities used to treat GSV reflux. Recurrence rates and QoL instruments

were superior in patients receiving ablation modalities compared to surgery. Percutaneous modalities are therefore preferred, providing it is cost equivalent.

The ESCHAR trial is a landmark study comparing compression alone versus compression plus GSV stripping in healing and preventing venous ulcers. The groups were comparable with respect to age and percentage of patients with PTS. Patients in the surgery plus compression group were less likely to have an ulcer at four years than those who received compression alone. Notably, while stripping reduced the recurrence rate, it did not accelerate ulcer healing.

This 2013 evidence summary included peer reviewed papers with data on a total of 1,500 patients undergoing iliocaval stenting and meeting eligibility criteria. Long-term patency was greatest in non-thrombotic lesions and resulted in clinical improvement of pain, swelling and ulcer healing in the majority of patients.

The SVS and AVF have a high, score four level of confidence that for adults with

varicose veins and venous insufficiency, interventions to ablate refluxing superficial veins improve long-term health outcomes.

The SVS and AVF have an intermediate, score three level of confidence that for adults with chronic venous insufficiency, interventions to stent iliocaval lesions improve long-term health outcomes.

There is no evidence that interventions to treat patients with asymptomatic varicose veins are medically necessary. The SVS has a low, score two, level of confidence that interventions improve long-term health outcomes in asymptomatic patients. However, the risk of developing superficial thrombophlebitis in the setting of very large varicosities is real and warrants consideration of intervention in good risk asymptomatic patients. Thank you very much for your attention.

DR. REDBERG: Thank you, Dr. Shortell. Next is Dr. Peter Henke, who is the Leland Ira Doan Professor of Surgery at the University of Michigan.

DR. HENKE: Thank you very much. I'm

honored on behalf of SVS and AVF to focus on chronic venous thrombosis and really highlight the guidelines from our society. This is my disclosures, focusing on postthrombotic syndrome.

Question two you have in your packet and I won't repeat that. The treatment of chronic venous insufficiency, I'll try to highlight some of the bulleted points in the top part of this slide, and no time for those below. You've already heard about sustained compression and we believe based on the guidelines that compression will increase venous leg ulcer healing with a 1A level of evidence, and decrease the risk of ulcer recurrence at a 2B level. Intermittent pneumatic compression may be useful in those who have failed the compression therapy, at a 2C level.

Treatment of C2 disease you just heard about from the prior two speakers and I'm going to skip that slide.

There are certain medications and nutrition, a nutrition assessment should be performed, kind of common sensically and in the

best practice in our guidelines. Pentoxifylline available here in the U.S., or MPFF which is available in Europe, used in combination with compression, has been found useful to heal venous ulceration at a 1B level of evidence. Active exercise will improve calf muscle function and reduce pain and edema at a 2B level of evidence in patients with active leg ulcers. Balneotherapy, 2B level of evidence.

With regard to correction of superficial reflux, ulcer healing at C6 is improved with ablation of the incompetent superficial veins combined with compression therapy, 2C. Ulcer recurrence at the C5 level is significantly reduced with ablation of incompetent superficial veins at a 1B to C level. For patients with significant skin changes but no ulcer yet, C4b, it's recommended at a 2C level. For patients with active ulcers, C6, and incompetent perforating veins with some of the parameters shown here, or a healed ulcer, ablation of superficial veins and the perforator is recommended plus standard compression therapy at a 2C level. And

patients with advanced venous disease, again at C4b, superficial ablation and perforator interruption is warranted at a 2C level.

Patients with venous obstruction now, with infrainguinal deep venous obstruction and skin changes at risk, C4b, C5, or active ulceration at C6, autogenous venous bypass or endophlebectomy in addition to started compression aids in venous ulcer healing with a 2C level of evidence. We do recommend against deep vein ligation of femoral or popliteal veins.

In patients with IVC and iliac total occlusion or severe stenosis, you saw some evidence on this with either C4b, 5 or 6, venous angioplasty and stent recanalization with compression aids in venous ulcer healing.

This is just a summary of some of that data showing good patency, and the majority of the ulcers healed anywhere from six months to five years.

In those with the same level of disease and CF classifications who have intact valve or valve repair, or those who don't have an impact valve transposition or

transplantation or autogenous valve substitutes, there's a 2C level recommendation. This is a summary there showing good valve competence overall and symptoms resolved in the majority of patients in the majority of series.

Similarly, internal valvuloplasty, an older series that was considered in the AHRQ summary, and finally, valve transposition.

Lastly, prevention of chronic venous insufficiency in postthrombotic syndrome, initially for years we thought the symptoms were reduced with compression stockings, a good level of evidence there, and walking does not increase the risk of pulmonary embolism and does decrease the severity of postthrombotic syndrome. But the SOX trial that came out a year and a half ago, a randomized control trial of active compression with placebo compression threw this into question, I don't think the question is fully answered yet, but that is where we stand. Thank you very much.

DR. REDBERG: Thank you, Dr. Henke. Next is Dr. Michael Dalsing, professor of surgery, Division of Vascular Surgery at Indiana University School of Medicine, and he

is representing The Society for Vascular Surgery and the American Venous Forum.

DR. DALSING: Thank you, thanks for the opportunity of presenting evidence gaps. These are my conflicts of interest.

The first three topics I'm going to present are really, I think they'll help and benefit our patients and would actually help in research, and the gap really here is implementation, so we need to be able to standardize how we classify our patients, possibly by the CEAP classification, and we need to have tools that measure properly and that we can use to see how all of us are doing in our practice, and that basically is the SVS Generic and Disease Specific Quality of Life Initiative and how our procedural outcomes are taking place, so these need to be implemented.

The same with our guidelines, we have guidelines available for multiple societies, I just present two here, but by decreasing variation we know we improve care.

And then finally is standardization of our venous testing in chronic venous disease. We have accreditation processes that are in

place and again, standardization helps us to treat our patients the best way we can.

Compression is effective for treatment of chronic deep venous disease, and treatment should not be a financial burden to the patient who plans to be compliant, and in some cases that is a problem for our patients.

Certainly there are gaps. We don't know exactly the level of compression for the early stage disease. The same is true for advanced disease, or possibly the absolute best method or device to use in those patients, and we need to study long-term results better. We have pretty good intermediate and early results, just not long term.

The incidence and rate of early stage chronic venous disease which progresses to advanced disease, we have little data here. We need longitudinal studies with appropriate imaging which defines the patients with low, medium and high risk of disease progression, and this has to be divided by gender, age, initial clinical class, anatomic involvement. Such studies would provide a clear basis for conservative versus aggressive approach to

prevent disease progression but would have no change, should have no change on the need to treat those based with symptoms.

A comprehensive understanding of venous physiology in terms of the vein, the conduit, as well as the end organ, soft tissue or skin, in the Medicare population, we need some basic understanding, basic science understanding so that we can improve the venous conduit, the valve as a valve and the calf muscle pump as a functional device to push blood out of our legs.

We need well designed long-term clinical trials to evaluate venous interventions used to treat advanced stages of chronic venous disease in the Medicare population. These can be clinical trials or real life registries, which I think may become the most important part. We need to know long-term results. With the advent of new stents and drug-eluting stents, we're going to have to go back and look at those patients to see how they're going to fit in. And for reflux disease, there probably will be newer avenues that we're going to have to address,

either in percutaneous interventions or in synthetic valves, that's really the end stage of venous disease.

We need well designed clinical trials for venous interventions of all types, focusing on quality for cost. We have studies up here to look at quality for patients in a number of ways, quality of life initiatives and how our interventions work, but often have not involved what it costs us. I present just one study here, the REACTIV study that did look at that, and cost in terms of benefit for quality was proven.

My last slide is really just references that will be available if people want to go back and look at it, and see why I came up with this list of knowledge gaps, and I thank you for your attention.

DR. REDBERG: Thank you, Dr. Dalsing. Next is Dr. Thomas O'Donnell, the Benjamin Andrews Emeritus Professor of Surgery at Tufts University.

DR. O'DONNELL: Thank you very much for the opportunity to address a subject that hasn't been addressed so far, that is treatment

disparities. These are my disclosures.

The question or topic is, discuss any current venous disease treatment disparities and how they may affect the health care outcomes of Medicare beneficiaries not justified by the differences in health status, preferences of the groups.

Well, to answer this question, first you need to look at the base case through epidemiologic studies, you look at the age, gender and ethnic factors, and them assemble studies to look at treatments addressing those three areas. Why this is important is shown in this slide that, for 2013 and 2014, and continuing in 2015, there were a lot of varicose vein procedures done, and for the Medicare population it represents about a third of those procedures.

If we use epidemiological surveys as a base case, five are listed here, one has already been presented by Dr. Allison, this provides the base case for age, et cetera.

When we look at potential varicose vein treatment studies there are 1,300 systematic reviews that we did, and then

looking at a large insurance database, gives us data on over 130,000 patients. When we look at the specific factor of age, it's important to know that these are the mean age, but all except the Edinburgh study did have patients in the Medicare generation. However, when we look at the treatment category, there are fewer patients at lower age than the epidemiologic survey, and because RCTs are explanatory studies, they limit to the exclusion of many patients in the Medicare generation but, and as I said, they're younger, but more importantly, one-third of patients, included patients were age 65.

When we look at the proportion of women in the surveys it varies all over the place, the important point being that if you look at women with varicose veins in epidemiologic surveys as shown earlier, they amount to anywhere from 50 to 60 percent, but when we look at treatment categories for women they are more like 70 percent, so there's a disproportionate number of women treated in relationship to men, which poses the question, why don't men seek treatment?

Finally, race ethnicity, the San Diego study is the only one U.S. based that addresses this subject, but they disproportionately selected a greater percent of minorities. I might point out that current insurance claims do not accurately capture this factor, wide insurance databases do not correctly report this factor, and indeed, the Medicare database uses Social Security Administration data to define race, so it's a very significant gap.

In the San Diego study it showed that predominantly non-Hispanic whites and was evenly divided among other racial populations. They did show, as demonstrated earlier, less common severe disease in African-American women.

I put this slide mainly to show that the VQI Registry does capture this data. So I conclude, varicose veins increase with age, treatment rate reflective. Varicose veins are more common in women, treatment rate higher for women. And finally, a huge information gap on the epidemiology and disparities for race and ethnicity, which we hope will be taken care of. Thank you.

DR. REDBERG: Thank you, Dr. O'Donnell. Next is Dr. Brajesh Lal, who is a professor of surgery in the Division of Vascular Surgery at the University of Maryland School of Medicine, and he's representing the Society for Vascular Surgery and the American Venous Forum.

DR. LAL: Good morning, and thank you for the opportunity. I have these disclosures.

The topic I'll be talking about is one of my favorites, how CMS can help us in collecting information that can help fill some of the gaps in knowledge of the important topics that have been presented throughout the prior morning.

Implicit in the assurance of reimbursement for health care delivery for Medicare beneficiaries is the assurance that treatment will be delivered according to established standards of care. And standards of care, of course, can be established when there is Level 1 available, and in the absence of Level 1 data, that's when guidelines based on expert opinions come into play.

The Society For Vascular Surgery and

the American Venous Forum have over the years jointly, and sometimes separately, published multiple guidelines, several of which have been quoted by the prior speakers. Imperfect but telling data suggests that not all the guidelines are being utilized or implemented uniformly across the country.

So in order to address some of these issues related to absence or gaps in knowledge, as well as the inability to implement established guidelines, the American Venous Registry was the country's first attempt to collect real world data. Important conclusions from that registry which mandated a standardized way of diagnosing and classifying varicose veins was that over 15 percent of patients had less than C2 disease that was being treated, more than 30 percent of patients had not been treated with compression stockings prior to treatment, and a large proportion did not receive compression stockings after treatment.

And in the absence of a mandate, of course, the American Venous Registry was not implemented and adopted across the entire

country, and there are of course hundreds of centers that are performing varicose vein procedures. And so, the AVR joined hands with the Society for Vascular Surgery VQI Initiative and subsequent to that the AVR and the VQI together have now data on over 13,000 procedures and we are increasingly encouraging participating centers to implement uniform ways of diagnosing, treating, and then following the results of their interventions so that there can be local, regional as well as national level interpretations drawn. So, we hope to introduce a venous stenting module and it will, again, follow similar outlines as the varicose vein module.

So, how can we encourage data collection? There are various ways in which CMS can help with this effort. One of them is, I would go so far as to say, there must be some linkage of reimbursement to an expectation to have standardized data collection. Two such models already exist in which CMS has actively participated. The first is CMS's support for the CREST-2 randomized control trial which is a national trial, and its companion registry,

where patients that don't qualify for the trial can still receive reimbursement for procedures provided they participate in an intensive data collection and data monitoring program in a registry.

And the same kind of experience, again, a similar coalition between CMS, academic societies and industry to form a registry that monitors and measures indications and outcomes for aortic valve replacement percutaneous. So those are several of our recommendations from SVS and AVF. Thank you for your attention.

DR. REDBERG: Thank you, Dr. Lal. Next is Dr. Suman Rathbun, who's a professor of medicine and director of vascular medicine at the University of Oklahoma Health Center.

DR. RATHBUN: Good morning. On behalf of the Society for Vascular Medicine and our nine-member venous care coalition representing more than a hundred thousand physician membership, and who are the majority of providers of venous disease, or that care for venous patients, I'm happy to review the burden of venous disease both to the patient and to

society.

As you know, chronic venous disease is common, it's more common than arterial disease, there's an estimated 25 million patients that are affected with this, six million with advanced disease. And specific to the Medicare population, almost three-quarters of women as well as nearly half of men will be affected with systematic venous disease. Importantly, chronic venous disease is much more prevalent than arterial disease. In this Davis study that only looked at venous reflux it was twice as common as coronary artery disease, but it's been estimated as five times more common if you include DVT and postthrombotic syndrome.

The presentation of chronic venous disease is variable. This is a pictorial not from the Internet but from my own practice at an inner city teaching hospital. We have the woman with a medial thigh complex; the college student who has congenital venous disease but can't hold a job because of pain and swelling; the patient who's 65 that has been fighting recurring ulcers; and finally, the institutionalized patient I followed several

weeks ago that has no access to either conservative or interventional care, that has been suffering with venous ulcers for five years.

Chronic venous disease causes significant mortality. We know that is, or morbidity, it is a very progressive disease; over five to six years, patients will progress to ulcers and a lower quality of life. We know patients with DVT, many will develop postthrombotic syndrome, many have skin changes, and we know the majority of ulcers that we treat in this country are due to venous etiology resulting in early retirement at peak earning potential, as well as lost work days.

Luckily, we now have good diagnostic tools to identify the typical signs and symptoms, and these have been incorporated into validated scores where we can rate both our treatment effectiveness as well as severity, but unless we identify these patients early, many will develop venous wounds.

This prospective data is some of the best, it was provided by an alliance of wound care stakeholders that represents over 19,000

patients, 2,000 providers, and 110 wound care centers. This shows that patients suffer for five months before they present to a wound care center, that it may take more than three months of treatment, 21 percent never heal, and more than 30 percent will have recurrent ulcers. This causes significant morbidity in terms of depression, time away from work, and pain. We know that patients have undiagnosed depression, as well as those with postthrombotic syndrome have impaired quality of life related to this disease.

These are specific prospective questions that were specifically asked to the venous ulcer patients. A majority complained of loss of sleep, being unhappy, affected their leisure time, as well as their financial situation. So what is not in debate today is that venous disease carries a heavy burden both to the individual patient as well as to society. What you will hear today, though, is opportunity for research for effective treatments, and the next five presentations will directly address the five MedCAC questions from my colleagues at the coalition. Thank

you.

DR. REDBERG: Thank you, Dr. Rathbun. Next is Dr. Mark Meissner, professor of surgery at the University of Washington School of Medicine.

DR. MEISSNER: Good morning. I represent the Venous Care Coalition, the American College of Phlebology, and am specifically going to address question two, but I'm going to veer a little bit from it because this was already expertly done by Dr. Peter Gloviczki before. I'm specifically going to talk about the hemodynamics effect of venous reflux which may either be primary, which is primarily degeneration of the vein wall, or venous postthrombotic changes, and in either event results in ambulatory venous hypertension with either symptoms of pain, swelling and skin change, which is a sign, or venous ulceration.

And where I really want to veer from this is, we've heard a lot of evidence today, but really what's important in this is the outcomes that are important to the patient and there are only two, that's quality of life and ulcer-free interval. These other outcomes,

talking about hemodynamics improvement, CEAP score, which is an evaluated instrument, not an outcome, and VCSS which has been presented several times as a collection of signs, it's not, it's a collection of symptoms that are observed by a physician, not by the patient. None of these are patient important outcomes, it's strictly quality of life, this is a quality of life disease and that's what we need to look at.

And the treatment of this is largely based on either conservative methods which are anchored by compression or superficial venous interventions, and as we've heard in every speaker today, these all have good outcomes which are very similar, and there's not much to recommend one versus the other. And the data supporting compression is marginal. I mean, it's two systematic reviews; neither one of them concluded that there was enough evidence to validate the use of compression in C2 to C4 disease, but what's really important is none of these studies actually looked at quality of life as an outcome, they looked at other things.

And this is a true evidence gap and something I think we need to get across in our studies on this area, is we need to be looking at quality of life, not VCSS, not hemodynamic improvement, don't lose the trees for the forest, which is what we do with all of this evidence looking at non-patient important outcomes.

In contrast, the evidence supporting intervention is very robust from that. We've heard several times about the Michaels trial, which randomized 246 patients to either standard compression or to intervention, and not only was there a significant improvement in virtually every symptom as shown in the right-hand panel, but there was a significant improvement in quality of life, and this is a very cost effective intervention. When you look at many things that are covered by Medicare, in the U.K. this was about 4,000 pounds per quality adjusted life year. It improves quality of life and it is very cost effective.

This is similarly shown in this randomized trial from Sell, which shows

significant improvement in disease-specific Aberdeen Varicose Vein Score both at one and two years. Robust data with patient important outcomes, that's what we need to make our decisions based on.

The evidence supporting compression for ulceration is far better. The data is heterogeneous enough to prevent pooled outcome, but you see of the six trials comparing compression to no compression, they all are consistent in showing a benefit which is statistically significant in four of six of these areas.

Similarly for surgery, the patient important outcome of ulcer-free interval, surgery is very effective. I'll move on to the next slide which is actually the surgery slide. Although compression does reduce recurrence to about 28 percent at 12 months, surgery plus compression reduces that to about 12 percent.

Patient important outcomes, it is important, which is why virtually every major society in both the U.S. and in Europe has recommended interventions as the primary treatment in patients who are appropriate

candidates. It improves quality of life, it improves ulcer-free interval, the outcomes that are important to patients. Thank you very much.

DR. REDBERG: Thank you, Dr. Meissner. Next is Dr. Suresh Vedantham, who is the president elect of the Society of Interventional Radiology and a professor of radiology and surgery at the Mallinckrodt Institute of Radiology at Washington University in St. Louis.

DR. VEDANTHAM: Thank you very much, it's a pleasure to be here, and I'll talk on behalf of the Venous Care Coalition here. My disclosures are here, nothing to me, but grant support from NIH and a number of companies.

So one important point, I'm going to kind of skim over some of the slides that have been covered by others, but I think that one study that was performed in the late 2000 first decade by Dr. Susan Kahn and colleagues, looking at, it was called the BICO study, it was a prospective registry, 387 patients, followed with an acute DVT, and 40 percent developed a postthrombotic syndrome. They also

evaluated venous disease specific and general quality of life in that patient population and importantly, they looked at different factors that predicted poor quality of life. The development of a postthrombotic syndrome was the number one factor in predicting a DVT patient's quality of life at two years followup.

I think that's very important because right now the study of DVT treatments is mainly focused on preventing recurring DVT, which is crucially important of course. On the other hand, whether or not a patient got a recurring DVT did not correlate with their quality of life at two years; what did was postthrombotic syndrome and in fact, the degree of impairment in PTS paralleled the degree of quality of life improvement.

It's been appreciated in recent years that venous obstruction results in a worse phenotype for patients both in anticoagulation studies, in studies of catheter directed thrombolysis, and other methods to remove clot in DVT patients. It's very clear that in the long run, if you have an open vein you're

likely to do better. I'm going to summarize, and that has led to more use, I think, in terms of venous stenting and angioplasty even in the chronic phase.

There have been some systematic meta-analyses of the case series that have been reported that suggest that stents improve pain, they improve swelling, and they result in healing of venous ulcers. Again, most of this is non-control studies without a control group, as the panel's aware.

There has been one recent well performed Dutch prospective cohort study, again demonstrating improved quality of life with use of stenting for people with an occluded iliac vein who have severe postthrombotic syndrome.

And also another comparison I should mention, a randomized trial that did compare standard therapy versus standard therapy plus stenting, and found significant improvement in pain, postthrombotic syndrome and quality of life in those patients during followup.

I'll mention that there have been a number of published practice guidelines including physicians that are involved in doing

procedures and those that don't, that all suggest the use of these procedures for people with severely symptomatic disease and iliac vein obstruction.

I want to mention the ATTRACT trial, it's an NIH sponsored multicenter randomized trial looking at the use of clot removal therapy in the acute phase. The results of this trial which has enrolled 692 patients will be available in March 2017 and will really provide strong guidance in terms of does opening a vein result in reduction of the postthrombotic syndrome, but we're also looking at venous disease specific and general quality of life in the long run.

In addition we are proposing, the same network that developed the ATTRACT trial, the C-TRACT trial, which is a multicenter randomized clinical trial comparing the use of endovascular therapy along with sort of standard usual noninvasive therapy versus standard usual noninvasive therapy alone for the management of patients with moderate to severe postthrombotic syndrome. And again, that's going to be a randomized multicenter

trial that really seeks to develop the evidence bases that we all know we sorely lack.

We appreciate that we won't have trials of 2,000 or 3,000 patients for this type of comparison. On the other hand, I think that well performed randomized trials of medium size supplemented by registry data can really go a long way towards alleviating our concerns about how best to treat patients with these disorders.

So I think PTS is important, practice evolution has been driven by more awareness of that, and we're going to be getting data from large collaborative randomized trials, that's coming soon, so thank you.

DR. REDBERG: Thank you, Dr. Vedantham. Next is Dr. Gregory Piazza, with the Cardiovascular Medicine Division at Brigham and Women's Hospital.

DR. PIAZZA: Thank you very much for the opportunity to lend a perspective on disparities in chronic venous disease treatments. I'm representing the American College of Cardiology in this coalition. Are my slides up? Here we go, thank you.

Disparities in the treatment of chronic venous disease exist for age, gender, race and specific therapeutic modalities. These disparities have the potential to negatively impact the outcomes of Medicare beneficiaries as well as health care costs.

Age represents one of the most important disparities. While the burden of disease and particular venous ulcers weighs most heavily on the elderly, access to chronic venous disease therapies is greater for the young. Furthermore, evaluation of the root cause of chronic venous disease, whether it's obstruction or venous reflux, is less likely to be undertaken in the elderly. The impact of this is that treatment of chronic venous disease in the elderly is often skewed towards treating the more advanced stages of disease such as venous ulceration, rather than addressing earlier stages based on pathophysiology.

There's an important gender disparity as well. Women are more often likely to present with earlier stage, C1 to C3 chronic venous disease, and more limiting symptoms than

men, and the impact of this is that there's a failure to treat earlier stage chronic venous disease that can result in a substantial systematic burden that's untreated, and then more rapid disease progression. We can see here a patient on the top with relatively mild venous varicosity, and then a patient with more severe venous varicosity that keeps her from going to work.

There's an important racial disparity. An analysis of the Nationwide Inpatient Sample demonstrated that African-American patients presented with more advanced chronic venous disease and were more likely to require later stage therapies, including ulcer debridement. The end result is the failure to recognize and treat earlier stage disease in African-Americans, resulting in greater severity at presentation and need for more costly treatment modalities. This is an example of a patient who for many years had very mild venous varicosity, but by the time she was referred to a venous specialist she had this massive varicose vein that required more advanced therapy.

There is an important treatment paradox to mention. While health care costs associated with treating the end stage of chronic venous disease, namely ulcers, far exceeds that for treating earlier stages, coverage is more consistent for end stage therapies like debridement and skin grafting. The impact of this is that patients progress to more advanced stage chronic venous disease before treatment's initiated, and the resultant health care costs and disability are greater.

There's a disparity when it comes to compression therapy. Compression therapy is evidence based as a recommendation for C2 to C6 chronic venous disease, but coverage is inconsistent among Medicare beneficiaries. The result is a greater proportion of the cost ends up falling on the elderly who cannot afford to pay for compression therapy out of pocket, and therefore, a therapy for chronic venous disease from early to the late stages often doesn't meet the standard of care in our elderly patients.

Finally, there's a disparity between guidelines and coverage. Evidence-based

clinical practice recommendations and multi-society sponsored accreditation guidelines have not been incorporated into coverage policies for Medicare beneficiaries. The end result is that coverage policies are not evidence based, and therefore access to treatments for chronic venous disease deviates from the standard of care. Thank you.

DR. REDBERG: Thank you, Dr. Piazza. Next is Dr. Joshua Beckman, who's the director of the Section of Vascular Medicine at Vanderbilt University and chair of the PVD Council for the American Heart Association.

DR. BECKMAN: Good morning. My name is Josh Beckman and I'm here on behalf of the American Heart Association, an organization that represents 30 million physicians, employees and volunteers. I will be discussing the evidence gaps in venous disease. Here are my disclosures, none are related to venous disease.

There are a tremendous number of evidence gaps basically along the entire spectrum of venous disease, running from epidemiology to how we actually figure out who

has the disease to the best methods, and then the translation to the community, the primary care community for whom on a board examination that lasts ten hours, there may be a single question about this disease process.

I'm going to list a bunch of evidence gaps, I think basically there is an evidence gap in this entire field and I'll just mention a couple, the others are listed here. For example, the incidence of superficial venous insufficiency ranges from one to 74 percent in women and two to 56 percent in men; this is not data.

Evidence gaps in medical therapy. What is the value of antiinflammatory agents in wall remodeling and valve failure? How about venoactive medications, all those herbal supplements that my patients take when they come into the office? There is very little information about all of these treatments.

How about invasive therapy? You've heard today a large number of reviews of different components of evidence but really, I think most of the data comes from relatively small trials compared to the other vascular

diseases with which we commonly deal. You can see here, for example, a simple question on the role of invasive therapy in patients with combined, arterial, occlusive and venous disease; we heard not one piece of evidence about this today and it's a very complex problem to deal with.

But I think the real key to this question is why we are here, and I think this publication in the New York Times was what raised the flag that this is now becoming an important issue. It's important to understand that venous disease and chronic venous disease is a relatively young field, because the minimally invasive technologies that are now used in a routine way to treat these patients really developed only in 1999 to 2000, so we are talking about a 15-year history of a disease process. And if you take a look at the literature base and you PubMed chronic venous insufficiency, peripheral artery disease and myocardial infarction, you can see the great disparity in information that's available, and in fact it is this problem that really sparks why we're here today.

This number may seem impressive, but you heard from Dr. Rathbun that there are five times as many patients with venous disease as arterial disease, and it should not be surprising that there are more interventions in patients with venous disease. The development of these technologies has not only made the physician community aware but it's made the patient community aware that there may be ways to make them feel better and they have previously been ignored.

So I think that there's been a joint interest in trying to figure out how to try to take care of patients with venous disease, it has not been driven by one side or the other. But what is clear to me is that this evidence base, even though it's growing over the last ten years, is really inadequate, it's dramatically inadequate. And we need to do something so we don't have to wait the 25 years to get to where we are in coronary disease and the 20 years for where we are in peripheral disease to understand what's happening now.

So, in summary, this field, the field of acute and chronic venous disease is rife

with evidence gaps in every area that's important. To list them all would take my entire time. I agree that we need to standardize endpoints so we can begin to gather information, and I think the acquisition of data is the most important thing that CMS can push along. And my colleague Dr. Lyden, who follows me, is going to tell you ways in which you can help the process of data gathering. Thank you for your attention.

DR. REDBERG: Thank you, Dr. Beckman. Next is Dr. Sean Lyden, who's chairman of vascular surgery at the Cleveland Clinic, and he's representing VIVA Physicians.

DR. LYDEN: Thank you very much. As noted, I represent VIVA Physicians and I'm going to talk about how Medicare or CMS can help us to attain these knowledge gaps. So here are my disclosures.

We clearly have heard all day today we need new approaches. Our understanding is in its infancy and really we need novel data sources to advance the field, and I think CMS can use their newly acquired capabilities to spur those novel methods for data acquisition.

Really the first thing I think they need to do and they've been challenged here, is understand variations of local coverage determinations. Some patients don't need compression, some need two months, some need three months, so we're not all studying the same population.

They've already used incentives and mandates to spur what we do, and I'll talk about those in a second, but they can use those to feed data into patient registries, they can push EMRs to create discrete data fields that can allow connection to registries in a much simpler fashion, and then creation or support of open mega databases, and then really working with physician coalitions such as the Venous Care Partnership to help define variables, study outcomes and improve quality of life.

Those two mechanisms are the American Recovery and Reinvestment Act of 2009 and the MACRA Act of 2015, and I think specifically, the MIPS system helps us achieve some of that. MIPS asks us to look at quality, resource use, clinical practice improvement and regional use of EHRs. And MIPS eligible professionals are

physicians, but also groups of physicians and virtual groups, and I submit that the people here today in this audience, as well as the Venous Care Partnership, fit these definitions.

MACRA asks you to look at your local coverage determinations on how and when to cover venous disease, and there are variations within the Medicare jurisdiction of how and when they cover disease, and I think Medicare beneficiaries should all expect the same coverage throughout the United States.

How can they help us increase our data collection? It will allow us to address the questions of epidemiology in outcomes. As we heard today venous disease is a broad population, both in chronic venous insufficiency, deep venous insufficiency, reflux with or without varicose veins, as well as deep venous thrombosis. As we've seen here today, it's covered by multiple physicians, multiple specialties, but the need for registry data can help make that happen, and virtual groups feeding to registries can be paid for under MIPS.

Venous registries as we've heard

today, there were three examples that were talked about earlier that I won't highlight, but there's data variables that are not standard across registries, there's some overlap between the registries but there's large gaps, there's no perfect registry. But unfortunately if you really look today, we have nurses sitting there trying to collect those data and there's no EMR interface into those registries, and that's where CMS can help us.

Through the use of the American Recovery and Reinvestment Act, we as physicians have all been made to use EMRs and we've all found the good and bad of it. However, EMRs in the hospital-based system is really focused on coding and billing, the outpatient systems don't talk to the inpatient systems, and our incentives clearly are not aligned. Through these new mechanisms, CMS can actually push systems to talk and interact, they can allow the capture of discrete data to be put in EMRs. That discrete data then could be pushed electronically without interface directly into registries and allow the creation of open mega database files. That will accelerate

infinitesimally the ability to study and collect data, and you can have a data that dwarfs everything seen in every presentation before now within one year. And I think really that we need to work with those physician groups and the partnerships to help define what data needs collected, what those discrete data fields should be.

So in summary, I think CMS now actually has laws to help push the field for us. They can eliminate variations in local coverage, they can use incentives and mandates as they have already to allow EMRs to have common discrete data fields. Those can feed into registries. Those registries will allow us to first study and understand these disease processes and if you have open mega databases, we can actually learn it a lot quicker. And I think really, we need to work with these physician coalitions to study those variables and to find what outcomes will improve patients' quality of life to prove what's reasonable and necessary. Thank you.

DR. REDBERG: Thank you, Dr. Lyden. Next is Dr. Mark Turco, who's the medical

director of aortic and peripheral vascular at Medtronic.

DR. TURCO: Thank you, and I'm pleased to be here today to present, Dr. Redberg, and on behalf of five medical device manufacturers, Medtronic, Vascular Insights, AngioDynamics, Boston Scientific and Bard, we worked under the auspices of AdvaMed to develop this presentation today.

I am a Medtronic employee and thus a shareholder.

I'm going to focus exclusively on question one this morning regarding on the evidence of intervascular treatments for symptomatic chronic venous insufficiency. The disease state has already been well covered, and I think it's important to understand and emphasize the incidence and prevalence of this disease, yet the under penetration of treatment with this particular disease. My time is going to focus on three key areas.

First, the evolution that has occurred in the treatment of venous insufficiency through painful stripping to endovascular treatment, and the data which supports this.

Second, the results of commissioned independent review on the endovascular treatments for systematic chronic venous insufficiency following the AHRQ criteria. And third, while we acknowledge the field has evidence gaps and heterogeneity of trials, we would like to highlight industry's commitment to continued efforts to further strengthen the evidence base.

The disease state has already been well covered so I'm going to skip through that.

I want to take a second to emphasize what we have from the standpoint of guidelines while we wait for continued evidence generation, and as was previously indicated by Dr. Beckman and others, this is a very immature field from the standpoint of evidence base, and it's a very immature field from its age, only really starting treatments for chronic venous insufficiency in the year of 1999 and 2000.

These are the societal recommendations along with commercial and global coverage policies, which include conservative treatment, guide appropriate patient care.

So here are the results of the

independent review that we commissioned with the other industry partners in this coalition. We commissioned a review that mirrored the AHRQ's original criteria. We found 126 studies that were analyzed with a study duration of one week to ten years, and a mean age of 18 to 79 years. We found that there were 67 randomized control trials, 40 observational studies and 19 systemic reviews.

When we look at the 40 observational studies, this is where we actually found a difference in the counts within the AHRQ report. As was previously identified by Dr. Jones, due to work load constraints, only observational studies with 500 patients or more were included. Within our study, I would suggest that observational studies, that within our study there were over 20 studies with at least a hundred subjects in these observational studies that were not evaluated in the AHRQ report that we feel are important studies and should be included in the evidence, as they speak to the durability of treatment of chronic venous insufficiency.

There were 67 publications of

randomized control trials. Of those, 28 were followed for greater than one year.

DR. REDBERG: Time to wrap up.

DR. TURCO: Similar to AHRQ, the long-term evidence of our review is supportive of the fact that endovascular therapy showed no difference in outcomes.

So in conclusion, if we look at our industry coalition there are more than 900 patients enrolled. We have seen a natural evolution in the field, these are, there are current guidelines that provide --

DR. REDBERG: Thank you, Dr. Turco.

DR. TURCO: Thank you.

DR. REDBERG: Next is Dr. Mark Garcia, from EndoVascular Consultants.

DR. GARCIA: Thank you for the opportunity to speak here today. I'm going to be focusing more on the postthrombotic chronic venous obstruction and where we are.

These are my disclosures and I would note, I am the study PI for the ACCESS PTS study.

So, we know that there is prevalence problems, right? That's been well stated

today. One of the biggest risks for PTS is recurring lateral DVT and it's very costly, as you can see, up to $70 billion in its whole entirety, much of which can be preventable.

The importance of early diagnosis and treatment to the progression of acute to chronic DVT is well known, and the current standard of care oftentimes is not enough, patients are told there's nothing that can be done with their chronic DVT. Well, if you look at it, the rationale for intervention would be that the severity of their postthrombotic syndrome is related to the degree of ambulatory venous pressure so therefore, reducing the venous hypertension should reduce the signs and symptoms.

As you heard earlier, endovascular treatments for DVT with central venous obstruction have already been recommended by multiple societies. We did an independent review for the evidence of endovascular therapies on chronic venous thrombosis and obstruction which mirrored AHRQ's inclusion criteria. And out of that we had 3,000 search results, but only one that actually showed a

randomized control study which is on iliac venous stenting, but there was nothing on endovascular interventions for chronic DVT. Long-term outcomes concerning that one study was on stenting for the iliac venous obstruction and when you look at the study group, the test group compared to control group, there were significant higher gained patency, one-year cumulative patency rates, as well as significant improvement in the post obstructive quality of life, the postoperative quality of life.

There were a couple of other studies that we're mentioning here. One that I do want to point out was our review that just came out actually this week, so I couldn't put on here, on the PEARL registry. It was a real world registry on acute DVT primarily. However, we did a sub-analysis on the CMS Medicare population and of that we pulled the chronic DVT patients that were treated, and found that 94 percent showed venographic improvement, 74 percent showed freedom from deep thrombosis, and quality of life measures actually showed a significant improvement in those that had

physical components.

There are two studies coming out this year. The ATTRACT trial which you heard about is the acute DVT study. There are three venous stenting studies that are going to be out in the next three to four years. The ACCESS PTS is a chronic DVT study that will be a prospective multicenter study on 200 patients looking at the improvement of postthrombotic syndrome in patients who have had a minimum of three months of standard of care therapy, and here are the three stent trials also. And this is just highlighting the ACCESS PTS study, again, which is really looking at chronic DVT postthrombotic syndrome and improvement with intervention.

So what's missing? Well, we obviously have seen today, good level 1A data demonstrating and confirming the benefits of intervening on chronic DVT as well as central venous stenting. And the key takeaway here, we know this whole population is very prevalent, it causes poor quality of life and lifestyle limitations. Endovascular therapy has generated clinical and quality of life

improvements for patients with DVT and venous obstruction. There is a need for good level one, excuse me, grade 1 level A data, so some of this is forthcoming with ATTRACT but we encourage support and collaboration with CMS, NIH, industry, as well as the medical providers in providing this data, and industry continues to support the progress of evidence-based medicine that will further strengthen the evidence, improve quality of care delivered to DVT and venous obstruction patients while enhancing innovation for improved patient outcomes. Thank you.

DR. REDBERG: Thank you, Dr. Garcia. Next is Dr. Gary Gibbons, who's the medical director at South Shore Hospital Center for Wound Healing, and a board member of the Association for the Advancement of Wound Care.

DR. GIBBONS: So, good morning, everyone. I'm also a vascular surgeon, I am a member of SVS, and this morning what I want to do is address the downstream effects of a disturbed venous anatomy and physiology, i.e., the venous ulcer population.

So, in a study that I participated in

over a year ago, what we have found is that these are sick patients. It's very rare to have a pure venous ulceration anymore. These people have hypertension, edema, 35 percent of the patients have diabetes, 25 percent of the patients have some type of arthritis, so it's a mixed model. 82 percent of patients had a previous venous ulcer and 56 percent of patients were recurring ulcers, and this is similar to other wound registry data.

I'm going to skip through some of the, what previous speakers had, but we know these are hard to heal wounds, their size directly correlates with their ability to heal, and by the time someone in a wound center sees these patients, some of these wounds can be greater than 12 centimeters and present for one to two years.

High recurrence rates, significant comorbidities. Previous speakers talking about quality of life, some of these have quality of life scores, low scores that correlated with some of the current cancers that we see out there.

What I really want to address, though,

is yes, there are disparities in patient populations, but there is also disparities in the prevention and treatment plans by various specialties, the treatment is fragmented, it's siloed, and one thing we really need to do is incorporate specialists that really know about wound care, we've heard very little about wound care this morning, and the duration of the ulcers, the work that's going to be involved, is it associated with PAD, what is going on with that ulcer, evaluate that potential, the nutrition, the comorbidities, and then what adjunctive therapy is going to be needed. We found that the discordance of treatments out there in the, in one trial, only 35 percent of patients were debrided 12 months prior to initiation of the trial. Compression therapy is widely variable. The access and delivery of interventional therapy is varied as well.

What we would propose as really what we need to do is come up with a unified set of guidelines, evidence based, that we can all agree to, and then hopefully with your help at CMS and other payers, is come up with coverage policies that are adopted towards healing those

patients, and really for those treating physicians that are following those guidelines. Thank you very much.

DR. REDBERG: Thank you, Dr. Gibbons. Next is Dr. Eric Lullove. He's the medical director of the West Boca Center for Wound Healing and a board member of the Association for the Advancement of Wound Care.

DR. LULLOVE: Good morning. I'd like to thank the panel for the time this morning. I'm going to quickly go through these, these are my disclosure slides.

So, today I'm going to be talking about -- there's been a lot of talk about compression evidence, it has been expertly discussed earlier so I will skip through that portion.

The biggest thing that we haven't heard today is about tissue perfusion, we're accepting these patients prior to these interventional therapies or even compression therapy. It is still a major point that we still have to assess these patients from a vascular and an AVI standpoint prior to initiation of therapy to ensure that these

patients will heal.

So one of the other things that we need to address is the fact that compression has the 1A evidence for preliminary therapy for C1 through C3, as well as exercise training, and these patients need to learn how to re-walk themselves again.

One of the things that Dr. Gibbons addressed was that the lack of compression therapy across centers was only 17 percent of physicians looked at compressing patients adequately on their first visit, and this was data extracted from the U.S. Registry on Wound Care. Again, patients present to multiple specialties, it is siloed, it is fragmented and we need to improve this. One of the other things is that there's nonadherence to the venous ulcer guidelines as proposed by all the clinical organizations and we do need to speak with one voice, and that's what CMS can help us out with.

With respect to question one, again, exercise assessment and education in a structured program is imperative, as well as arterial testing. We also need to address

nutrition and weight loss programs.

And with respect to question three, there is currently no evidence, or there's -- one of the biggest gaps, excuse me, is that there is no Medicare coverage for compression therapy for these patients posttreatment or pretreatment, and one of the things we need to understand is that 35 percent of these venous patients have diabetes and that 10 percent of those patients with venous ulcers have PAD. One of the biggest gaps is the fact that we treat our diabetic patients better than our venous patients. Diabetic patients get approval for therapeutic footwear and protective offloading garments, and our venous patients get nothing.

So, again, one of the other things is that physical therapy is not covered for walking exercises, it's not part of the program.

So again, in addition to continuing to question three, the wound care specialist is not engaged at any level. We need to engage the wound care specialist so that there is a continuity of care for these patients post and

pretreatment.

And again, we have to agree on common guidelines from the AAWC, the AVF, the SVS and the Wound Healing Society which would make things a lot easier for everybody with a unified set of ideas and ways to treat these patients.

Again, another gap is that when we talk about MACRA laws there are no data sets that track venous leg ulcers in any MACRA laws. You're going to ask us to treat these patients with no way of tracking it. So one of the recommendations to CMS is to at least delay MACRA or include a venous ulcer registry so that we can track it so you can see what we're doing.

Again, ways to help us out is to require wound care specialist evaluation at the earliest indication of chronic venous disease, help us develop data from these different registries, and allow the databases to compare the impact of pre and post education on it, as well as a wound care specialist involvement.

And again, in conclusion, allow these beneficiaries to get access to the services,

the devices, the therapies, the interventions, as well as the education that can help manage their disease better, to save the limbs, heal the ulcers, and reduce recurrence. Thank you very much for your time.

DR. REDBERG: Thank you, Dr. Lullove. Next is Dr. R. Daniel Davis, president of the American Podiatric Medical Association.

DR. DAVIS: I want to thank you for the opportunity of presenting to you this morning some of the updates from APMA. We represent 80 percent of practicing podiatric physicians within the United States. And I know that we've hit, my disclosure slide shows you that APMA does not have a direct conflict with what I'm going to present this morning.

The venous leg ulcer is something we see as part of a wound care team, and we are a team. Everyone in this room would not be here if it was not a goal to heal these patients and keep them healed. We recognize the fact if we look at all the good things that we have here, we recognize, again, five times more common than arterial ulceration, 15 percent never heal. 15 percent.

The question here is, are people doing appropriate biopsies of these lesions? We've looked at and we've had patients come in 30 years of duration without a biopsy, for heaven's sake. We've got to look and say what else are we missing here, and we need to look at that.

Annual costs, $5 billion, and we just looked at Dr. Lullove, who mentioned that we have no coverage for probably the mainstay foundation of compression therapy. These patients don't have two nickels to rub together, and we're asking them to put on these stockings day after day. And yet, we don't address also the fact that many of our patients belong to the NCAA, the Noncompliant Association of America. They don't wear their stockings. They're not comfortable to put these stockings on. If they're not comfortable today, they take them off, and what do we do? We advance this particular option again, it continues again and again and again. We have to take this into account.

We recognize, again, that all of the complications that we have here, between the

pain, and all the good things in here, we look to try to make sure that we, A, heal these patients as fast as we can, prevent the hospitalizations, the costly time and duration that they're going to have these. We want to save that limb; many of them are limb-threatening and if we save that limb, we save their life.

We are looking, again, team approach, there's no question about it, we work together to heal these patients. The conservative care, we recognize again compression stockings, maintenance care is compression therapy, but we recognize, again, quality of life. How many women are going to wear these wonderful dressings and all these compression stockings out to the shore? Are they going to go to a really nice function wearing a dress with these? We're not going to see that. Quality of life issues cost this country billions of dollars.

We recognize, again, that advanced care for biologics makes a difference. We recognize the fact that there are several studies between the Balanga study, O'Donnell,

Vassar, who quoted SVS and IVF people, the experts, that recognize the fact that these patients have biologics available to them and we are waiting too long to use them. We can heal these patients, literally a 60 percent closure rate that these studies have shown time and time again between Jones, O'Donnell, Balanga, Marcand, study after study showing that the use of biologics can heal these patients much much faster and more effectively and, again, recognizing that with this kind of therapy with compression, we heal them even faster. We know, again, we recognize the algorithm, we need to follow it. I would challenge the fact that we need to use biologics, perhaps a little bit sooner.

Needs. We recognize the fact that research is something we need, not just on the treatment of the ulcers, but we need to look again at the compression therapy, of something that allows the patient a little bit more flexibility, not to remove the stocking but perhaps relieve some of the compression as the day goes on.

The APMA has just begun a registry.

We've heard registries being utilized that actually collect that data to fill that evidence base. We have now begun a podiatric specific registry to help collect the evidence to fill those evidence gaps. We recognize the fact that it is a critical part of wound care and again, Eric mentioned that this is something that we would like to see as a measure coming forward, so we could hold ourselves accountable for this treatment.

We look forward to working together. We need this data, we like this forum. Understand that there are therapies that can heal people faster, we can keep them healed, and if we work together, this won't be an issue that we have to come back and visit again. Thank you very much.

DR. REDBERG: Thank you, Dr. Davis. Next is Jim Harmon, vice president of global market access for BTG International.

MR. HARMON: Thank you very much for the opportunity to speak and be a part of this program. I'm a bit intimidated to be up here after the progression of accomplished and respected people that have spoken before me,

but I'd like to kind of walk through a little journey that we've taken at BTG, but it's not a commercial message and I want to make sure that I'm not going to be spending my time for a commercial advancement of our product. But at the end of the day, though, it's all about, what resonates with us, is that this is really a patient centric world that we're in right now, and we've gone down the journey with our products and our development of products which really makes relief of symptoms a new way of looking at the treatment of venous insufficiency.

My disclosures, I am an employee of BTG and I certainly have a financial association with the company.

We've been through this slide already and everybody's seen these things. I think one of the big points here, just to reiterate, is that 33 percent of the patients experience clinical worsening within six months, and these people do progress, but it's also a matter of looking at how they feel about their disease and how they feel they're being treated, and as we all know, this is a future stake in terms of

the measures associated with treatment.

So we know that, we've heard that patients seek treatment because of symptoms more than appearance. We also know that this is a provocative, that vein closure is a surrogate outcome, it's not a clinical endpoint, but this is a point that was made very very clear to us because it only measures technical success and it fails to capture and may not correlate with patient benefits, and we've heard about patient benefits here from other speakers this morning. The closure may not be an evidence of symptom relief, and resolution of symptoms independent of closure can be considered to be a successful clinical outcome.

So when we went forward with the development of our product, we learned very quickly from the FDA that they actually required patient reported outcomes as a primary endpoint, and that was a revelation to us. So we then set about developing a patient reported VVSymQ tool, it's called VVSymQ, trademarked by our company, developed by our company. It's a symptom scoring instrument which is the primary

endpoint in studies done in collaboration of its development, so the primary endpoint I'll show you momentarily, which was related to patient reported outcomes as measured by these studies and required by the FDA. So it did satisfy the FDA requirements of endpoints that demonstrate clinical evidence by function.

Again, the evidence to support treatment is what we're talking about here today and we hope and believe as a company and as a member of the community who care about these patients, physicians, clinicians, researchers, CMS, payers, everyone together that we can collaborate to make this, I think to another level later on perhaps, another way of looking at these patients and diagnosing and treating them, screening in or screening out patients who are symptomatic or not relative to cosmetics.

But we came to market with an NDA, drug application, which is the only drug in this space we're speaking about, venous insufficiency. 1,333 patients were enrolled in our clinical research program and again, closure as a measure of outcome was deemed

insufficient by the FDA, so it went down as insufficient. So they drove us to measure patient reported symptom relief as a primary endpoint and I'll show that momentarily.

I'm going to go through the rest of this slide pretty quickly, but with the VANISH-1 and VANISH-2 trials, they were pivotal trials. I won't go through this all, this is in the record and on the website, and it's in an array of publications that we've collected and submitted as well.

Two trials, 519 patients looking at patient reported outcomes as the primary endpoint, improvement of symptoms as measured by change in VVSymQ score at week eight and again in a year. This is an example of, this is a schematic of that, and you see the primary of VVSymQ, and of course duplex response is also a tertiary endpoint in our trials.

This just looks at the way the patients reported their symptom relief via the VVSymQ tool. At week eight the score is improved on both sides, on VANISH-1 and VANISH-2. And there's another way of looking at this as well across the different subgroups,

that's CEAP class or any vein diameter, and you can see those vein diameters here as well.

And then this looked at durability. Again, this data is available for anybody who wants to look at it.

At the end of the day for us, the conclusion is that there is a variability between the Medicare contractors within CMS on coverage in terms of the treatment of policies, and we would urge that this data and this gathering, all this information, we're happy to be a participant in that looking at patients as a way to do that going forward, and measuring and implementing these policies. Thank you, everyone.

DR. REDBERG: Thank you. Next is Dr. Caroline Fife, executive director of the U.S. Wound Registry, and she will be our last speaker before one public comment.

DR. FIFE: Thank you. My disclosure is that I am a shareholder in Intellicure. I'll discuss the mechanism by which CMS can support, generate and improve the evidence base.

The U.S. Wound Registry is a 501(c)(3)

nonprofit organization which sponsors the Venous Leg Ulcer Registry. It's a specialty registry for meaningful use and a qualified clinical data registry. We have no funding, no sponsorship, no grants, no specialty society supports us, and physicians have absolutely no incentive to report their data. However, more than 2,000 physicians and 129 hospitals participate. We're successful because we harness the capability of any certified EHR to transmit continuity of care documents, which are rich in the structured data needed for research. Currently we have more than 59,000 venous leg ulcers with exhaustive longitudinal data and outcomes.

Wound data, however, outcomes data is missing from the CCDs, and so to obtain this we have harnessed the structure of electronic clinical quality measures. The U.S. Wound Registry was among the first QCDRs that CMS recognized. In collaboration with the Alliance of U.S. Wound stakeholders, we developed 21 quality measures, seven of which are specific to venous disease. We have also developed our patient reported wound outcomes as a quality

measure as well as wound quality of life as an outcome measure, which physicians can receive credit for under PQRS through the QCDR.

We even developed a risk stratification system in conjunction with the University of Utah, so that physicians can report venous leg ulcer outcomes in relation to the predicted likelihood of wound healing.

We've shown that reporting venous quality measures can improve the quality of venous care by increasing the likelihood of arterial vascular screening as well as venous compression. However, there are huge barriers to quality measure reporting. The biggest barrier is that of the EHR vendors that are unwilling to install electronic clinical quality measures, even when we provide the ECQMs free of charge and open source.

But the next biggest barrier is CMS itself. Physicians have absolutely no incentive to report nonstandard quality measures, there are no PQRS measures, there are no venous measure in PQRS. And under MIPS, physicians are actually going to be indirectly penalized for reporting nonstandard measures.

In fact, you could go so far as to say that PQRS has become the GED of quality. It is a test that anyone can pass and the results of which are essentially meaningless.

CMS can support the generation of an improved evidence base by mandating the reporting of quality measures, seven of which already exist as electronic clinical quality measures within our QCDR. It's possible that in 2018 the Open API Initiative will drive this forward, because our quality measures can be installed as apps inside the hospital EHR, and this may obviate the need for the interfaces which were mentioned previously.

CMS could also support the development of more venous quality measures. Guidelines abound, but there are virtually no quality measures that have been created from these guidelines.

Automated data transmission of quality measures is how we managed to create an enormous venous ulcer registry, improve the quality of care of venous ulcer patients in the absence of any funding whatsoever, and any other type of incentive for physicians to

participate in this project.

DR. REDBERG: Thank you very much, Dr. Fife. I want to thank all of the speakers for their comments, and also for staying on time.

We have one person who has signed up to speak, that's Stephanie Yates, and she is a nurse practitioner at Duke and is representing the Wound Ostomy and Continence Nurses Society, and you have one minute.

MS. YATES: Thank you. I appreciate the opportunity to speak today, and I am one of the members of the Wound Ostomy and Continence Nurses Society with over 5,000 health care professionals, mostly nurses.

We would like to reiterate the fact that, how important compression therapy is, and the advanced coverage of more variety of garments as well as the devices that may assist with applying and using the garments, also with compression pump therapy.

We developed an algorithm to help our members and primary care providers and other people to develop, to be able to choose better the appropriate level of compression. It's

available free on-line at our website www.wocn.org, and it also has guidance to help people in deciding which garments, what level of compression and what other things might be helpful to help our patients to be more compliant, and those would benefit also the Medicare beneficiaries. Thank you.

DR. REDBERG: Thank you so much for your comments.

So we have reached lunch time, and it is 12:49, so we have, we're scheduled for an hour. Why don't we come back at five to one and then we will start with questions to the presenters and then follow with open panel discussion. Thank you.

Oh, yeah, sorry, it's 11:49. We'll come back still at five of one.

(Luncheon recess.)

DR. REDBERG: I'd like to welcome everyone back. Hope you had a good lunch, and we are going to start our session with questions to the presenters, so we will welcome the presenters to the first two rows.

And just to the committee members, I want to remind you for the questions and

particularly for the panel discussion that will follow, even when you're talking to each other, be sure to talk into the microphone because our remarks are being transcribed.

So, I will take the chair's prerogative and start with the questions. I've written down a bunch, I'm just going to start with a few, and then go down the line and then we'll see how much that covers and how much is left, or if there's overlap.

But I particularly did want to get, let's see, in terms of the evidence review, and again, I really appreciate, clearly it was a lot of work to go through all the studies, but what was very striking was that there was a lot of heterogeneity, there was not a lot of kind of -- I mean, first of all it wasn't even clear to me that we were, all the studies were in agreement of what the diagnosis is of chronic venous disease and that we're all talking about the same thing.

And then the other thing that concerned me was it wasn't clear how the diagnostic tests related to patient reported outcomes because you could do a lot of those

diagnostic tests, it seems to me, but not have any difference in patient reported outcomes. I mean, you could measure differences in ultrasound but patients might not feel any differently for it. I wanted to hear a little bit more about how much of that was separated out in those studies.

And then, you know, some of those patient reported outcomes that were reported as being how patients feel, again, didn't seem to me -- I was taught very carefully that symptoms are things patients feel, signs are physical exams. So things like varicose veins would not be something patients feel. The symptoms that seem to be reported with that were things like leg heaviness, itchiness, fatigue. The problem is, those seem very nonspecific to me and it wasn't clear how well that correlates with a venous disease since a lot of people might have those symptoms, and were those things that specifically got addressed as outcomes that seemed to respond to treatment for chronic venous disease or varicose veins. Those were my beginning questions.

DR. JONES: Thanks for the comments

and the questions. We're going to take this together, a lot of it has been a combined effort. So, I would say to your point and to the other speakers' points about patient reported outcomes, the difficulty you had in hearing that from us is because there was not a lot of patient reported outcomes in any of the literature that is present in venous disease.

There, like many clinical trials across many spectra of diseases, a lot of it is based on physician assessment of disease and outcomes, or clinical research coordinator assessment of outcomes, and so that is an evidence gap. If it wasn't there, we couldn't report it. We had to report what we found, which often was a CEAP classification, VCSS score, because that was what was in the literature. And it may not be important to patients, like many presenters stated, but it's not there.

DR. VEMULAPALLI: I would just add that we did try to highlight the AVVQ when that was actually available to meta-analyze or to present, and I'd just echo what Schuyler said, which was that many of the outcomes were

non-patient reported outcomes, and the clarity as to the changes in those outcomes being related to the intervention, very difficult to comment on that, other than patients were often asked in very heterogeneous ways, do you have leg heaviness before and after, and that's it.

DR. REDBERG: If I was clear, that venous clinical severity score, the components of it were pain, edema, inflammation, and duration of active ulcers. So of all of those, the only patient reported outcome would be pain. And then again, my concern was in the intervention, the active intervention versus placebo arm, it wasn't blinded, so you know, we know that there's a placebo effect getting a procedure, and how could you separate that from whether the actual procedure was of any benefit?

DR. VEMULAPALLI: Yes, so I think this gets a little bit to maybe a larger question of what the standard for blinding should be in trials of interventions. Certainly there should be blinding of assessors, I think we would all agree to that. Should there be blinding, double blinding, blinding of patients

as well, I would say in most device trials that does not occur, however we've had examples recently presented, say in resistant hypertension where there were double blind trials. So I think this is what you're asking about, and also part of what goes into the strength of evidence.

DR. REDBERG: Right. I think you're referring to the SYMPLICITY trial of renal denervation where surprisingly to all, I think, there were no benefits to the intervention in a double blinded trial.

And my last question, I have more, but the last one I'll ask, was there any studies that reported back to work data as a measure of functional status?

DR. VEMULAPALLI: There were a handful of studies that did report back to work data and you saw some of the subsequent presenters highlight some of those. That was not one of our prespecified endpoints, and so I'm telling you anecdotally that we saw that, but we did not specifically systematically analyze that.

DR. REDBERG: Thank you. Art Sedrakyan.

DR. SEDRAKYAN: Thank you. I have a few questions continuing that evidence, quality of evidence discussion. I think you talked about, this is a technology assessment group, you talked about high quality, intermediate quality of the AHRQ methods guide, and you also highlighted the allocation concealment as one of the most important metrics of quality for this trial of interventions, but different interventions, and that patients, physicians obviously know what therapy is offered, and yet you have quite larger number of high quality designation, or at least higher than intermediate quality. Can you comment, did they really meet the criterion for allocation concealment in your classification, because I think that's important. I was surprised that you found so many with high quality from that perspective. My evidence reviews usually find very few trials where they truly do proper allocation concealment.

DR. JONES: I think in my judgment, and this is an opinion, was that we had actually very few high strength of evidence determinations here, and I think some of the

comments that I've heard from the group at large is you kept saying insufficient, you didn't say anything else other than insufficient.

So there are five domains for AHRQ methods to determine strength of evidence, which is likely different than grade of evidence, which you saw in some of the SVS and AVF guidelines. What we do, and Dr. Sedrakyan, I know you know this, but for the rest of the group, we look at a specific outcome in a specific time point and we say, did the comparison of interest have enough evidence for us to think that it was unlikely that it would change if we continued to do the same type of study.

And I would say if I remember correctly, only one or two studies had high strength of evidence in our review, okay?

DR. SEDRAKYAN: With proper allocation concealment?

DR. JONES: Now, to answer your question about allocation concealment, it's one of the domains, it's in the risk of bias or the study limitation domain under the AHRQ Methods

Guide, and so it's a component. Another, you know, the other components are precision, directness, consistency, and then reporting bias.

I think that, we'd be happy to go back and look, but I think that in that one or two cases, we did feel comfortable that while there was a problem with allocation concealment, the strength of evidence was still high.

DR. VEMULAPALLI: The corollary comment I would make is when we talk about allocation concealment, certainly we just mentioned the idea of double blinds, whether the patient is blinded or not and remains blinded. There's certainly also the assessors. And there's a gradation there in studies, and some studies are very explicit that blinded assessors who are not involved in the therapy were actually used for outcome assessment, whereas others, not so much.

DR. SEDRAKYAN: I just wanted to separate that from blinding, because this is about inability to guess the assignments so that patients cannot be withdrawn selectively out of the study if they didn't like the

allocation or if physicians didn't like the allocation after randomization was announced. That's very separate from blinding and it's found to be one of the most important quality criteria for non-pharmaceutical trials.

The second question I have for you, in your assessment of evidence, how often -- I mean, how did you find the final selection eligibility for both therapies, let's say surgery versus RFA or laser, what percentage ended up included into the trials? So in a continuum of comparative evidence, there's always the patients who will only benefit from the surgeries to advance, and to apply any less invasive radiofrequency or laser or sclerotic therapy, or do you think the designs and clinical development of this technology that's now less invasive allow every patient to be treated? In other words, are these trials ending up being generalizable, and what percentage ended up, and maybe we can hear also from clinicians, but are RFA and sclerotherapy and laser already ready to take on every patient? So this is kind of important for us to understand, are they like direct comparisons

or only in selected groups that they're possible to apply?

DR. JONES: We'd love to hear the experts' opinions on the generalizability for this. From a methodologic standpoint, applicability is one of the other measures that we graded every study on. So when we looked at both the strength of evidence and the applicability to a generalized population, there did not seem to be a signal that suggested that these patients were either, I'm sorry, were different than the standard population that's being treated in the United States. But happy to hear what the experts say.

DR. SEDRAKYAN: So are RFA, laser and sclerotherapy ready to take on every patient, a quick question two.

DR. MEISSNER: You know, with all due respect, I'll address that question on the question of quality of life. You know, there is abundant literature on quality of life, it doesn't lend itself to meta-analysis in these things because there's at least three or four quality of life scales that are used in venous

disease. All of them are validated, all of them work well, there is no standard, but they're reported differently in different papers, which doesn't lend itself to meta-analysis at all.

Also the way the meta-analysis was done, it was broken up into, just like you're saying, sclerotherapy, RFA, laser, and virtually all of the data from several trials suggests that these are functionally equivalent, there's some differences in early postoperative pain but the long-term results are equivalent between them. So if you consider all of that together, if you include any way of taking care of the saphenous vein, surgery, RF, laser, foam, it can be combined because the outcomes are the same. And there's abundant data that quality of life using several different measures is improved following those procedures, but it doesn't lend itself to meta-analysis, you'd have to read the individual papers and understand what they're looking at.

That being said, you know, there are subtle differences between them. For RF and

laser you have to have a straight enough vein that you can drive a catheter up, for sclerotherapy you don't. So it's not going to be applicable to all patients, there will be differences between them, but the outcomes are similar at six to 12 months, and I think most of us believe that, you know, you can combine these into an interventional category and when you do that, there is abundant quality of life data in there which as we talked about, is the only really important outcome for these.

DR. REDBERG: Thank you.

Dr. Campos-Outcalt? No? Jeff.

DR. CARR: Many of the speakers talked about the need for realtime clinical data and several of the speakers spoke about registries. CMS has recently started covering lung cancer screening, which I believe they're using a unique approach where they require a shared clinical decision-making visit prior to the procedure, as well as enrollment in a registry and reporting nationally. From the surgical perspective or vascular medicine specialists, or maybe a patient perspective, how easy would you feel, or how warranted if CMS were to

mandate some type of visit before or after these procedures to collect core variables, how would that be received by the community? I don't know, I think Dr. Lyden mentioned some of that, but anybody in our group?

DR. LURIE: Well, thank you, I think it's a very important question and I completely agree with you as you imply, that if CMS really in some form mandated participation in this registry, that would grossly enhance our activity to collect that data.

It's also important to point out that those registries are, serve a different role in improving the quality of care. One particular aspect of the registries, and there are different registries, but I would emphasize that one aspect of the Vascular Quality Initiative is that requires a hundred percent participation, so each practitioner who enrolls a patient in the registry should have to enroll all his patients, so on one hand it can serve the quality issues, and on the other hand it will collect the real data with minimized bias.

DR. REDBERG: Yeah. The issue is that registries can be very helpful, but they don't

replace randomized control trials, so lung cancer screening was following the randomized control trial but in this case we don't, I didn't see randomized control trial evidence yet clearly directing us one way or another. There was a lot of heterogeneity of data, it wasn't clear that patients were better off in any particular treatment. The data looked pretty good to me for lifestyle therapy, weight loss, exercise, and that's something as a cardiologist I think is always going to be good for you. I didn't see that any of the treatments were better, and so a registry could give you information on a particular treatment but it's going to answer the question I think we need to first answer, you know, what treatment, if any, should we be offering, because there were a lot of, you know, as I said, exercise, medical therapy, the compression therapy and then all of the invasive ones, and it wasn't clear.

DR. LURIE: That's certainly correct because they're different questions that I think are answered by different means, but I want to point out that the randomized trials

are not always feasible in that field, especially in an environment when you already have established therapies, so it's very difficult and it can take time. In the meantime registries can answer some of the questions, maybe not the question that you implied, but some of the questions that will help to even design the correct randomized trial and to get to the more precise questions, make it easier, so there is room for both of them.

And if I just may, to extend a little bit Dr. Meissner's comment about quality of life, because I think it's a very important, that is correct, there are different instruments that are used, and it's very difficult to do a meta-analysis of that. But if you look at the quality of life, that was included in randomized trials for endovascular therapy, and you cannot find a single trial where there is a quality, for example in quality of life, or what's negative about the quality of life. So they're all consistent in their findings, the difference in magnitude of effect with a different instrument, the

consistency is there, and so I think that's a criterion that you should take in consideration. I mean, the data may not be high quality but it is very very consistent throughout the studies.

DR. REDBERG: Thank you, Dr. Lurie, and if people could just identify themselves before they start speaking, for the transcriptionist.

Jeff, did you have other questions?

DR. LEE: Hi, Francis Lee, from western Massachusetts again. I think registry is an absolute, it's fantastic, I think it needs to be supported. I think accreditation is also very important. If there's anything that CMS could do to help along this field, and many of your beneficiaries, is to somehow link the requirement of registry and accreditation to the vast number of vein specialists in this country who are practicing many different styles of vein treatment, that's number one.

Number two, you're right, I agree with you a hundred percent. Even though registry is important, it does not address the evidence questions that you are seeking because there

are certain inherent limitations as to what kind, the quality of evidence that we're all seeking. I think it's highly unlikely that we'll get 1A evidence on most of the questions that we're seeking. Why? Number one, Dr. Meissner just briefly mentioned different treatments, venous treatment is different from arterial in the sense that there's many different kinds of veins and the endpoint for well physiologically working venous return is somewhat different than from arterial. Foam sclerotherapy is not even a question to be used in certain type of veins that laser ablation or RF ablation could be used, and the same with phlebectomy, very different types of technologies. So the kind of studies that they have looked at, the two gentlemen from Duke, they don't really answer the kind of evidence that you're seeking.

And lastly, and this is the important part --

DR. REDBERG: I just want to say, we're going to have to be short. I'm just looking and we have ten more people here, we've got six people lined up to answer one question.

We're going to have to limit the time.

DR. LEE: Sure, I apologize, okay.

DR. REDBERG: And we can't have six people answering the same question.

DR. LEE: I'll just limit it to a couple of sentences. It's just that this has become such a standard treatment, endovenous treatment, that you're going to find it very difficult to randomize going forward, both in the minds of the patients and also in the minds of the providers.

DR. REDBERG: Yeah, but that is not a persuasive argument.

DR. BECKMAN: I'll be very quick. I totally disagree with my colleagues here. I think this is a tremendous opportunity, and the biggest problem is the opportunity, that presents the opportunity for you guys. This lack of standard definitions is the biggest problem. So, I think if CMS could use its authority through the most recent legislation as described by Dr. Lyden to create a set of data fields that need to be available through electronic medical records that can then be aggregated, those specific endpoints can form

the basis for larger clinical trials to be done. Once you have standard outcomes that can be measured, you can then do standard types of trials that we've done in other spaces, and that will allow us to move the field forward.

So I think the first big step is to use the 800-pound gorilla in the room, mandate the collection of specific kinds of data, and everybody in this room will be very happy to help figure out what those discrete fields are so that we don't have differences between registries, and then the ability to put all that information in a central data repository will help us figure out what's happening now, what we need to figure out and where we need to go.

DR. REDBERG: Thank you, Dr. Beckman. I'm going to end the discussion now because I want to move on to Dr. Cuyjet.

I'm going to just make a comment on that last statement about randomized control trials, because I also serve on the California Technology Assessment Forum, and about five years ago we were looking at metal-on-metal hips, and I asked a similar question to an

orthopedic surgeon who had come to talk about why there was no randomized control trial on metal-on-metal hips, and yet we were told this was the best thing, patients loved them, and he looked at me and said it would be unethical to do a randomized control trial because we know metal-on-metal hips are better than conventional. Well, a year later they got recalled from the market and as you know, the revision rate is 40 percent and you know, there's problems with cobalt ion. So, I'm just a little skeptical when I hear we know this is better, we don't need a randomized control trial. That's one example, I can think of a lot of others but I'm not going to take the time now. I'm going to let you ask the next question.

DR. CUYJET: Al Cuyjet. I have a question for Dr. Jones and Dr. Vemulapalli. It's kind of a basic question that will probably speak to my own ignorance but in the studies that you reviewed, adherence is a big issue. I mean, in trials I've done you can do fill counts as an intervention or treatment for TB. I don't know how you validate or what was

validated on the use of compression stockings for initial treatment compared to, because if you feel good one day and you don't wear your stockings, or you wear them as prescribed, it skews the data hugely, so I'd appreciate what you found in your research.

DR. VEMULAPALLI: So again, what I'm going to say here is anecdotal because that was not one of our prespecified endpoints. However, there was a large variability in how studies assess that question of compliance. The majority of the studies, again anecdotally, do not assess compliance in a standardized way. And I would also say, it's sort of a theoretical question whether that matters.

Unless, if you assess compliance every week in your trial, you think you can translate that to clinical medicine whereby you somehow assess compliance with the patient, because we know a little bit in the PAD space that bringing patients back and assessing compliance or providing their feedback improves, say, exercise therapy, so one could imagine that could happen here as well. But if you're just looking at an endpoint where you say here, we

gave you this prescription, which is what clinical medicine is now, and here was the result, it's a question about whether assessing compliance is relevant there.

DR. CUYJET: That's true, but it could potentially skew your interpretation of the quality of the evidence.

DR. JONES: Agreed.

DR. REDBERG: Thank you, Dr. Vemulapalli. Dr. Lawrence.

DR. LAWRENCE: I'm Peter Lawrence, I assume we're going to do these one at a time though most of us have three or four, so let me start with the first one.

And I'd just ask Dr. Piazza, I believe you were the person who implied that early treatment of C2 disease would prevent the progression of patients to venous ulcers and C6, I believe that was your statement, or one of you. And so, obviously the elephant in the room is that there's a huge number of these cases being done with a 1,400 percent increase in the last couple of years, and many of them are C2 patients.

So is there real evidence that

patients with primary varicose veins can be prevented from getting venous ulcers by treating the varicose vein, or are they two different groups of patients that we should be looking at differently?

DR. PIAZZA: So, I think that's a very important question. My point about treating wasn't specific to sclerotherapy or any interventional approach, it was having to do with also compression and other measures for treating early chronic stage venous disease. We do know that patients who present with milder forms of chronic venous disease, C2, C3, can be terribly symptomatic, and waiting for patients to present with more obvious later forms of chronic venous disease is doing them a grave disservice. Even if they don't develop ulcers, you have this population of C2 and C3 patients that may have severe pruritis, severe edema, pain that keeps them out of work or limits their life in other ways, and if we're not giving them therapy that we know helps for that, you're just not treating patients, regardless of whether there's progression or not.

We don't have, and you've heard this from the group that has analyzed the data, definitive evidence that shows that we can interrupt the progression with the things that we currently have, but treating symptoms, we can treat symptoms, and to ignore patients with milder forms actually leaves the burden of disease on a large population of patients.

DR. LAWRENCE: So it's more of an emphasis not on progression but the symptomatic. I must say that I have a huge venous practice and I would say the majority of my patients are C2; it's not that they can't benefit, but that they are terribly cosmetic rather than terribly symptomatic, and it's a very small proportion that really have bad symptoms with C2, but that's a different issue.

So you're not saying there's going to be progression necessarily, but just that the C2, some of them should be treated.

DR. PIAZZA: Right, especially with the data, you know, fairly strong for women presenting with more crippling symptoms at an earlier C2 stage, and oftentimes providers won't treat that, or they won't recognize the

disease and treat it, and then we have all of these patients that are essentially out of the work force or limited in some other way, when we should be paying attention and treating them.

DR. REDBERG: I did write down for one of the presenters that there was no benefit of treatment for asymptomatic varicose veins, so people that are itching, you're saying, or heaviness. Thank you for that distinction.

DR. LAWRENCE: But I would just comment that many of those patients come in because they know the insurance criteria, and they've all read it or been to another doctor, so the symptoms are often something that they've learned that they need to have in order to get treated. So how many of those people are truly symptomatic versus cosmetic, I think still remains up in the air.

DR. REDBERG: Roger.

DR. ROGER LEWIS: I'm Dr. Roger Lewis. I have a question for Dr. Vemulapalli and while he's getting up, I'm going to make an editorial comment. There is nothing about the use of different measurement tools that preclude a

meaningful meta-analysis, one simply has to put those things on a common scale, and so I would urge people to look at ways to do those meaningful meta-analyses rather than be responding to false barriers.

So, my question, I'm going to use your slide 41, compression versus placebo, as an example of something I just need to understand a little better. So in my mind, in assessing the potential value of a therapy or a set of therapies, there is a qualitative question, almost a hypothesis testing question of, is there evidence that at least somebody benefits from it, even if I don't know who that is. So that's sort of a null hypothesis that there's no benefit for anybody, and there's value in projecting that null hypothesis if you can do so with some assurance, because then it moves you to the task of figuring out who benefits, how much, at what cost, and what side effect profile.

It appears to me if I understand correctly, and I'm going to first ask for verification, that the grading of strength of evidence being insufficient by the system you

used was really grading your ability to have an estimate of a treatment effect for a particular endpoint at a particular time point and for a particular population that you expected to be robust through additional knowledge, and if so, that's a very high bar. First of all, am I interpreting that correctly?

DR. VEMULAPALLI: Yes. And I would just bring up the point that Dr. Jones made earlier about the various components to that, so heterogeneity, directness, precision, some of the things which you just mentioned.

DR. ROGER LEWIS: Great, so that gets me to part B of my one question. So when one considers heterogeneity of treatment effect, one could consider heterogeneity with respect to the outcome that you're looking at, it could be the time point at which you're looking at that outcome, and it could be the populations based on symptomatology or perhaps some sort of functional measures, so there's at least three different dimensions at which we might want to assess heterogeneity.

So my question for you with respect to compression versus placebo is that I'm reading

your language as suggesting that you've rejected the idea that there's no benefit, but that the statement that there is insufficient evidence really says that you're meaning to communicate that it's unclear at what time point, what population, what severity that benefit exists, and if so, can you tell me, do we know anything about that?

DR. VEMULAPALLI: So I'll make a few points about this because I think this is important. So number one, we started our assessment from the year 2000, a lot of the data regarding compression predates that, so first off. Secondly, when we do this with the AHRQ methodology these grades, evidence grades are done, as you point out, for a specific time point, for a specific outcome, et cetera. And so when we have heterogeneity of outcomes at different time points, it does become a little bit more difficult to give higher grades of support to our findings.

DR. JONES: I completely agree, I think that's where a lot of people are getting hung up here. We were asked to do a very specific job, which was to look at specific

outcomes at specific time points for treatment comparisons, and that's what we presented you. We were not asked to provide guidelines, which you've seen, which often take into account all of the outcomes and all of the time points, which may be a big disconnect here, because some of these therapies may be shown to be beneficial, a net clinical benefit when we look at that versus risk, but it's not what we assessed. We assessed the specific, very specific questions that we were asked to do and I think if, this is an opinion, that is the crux of the conversation, is there benefit, is there evidence for some benefit? That's not what we were asked, we were asked a more specific question.

DR. ROGER LEWIS: Thank you.

DR. REDBERG: Dr. Lewis.

DR. SANDRA LEWIS: So, I'm going to take a slightly different turn here. I've been struck by the fact, and I do a lot of women in cardiovascular disease, the majority of patients being women, and how unique that is in the cardiovascular world where women tend to not join studies, and although cardiovascular

disease is the number one cause of death in women, they aren't participating in our studies.

Why is this happening? Is this because this is a cosmetic disease, is this something we could dig into on a more specific level if we go ahead with more studies, are they symptomatic, are they -- and it goes back to what we just heard about possibly, they know what symptoms they're supposed to report. I'm fascinated about why more women, do they really have more venous disease or is this a particularly appealing disease for them to have treated?

DR. O'DONNELL: Tom O'Donnell. I did address that in my talk, thank you.

First of all, if you go to a vein practice you will see in the waiting room, most of the people are women. They do it because they have, there's a greater predominance of varicose veins in women than men who have deep venous disease, so I think we start out already with a bias towards women. Secondly, women for whatever reason may seek treatment of the disease beyond a cosmetic concern. Patients

that I and my colleagues treat are symptomatic.

If you look at the randomized control trials, the patients predominantly are women, up to 75 percent in meta-analysis we did. Secondly, they have milder disease, C2 or C3, as opposed to the case series trials which are pragmatic, which have a higher proportion of men to women, or not higher but comparable proportion of men, and also have higher CEAP grades. So it's a combination of many factors about why women, but it is unique in cardiovascular disease as you point out. Would that help at all?

DR. SANDRA LEWIS: Well, I'm wondering if you took a random sample of men and women and did venous doppler ultrasound or other diagnostic tests, would you find the same discrepancy?

DR. O'DONNELL: Yeah, Dr. Allison talked about that earlier but if you look at all the epidemiologic studies using duplex ultrasound as you suggested, which would have been the Edinburgh, Bonn and the San Diego trial, these all with the exception of the Edinburgh had a higher proportion of women with

superficial venous disease. So you start out with that, and then you have the factor of why do they seek treatment, I don't know, I haven't taken care of a lot, but maybe they are more concerned than their husband or significant other about getting it done, but they are symptomatic.

DR. SANDRA LEWIS: Like we're talking genetic brothers?

DR. O'DONNELL: Yeah.

DR. PIAZZA: So just to see if I can lend some more to your question, many of the risk factors for chronic venous disease are found in higher prevalence in women. There's certainly an impact or an effect of estrogen, there's an effect of multiparity and so that's one of the explanations that has been discussed as to why we might see this more commonly in women.

It's important to distinguish asymptomatic from symptomatic disease. I think that physically seeing varicose veins, which women may be more likely to do, doesn't mean that they don't have symptoms, they may actually have the symptom and have the

appearance, or notice the veins in that area that are causing the symptoms, so they may present more frequently for therapy.

Another thing that I would caution all of us to do is not to dismiss the cosmetic impact of varicose veins. Now I don't do procedures in my vascular medicine practice, I see mostly people who are symptomatic, not coming to me for the appearance but because they have very disabling symptoms, but we should be very careful not to dismiss the embarrassment and the anxiety and the psychologic impact of patients, men and women, who have varicose veins that keep them from going to the beach, keep them from wearing shorts.

DR. REDBERG: Thank you, Dr. Piazza, and please do say your name. That was Dr. Piazza.

DR. SHORTELL: Cynthia Shortell, I just had a couple of other comments regarding your question. I do think that the incidence of varicose veins is more common in women, especially symptomatic varicose veins. I think there are two factors that cause the difference

in treatment seeking behaviors. Number one is, although it's becoming less and less, there is a stigma for men to seek treatment for varicose veins. Number two, a lot of women with varicose veins, more than men, have occupations such as teachers, hairdressers, and OR nurses, even surgeons, that tend to exacerbate their symptoms.

DR. REDBERG: Dr. Salive.

DR. SALIVE: Marcel Salive. I wanted to focus on the registry issue again, I had kind of a followup question.

We've heard, I think, about a variety of registries which had many different, I think, entry criteria, and it seems like to make some progress we would need some collaboration or consolidation or coordination among the registries, especially if you want to draw conclusions, and I think the statement about what registries could answer by one of the speakers on the Vascular Quality Initiative went a little bit far afield, and I would say I agree more with the chair about difficult, you need some trials up front to figure out what should go into the registries perhaps.

But another point is, you know, the natural history isn't there if everyone gets intervened on as well, so my question relates to the statement about a hundred percent completion, and I think it's a very key issue for the registries, is, if you have completeness, you know, how do you know that, and how are you going to continue to know that regularly and routinely, because that's, I think, also a key issue for drawing any conclusions out of the registries.

DR. FIFE: Caroline Fife, U.S. Wound Registry. Our registry is not related to any intervention. 100 percent of the patients seen in these facilities become part of the registry because they're linked to the reporting of quality measures. I think that is potentially a way to get past the observation bias is, if you're linking some things to reporting of things you already want to know, since you don't necessarily, since you would like to know more about natural history, then linking them to the reporting of things like compression or vascular screening will give you information on patients who do not get interventions, as well

as whether the appropriate conservative care is being completed, and I think that would be the direction you would want to go in order to obtain the information on natural history.

DR. SALIVE: So how do you know they're complete?

DR. FIFE: A hundred percent of the patients in the clinic --

DR. SALIVE: Is it audited?

DR. FIFE: It's part of the EHR so yes, you're able to know that all of the individuals who are seen, it's a numerator-denominator like all of the quality initiatives are, and you know exactly what percentage of data you have access to.

And with regard to the issue of the RCTs, we did a study in which we looked at the percentage of patients with venous ulcers who would have been eligible for RCTs, all of the RCTs in wound care in the last decade, 75 percent of the patients seen in those wound centers would have been excluded because the patients were too sick or their wounds were too large. So with regard to the kinds of people we really take care of, they're not enrolled in

RCTs.

DR. REDBERG: I think you're just bringing up another problem with RCTs, is too many inclusion and exclusion criteria, but thank you. There's three more commenters, so if you could all be brief, that would be great.

DR. WAKEFIELD: Tom Wakefield from Michigan. The VQI is part of a PRO and so it has audits that come in to make sure it's a hundred percent participation for every case, and I think that's a really important point.

And I certainly think RCTs are important, but if you just look at sort of the history of RCTs in vascular surgery or venous, you can't just generalize the way you need to based on the inclusion-exclusion criteria which is so strict for many RCTs, so I think you need to have parallel process. The registries can certainly give you some information, RCTs give you other information, I don't think they're exclusionary, I think they're complementary.

DR. REDBERG: Thank you.

DR. SCHUL: Two points, my name's Marlin Schul. When you are using an electronic medical record that is automated dumping into a

registry, you get a hundred percent of the cases. That's one. You also get the epidemiology and everything else.

If you are doing manual entry of data, that's when I think you're going to get some selection bias of who goes into the registry and who doesn't, so the charge of a hundred percent is a very noble one, and the way to back up a manual data entry is with claims data, which is the way manual data entry should be done.

So there are definitely ways to encourage a hundred percent participation, but on the other side of that is what's on the other end, okay? Three different registries trying to help answer these questions, different groups of providers, there has to be collaboration and there has to be access to that database by CMS so you can find out what the results really are for these patients.

DR. LYDEN: I'll be brief, Sean Lyden. It's a heterogeneous population, registries help, there's not a perfect registry. All the meaningful uses come on the backs of clinicians. I now spend an hour and a half

more a day doing this stuff. If you require discrete data fields, clinicians could help to determine specific data sets that go into building data sets that leads to data to drive randomized trials. So, I think that CMS now pays for a lot of this care. If you create the discrete data fields in both outpatient and inpatient EMRs, you would amass a massive amount of data in a short period of time and at no cost.

DR. REDBERG: Thank you.

Dr. Zuckerman.

DR. ZUCKERMAN: Thanks. I have a couple quick questions regarding the AHRQ report. The first one is, it seemed that there were no differences in results from the diagnostic, there were no differences pertaining to the diagnostic tests, but it wasn't clear to me whether that included a clinical, a diagnosis based just on clinical review.

DR. JONES: Thanks, Schuyler Jones from Duke. So, remembering that much of the evidence for diagnostic testing for chronic venous disease existed before 2000, the limited

studies, seven studies total for diagnostic studies were comparative, remembering the comparative is the important part, because that's all we looked at.

DR. ZUCKERMAN: Okay.

DR. JONES: There was not evidence for direct comparisons of clinical assessment versus duplex or versus another modality.

DR. ZUCKERMAN: Okay. And then my second question is, so, you talked, you have all these different studies, but you didn't mention age and you didn't mention if there were subgroup analyses by age, or how many people were over 65. You also didn't talk about subgroup analysis for people of color or separate analyses for men and women. So, I just wondered if there were any, and do you have any information about it?

DR. JONES: Thanks. We did look at modifiers of effectiveness, that was one of our key components in each of the questions. I need to get this right, Sreek can back me up, 15 percent of patients had a mean age greater than 65 in all of the studies. Unfortunately, most of the studies don't report the age of

patients, they report a mean age like many of the registries have reported, so 15 percent of the overall hundred studies had a mean age over 65.

About 80 to 85 percent of all the studies included patients of Medicare age, meaning at least one patient over age 65. However, there was no way to do stratification based on age, because most of the studies just reported a mean age. We certainly can do that, but remember, the number of studies that we meta-analyzed in the first place was very small, those we're happy to produce. I just think it's going to be a limited thing.

Additionally, a lot of the demographic characteristics that everyone's interested in for disparities research and for other modifiers of effectiveness, were not present in the Table 1 of studies that we looked at.

DR. ZUCKERMAN: Yeah. I mean, I guess I'm particularly concerned with all the comorbidities, and we have to wonder if these older patients are sicker as well and whether they respond differently to different treatments.

DR. JONES: As an editorial comment as a cardiologist, I was interested in the number or percentage of patients who had diabetes or arterial disease in addition to venous disease, and very informally I will say that was almost never seen, it was seen in a handful of studies, so that was a limitation.

DR. ZUCKERMAN: Reported not seen.

DR. JONES: I'm sorry?

DR. ZUCKERMAN: Reported, but not seen?

DR. JONES: It was not reported.

DR. ZUCKERMAN: And no separate analysis to see if women and men did differently, you know, had different benefits from different treatments?

DR. JONES: Yes, as many of you have commented, the majority of these patients were women, we have the percentage of women, but outcomes were not specifically reported in men and women in these studies. Sorry to be -- I could hold my tape recorder up, but that's unfortunately the evidence base.

DR. REDBERG: And just to be clear, you said 15 percent of the studies had a mean

age of 65 or greater, but the mean age for Medicare beneficiaries is 74, would that be correct?

DR. JONES: I'm sorry. To clarify, the mean eligibility for Medicare, the eligibility for Medicare is 65. We only were able to study that included patients of that mean age, does that make sense, in the studies. Does that clarify your point?

DR. REDBERG: We don't have to go on. I think the mean age for Medicare beneficiaries is older than 65, because entry is at 65.

DR. VEMULAPALLI: This is Dr. Vemulapalli from Duke. One last comment about the disparities question is many of the studies were done in Europe and the racial breakdown in Europe is certainly different than here.

DR. ZUCKERMAN: Well, just, my editorial comment would be to encourage the researchers in the room to try to get that kind of subgroup analysis for people of color, women and men, and definitely people over 65.

I have one other quick question for, pertaining to the AHRQ report, and that is that

there were several different analyses comparing compression to other treatments and other treatments to each other, but were there data on compression compared to placebo?

DR. REDBERG: Insufficient. I think that was slide 116.

DR. ZUCKERMAN: Yeah, was that insufficient on all the major outcomes?

DR. VEMULAPALLI: Yes. So there are data on compression versus placebo, but again remember, the majority of this data would have predated 2000.

DR. ZUCKERMAN: Yeah, I was wondering about that.

DR. VEMULAPALLI: And when we say insufficient, remember, it's for each specific outcome, not looking at the totality of all the studies.

DR. REDBERG: And just, when you looked at compression, was it compression like stockings and mechanical compression? Because we heard about different kinds of compression.

DR. VEMULAPALLI: So, there's a wide variety of compression used. Oftentimes, and again anecdotally, we did record actually the

amount of compression but it wasn't given in many of the studies, so we don't even know the level to which they were compressed, much less whether it was only stockings or pneumatic devices, et cetera.

DR. REDBERG: It seems like a recurring theme is insufficient data.

DR. JONES: Last comment for me, sorry, for this one. We had a technical expert who actually commented and said we want to know the exact, or the answer for what is the exact number of millimeters of mercury, and so we set out to try to answer that but could not.

DR. REDBERG: Thank you. Did you want to address Dr. Zuckerman's question?

DR. GIBBONS: Yes, Gary Gibbons. I'm having trouble understanding the difference in number of diabetics. So, in the study we participated in and in the U.S. Wound Registry, the incidence of diabetes is 35 percent, in PAD it's up to ten percent. So I don't know where, I don't know how you can say it was less than one percent.

DR. ZUCKERMAN: I don't think I did. I didn't say that.

DR. REDBERG: Okay. Let's make one brief comment and then I want to give Leslie a chance.

DR. LULLOVE: One more brief comment, I'm sorry. Dr. Lullove from the AAWC. I just want to make a point of reference that the majority of patients that the panel is asking questions about regarding evidence is very difficult to ascertain in RCT studies. Whether from a compression side or an interventional side, it's just too difficult. The patients that we treat are realtime real world patients and the registry data is going to be your best evidence on seeing where those patients are coming from.

I'm not saying that RCT data is like invalid, but in this particular patient population where they are so often, these patients who are Medicare beneficiaries are not part of an RCT, they're excluded because of their other comorbidities, their other issues that are being treated. You can't get the data that you're looking for without looking at the registry data, whether it's the USWR, the Venous Initiative, you need to start looking at

that registry data as part of compiling your data sets for these meetings, and not just revolving around what's happening on an RCT level.

DR. REDBERG: Are you suggesting RCTs would be more useful if they didn't have so much inclusion and exclusion criteria, because that's a problem.

DR. LULLOVE: Yes, absolutely, that's a big problem with the wound care industry as a whole, it's realtime data based on real patients that don't, are never part of RCTs so, thank you.

DR. REDBERG: Thanks. Leslie, did you have a question?

MS. WISE: Yeah, I do. So, I guess my question actually was around the disparities issue. So when we went over the San Diego study, the results were only that, I think seven percent of African-American women had an advantage in terms of having chronic venous insufficiency. However, and maybe it was later in the wound studies presented, African-American women when they did present had the worst disease and I just wondered as I

listened to that, does that have something to do with the CEAP classification system itself? Because part of the classification is based on visual diagnosis, and are we missing the disease process in these women because they don't have varicose veins that they can see, they're not going in for cosmetic treatment? And additionally, 35 percent of them have diabetes, or a high prevalence of them have diabetes where they maybe not even feel the discomfort in their legs.

So I felt that number, I found that to be very interesting, that they don't show up for early disease, but they have the worst late disease. So, could someone speak to the whole CEAP classification system, and is it appropriate for people of darker skin color?

DR. REDBERG: Dr. Comerota.

DR. COMEROTA: Sure. Actually, it's a comment that I was going to make so if no one stands up to answer this, I'll volunteer. The CEAP class was never intended to monitor outcomes, the CEAP class is purely a description of the disease, magnitude of disease, the etiology of disease, the anatomic

location of the disease process, and the pathophysiology involved in that patient at the time they present. The clinical classification of CEAP should be eliminated from outcome analysis or treatment success. The reason is, if you have a patient that has an enormously swollen painful red leg that they just healed their ulcer, and your treatment magnificently restores their venous system to normal, they're totally asymptomatic and enjoying life, they will never get past their initial C5 level, that's where they end up for the rest of their life. So we can't use that as a method to monitor outcomes.

MS. WISE: Okay, and I can respect what you're saying, but I think maybe the point of my question was not addressed and if someone could address it I would appreciate it. Because how can you appropriately diagnose, that's what I'm saying, how are you going to recognize this? Like you just mentioned, if someone has a red leg, well, people with dark skin, their legs don't turn red. And so I want to know, have you guys thought about expanding what this looks like, because I know the

studies that were used to develop CEAP, and people of color weren't in those studies.

DR. O'DONNELL: You're exactly right. I mean, one of the things that has come out -- I'm Tom O'Donnell, sorry -- is the lack of data on race and ethnicity, it is absent. You can't get insurance -- Medicare has it but it's, as I said, handled by the Social Security Administration so you don't know how valid it is, so we need that data.

Getting to the point of making the diagnosis of advanced chronic venous insufficiency in an African-American versus a Caucasian, you can make that diagnosis as an experienced clinician, but it's a little more subtle. You definitely will be able to see varicose veins and palpate them in African-Americans or Caucasians, I don't think that's the problem. I just think that we're not getting data on that segment of the population as we should. In our randomized control trials and any other database, we need to be able to capture that data, and currently we're not. Does that help at all? Thanks.

DR. REDBERG: Thank you. Dr. Carman,

did you have a question?

DR. CARMAN: Teresa Carman. I just have a couple of methodologic questions regarding the AHRQ report. You included 108 studies out of 10,000 in the literature, so less than one percent of the available venous disease literature, which seems like a vast minority, and the point's been made before, we are significantly probably understudied to begin with, so you have a high exclusion rate. And yet in the report and in the data you present, you've included 17 studies that you deemed to be poor quality, you included multiple studies where it was unclear if the patients were symptomatic or asymptomatic, even though these may include randomized control trials, et cetera.

So, do you think if we looked a little more at the truly high quality data, your level of evidence would be different for all levels, whether it be compression therapy, whether it be some of the interventional therapies, et cetera?

DR. JONES: Schuyler Jones from Duke. So, a very nice question. You're right, one

percent of the overall studies, remembering that we spread a very very very wide net and got almost all the vascular disease into this net, and were included in the venous disease analysis. The answer I think for your question, which is if you only look at higher quality studies, will that improve or not your strength of evidence? I don't see it improving it, because you're narrowing your net even farther, and when you're talking about in order to meta-analyze we needed three studies, not grading what type of studies they were. My guess is if you're going to reduce that to only good quality studies, you won't have any comparisons with more than one or maybe two studies, so I don't think it's going to improve the strength of evidence, it would only weaken it. Do you have a comment?

DR. VEMULAPALLI: Sreek Vemulapalli, Duke. So along the same lines, part of our strength of evidence if we abstract it back, is how confident we are in the statement, and so as Dr. Jones was saying, when we decrease the number of patients, I'll say not the number of studies, but by reducing the number of studies

we're actually decreasing the number of patients as well that we're looking at. So we may have a fairly high, what we would think of clinically as quality study, an RCT, well allocated, well blinded, et cetera, in 50 patients. Now, is that sufficient by AHRQ criteria to say we can give something a strong strength of evidence? Now certainly on a guideline level, that might get a 1B or so, because it's one very good RCT, but it would be a little bit different in the AHRQ methodology.

DR. CARMAN: But do you think it would take care of the heterogeneity, because we are talking about a tremendously heterogeneous population, and I'm certain these studies included patients why C1 through C6, and if we really want to get to the crux of the matter, right, C3, C4, C5, CG disease, would it help with the heterogeneity in those issues?

DR. JONES: My opinion is no. I didn't present, or we did not present the I-squared values for heterogeneity that we did look at, but it's not going to change the heterogeneity that's seen within a study, which I think is the population differences that

we're looking at, right? Most of the heterogeneity between studies was the outcome that was assessed and the time point of outcome assessment. Inside the comparison or inside the study, there was still differences of C2 through C6 being included in the same study for treatment comparisons.

DR. REDBERG: Dr. Comerota.

DR. COMEROTA: Thank you. I have some quick questions for five different people, they will be quick questions, and then I have a comment. So my first is going to be either Dr. Jones or Vemulapalli, then Dr. Allison, Dr. Fife, Jim Harmon, and then I want to get my friends Dr. Gloviczki and Dr. Shortell to answer my last comment, or question.

And while they're going up to the microphone, I do have a comment about the term chronic thrombus or chronic DVT. Now I understand that this was given by MedCAC to the speakers, but there's also some speakers that used it spontaneously and I would say this is an exceedingly deceiving term. It's not been defined, it implies that thrombus is part of the immediate pathology that the patients had,

they present with, when in fact that is not the case. So I would suggest for the purpose of this panel and the purpose of discussions about chronic venous disease, that we eliminate the term chronic thrombus or chronic DVT, it's a comment and a suggestion.

So, Dr. Jones, Dr. Vemulapalli, a compliment to you on the thoroughness of the work that you've done, and you've presented it beautifully. How are we on this panel to use what you have presented to us?

DR. JONES: Dr. Comerota, this is the second year I've presented at the MedCAC and I can tell you that my confidence in being able to present it at MedCAC is actually pretty high now, my confidence in being in your position as a voting member of this committee is much much lower. From my stand, I think you're asking an opinion. My opinion is we were --

DR. COMEROTA: I'm just asking how are we supposed to use --

DR. REDBERG: You said quick question, I don't think that's fair.

DR. COMEROTA: How are we to use what you presented to us?

DR. JONES: I honestly can say that I would feel very, it's very difficult for me to tell you that. We asked very specific questions, you asked very broad questions. You have to use the accumulation of what we presented to you, and that is a very separate question than a methodologist is able to answer.

DR. REDBERG: Right. I would say we take the evidence review, you know, we'll discuss it as soon as we finish these questions more among ourselves on what our charge is to look at in the voting questions, and you take that altogether with your own experience and judgment, and make a decision. It's not up to the TA to tell us that.

DR. VEMULAPALLI: This is Dr. Vemulapalli from Duke, I'll make two comments to echo that. One is, nothing we presented to you incorporates a risk-benefit analysis, which is what clinicians do every single day. And then the second is, what we have presented in terms of data and strength of evidence is very very different than what's taken into account in clinical guidelines,

because clinical guidelines have to take into account the breadth of patients that are seen. Those are the points I'll make.

DR. COMEROTA: Okay. Dr. Allison --

DR. REDBERG: You have four more quick questions?

DR. COMEROTA: Yeah. You presented that hypertension and smoking were risk factors for chronic venous disease. Could you tell us why hypertension is a risk factor, and the link?

DR. ALLISON: I don't know the answer to that question.

DR. COMEROTA: Okay, fair enough. Was it a risk factor or an association? It could be an association. Okay.

Dr. Fife, your enormous database in over 59,000 venous ulcers, could you give us some important facts about venous ulcers that we should consider as a starting point for discussions on management, and perhaps --

DR. REDBERG: Dr. Fife, I'm sorry, one moment. But I think strictly speaking, a risk factor is something that if you intervene on, you will then reduce the endpoint. In other

words, if we treated hypertension then we would see less chronic venous disease. So it's not clear, I believe, that would be true. I mean, I think that you also showed obesity as a risk factor, female sex, age.

DR. ALLISON: So, I think you have to be careful in making that conclusion, because we're talking about an observational study design that's confounded potentially, and if you intervene on that it would result in. Potentially it may, but it may through a confounding factor that's posed with the outcomes of the exposure.

DR. REDBERG: Thanks.

DR. FIFE: Caroline Fife. The average patient has three venous ulcers, they're huge, square centimeter wise by surface area they're over 20 square centimeters, which is much larger than any RCT that I can think of. When they are seen in a wound center, by the time they're seen in a wound center they've been present six months. They will stay in service at least 60 days, about 30 percent will never heal, even though they may be seen for more than two months we do not have an outcome of

them as ever being healed. Although many of them will get healed very quickly when adequate compression is applied, which means they weren't getting adequate compression for months before they were sent to a wound center, so very simple care that should be first grade is not being provided by their primary care physician.

The average patient has six comorbid conditions, 30 percent of those patients have diabetes, eight percent of them are on dialysis, eight percent of them are on steroids, eight percent -- eight percent is a very popular number -- have congestive heart failure, and most of them would not be included in a randomized control trial.

DR. COMEROTA: Thank you. Jim, the VVSymQ has been quoted and referred to by a number of speakers and seems to be an important endpoint, quality endpoint. Is that available for all of us to use in future trials?

MR. HARMON: Yeah. I have to say also as fifth line, I was almost having a heart attack as I was walking up --

DR. REDBERG: Speak into the mic.

MR. HARMON: Jim Harmon, I'm just being facetious here. Yes, the VVSymQ is a tool that was developed for the clinical trials associated with the approval of our brand Varithena for treatment of venous insufficiency. It was also something that we believe strongly should be available for the community because it's something that we believe strongly, patient's input on a validated robust measure is something that should be available to everyone, and we're willing to work with just about anybody that comes to us to discuss that, including CMS, including commercial carriers, physicians, societies, anybody else, we are marching down a path that's not easy, but we are happy to talk to anybody about it.

DR. COMEROTA: Okay. And Dr. Gloviczki, one of your conclusions was a very low confidence level, a confidence level of two for stenting, venous stenting in symptomatic patients, so that's an overall term, in overall stents. If I were to narrow it down to iliac stents for symptomatic, because I think Dr. Shortell gave a little more

compelling data for a stronger recommendation, would you change your recommendation to a higher level of confidence if it were for proximal, say iliac disease, in a symptomatic patient?

DR. GLOVICZKI: I was referring to iliac stents in those studies because it was really the major type, the iliac occlusion is where we have the data from. Unfortunately as you know, there is no good prospective randomized study on that and there isn't, the validity is relatively low because of the meta-analysis, actually systematic review that was published in Phlebology.

And we discussed it with Dr. Shortell and we thought based on the core study specifically from Roger and Neglund, there's more evidence in the long-run advanced disease, stenting actually is better.

DR. SHORTELL: Yeah, I think that we did make a distinction between short and long term. One of the big advantages is prevention of long-term sequelae of a variety of types of symptoms and signs that result from proximal venous obstruction.

I think that while the systematic review which Dr. Gloviczki referred to concluded that there was insufficient evidence to support stenting, it also in their conclusions said that they thought it would be very beneficial, and this was more of a similar type of problem that we have with the AHRQ where the evidence itself didn't meet the standards that we hoped to have in order to create high levels of certainty, but that the before and after data was compelling enough to lead the authors to conclude there probably is benefit.

DR. REDBERG: Okay. I'm going to just follow on that, and we've cut a little bit into our panel discussion, I'm sorry to say, but because we didn't get to, if you could, again back to Dr. Jones and Dr. Vemulapalli, if you could define for us short, intermediate and long-term outcomes?

DR. JONES: Sure. So, we argued about this for a week or two. Short-term outcomes were one to 30 days, intermediate-term outcomes were 31 days to six months, and then long-term outcomes were greater than six months for this

comparative effectiveness review.

DR. REDBERG: And would you say in the trials you reviewed, how many had short-term and long-term outcomes?

DR. VEMULAPALLI: This is Dr. Vemulapalli, Duke. So I would say, if you're asking how many had both short and long-term outcomes, many, but I think I would qualify that by saying that the outcomes assessed at those time points were often different, so there were periprocedural complications that were often assessed in the first week, ten days, sometimes up to a month, whereas quality of life assessments, AVVQ, et cetera, were not often done at that time but were often done later, so there would be multiple time points in there but different outcomes, and sometimes those things would be spread over multiple publications.

DR. REDBERG: Don't go. My other question relates -- it's a little more specific. On slide 130, and maybe you'll remember it, but is was RFA versus high ligation plus stripping adverse events where you compared the two, but I'm interested in

what was the absolute percentage of adverse events in the two groups? You said there was insufficient evidence to show any difference, perhaps it favored RFA, but I'm interested in what was the absolute rates of adverse events.

DR. VEMULAPALLI: So what I would have to say to be completely accurate is that I could give you a written response to that.

DR. JONES: We'll have to look at the report. It's in the report but we don't have it in the slides, and this phone is big but it's not that big.

DR. REDBERG: I have your report but it's huge.

DR. JONES: We'd be happy to email it to the panel, if you'd like.

DR. REDBERG: Okay, thanks. Dr. Sedrakyan.

DR. SEDRAKYAN: So, I'm thinking the same way, Art Sedrakyan. I have a question for the tech assessment team, but also any clinician who would like to answer this. So, the long term and intermediate term, in my head I thought you were going to talk years. In a natural history of post-surgery recurrence,

what are we looking at, are we looking at five-year or ten-year recurrence, and it seems to me all the short term comes out of the technology, the new technology that came, it was convenient to study short term because it's hard to go long term and it's easier to document short-term benefits. But I'm not really sure, I have a picture of epidemiologic history of postsurgical recurrence, repeat interventions, and what are we looking at, three, five, ten years, and what does it look like with new technology and surgery that we seem to be abandoning?

DR. O'DONNELL: O'Donnell again. We recently did a systematic analysis, a systematic review and meta-analysis of the endovenous ablation and narrowed it to those studies that had greater than two years followup. And what we found, there were eight comparative arms, and what was very interesting, and they were comparing it versus ligation and stripping, there was no difference in the incidence of recurrence between stripping and endovenous ablation.

DR. SEDRAKYAN: What time period?

DR. O'DONNELL: This was two years or greater.

DR. SEDRAKYAN: How about five years?

DR. O'DONNELL: There are several studies, particularly the Rasmussen, that was at five years, but what was different is the mechanism of recurrence was different between ligation and stripping and endovenous ablation.

The other important point, it is chronic venous insufficiency so it's a chronic disease, and one of the components that enters in as you go out is progression of disease causing more varicosities. So there is data out there, but it's very interesting, there's no difference whether you do it by surgery or by endovenous ablation.

DR. SEDRAKYAN: Based on one study at five years and a few studies at two years, is that right?

DR. O'DONNELL: I said eight at two years and there's one five-year study.

DR. SEDRAKYAN: Understood. So just continuing the same line of questions about, you raised, Rita, about how many of these devices, new technologies have specific

indication for treating, for key question two or key question three, stents or RFA and sclerotic devices, how many have obtained from FDA specific indication, not just for tissue ablation, so basically on label? Can anyone comment?

DR. COMEROTA: I can comment on stents. In the United States there is no stent on label for dilating a venous stenotic lesion or an occluded vein.

DR. SEDRAKYAN: How about the less invasive technologies, RFA, laser, any of them have specific indications?

MS. WISE: Yes. This is Leslie Wise, I work for industry. So yes, RFA and laser both, or EVLT, has a specific indication and radio frequency has a specific indication.

DR. SEDRAKYAN: What is it specifically for, for type of lesion, or any specifics that exist?

MS. WISE: To treat varicose veins.

DR. SEDRAKYAN: Blank, blankets?

MS. WISE: Yeah. They're not going to say chronic venous insufficiency. I can look up the indications for you.

DR. LURIE: To answer your question at the risk of being not precise, because I really have to look at the FDA documentation, but basically those devices indicated for treatment of saphenous reflux, not the varicose veins, and that's a big distinction.

DR. REDBERG: Thank you, Dr. Lurie. Thank you very much, I appreciate all of the presenters and their answers to the questions.

And we now have time for our panel discussion, so I'll start with a few comments and then we can have a -- well, actually if you want to raise your hand, I can call on people, whoever wants to discuss.

But I think, you know, we've heard a very good representation of the evidence and clinical perspective. I think what was most striking to me are certainly the evidence gaps and you know, we have the particular charge of thinking of a Medicare population, but even without having that charge of trying to look at people that are over 65 and have comorbidities so are not likely to be like the people in the clinical trials that were still very hard to come by, because they're generally younger and

healthier, but it still seems, we heard, I think 25 million people have varicose veins.

I got the strong feeling, and it's certainly my clinical impression from my own patients, it's very hard to be specific about these diagnoses. It wasn't clear to me at all how the diagnostic tests related to the diagnosis or more important, to patient symptoms and their prognosis. Because we could do a lot of testing, but it just wasn't clear that it was all helpful in terms of helping patients feel better or live longer.

And the same again with the treatments, there's a lot of treatments, but I think the first question even before comparing treatments is, are any of them better than sort of conservative therapy, again, exercise, lifestyle, weight loss, you know, the things we heard, that obesity is a risk factor. Age and sex are obviously not modifiable, and hypertension is a possible risk factor. And so I find we're in that situation now where there are a lot of procedures being done, and we've heard it would be hard to do a trial because everyone is doing the procedures, and it's a

little frustrating to me as a clinician because I want to recommend things that I know will help my patients, yet in this position of having to make decisions, it seems like the cart got ahead of the horse, and that seems to happen.

At any rate, I think we have to kind of, in our discussion, keep in mind the voting questions, which looks specifically at patient-related outcomes, they look at intermediate, near and then long-term outcomes, which is why I wanted to have that clearly defined. And then we're going to vote also separately on symptoms, and patients presenting without symptoms.

And again, it seemed that a lot of the diagnostic criteria that were called symptoms were not actually symptoms in that patients don't feel them. I mean, a symptom is something that you feel, so looking at a lesion and measuring it is not the same as having a symptom.

So, I think I certainly have a good feeling for what the evidence is and what the evidence gaps are and I think, you know, it's a

challenge. Jeff?

DR. CARR: I have one concern about the somewhat arbitrary cut point of 2000 for the evidence review, especially related to compression, and potentially diagnostic ultrasound, whereas much like coronary angiography, much of the validation work was done prior to 2000, and I see that we really haven't had a formal review or presentation of that, and I think as we interpret the voting on this, we need to explicitly realize that we're stopping our evidence at 2000.

DR. REDBERG: I'm sure they already got 10,000 articles, so it had to start somewhere, but I understand that probably a lot of the compression literature did not get included.

DR. CARR: Right. So to be accurate, we would have to say that the evidence review after 2000 is insufficient but the evidence prior to 2000 is unknown, or unreported.

DR. REDBERG: Doug.

DR. CAMPOS-OUTCALT: Yeah, I first want to respond to that question or comment. We did see presented a number of clinical

guidelines and other analyses that took into consideration prior data, so I think we have to keep that in mind, that while we have the AHRQ report from 2000 forward, a lot of these clinical practice guidelines and other analyses were from before. I mean, that did strike me in the difference, and particularly the enthusiasm for compression of the two different time periods.

I would like to get, before I vote, some definitions settled. On this sheet when it says in adults, does that mean Medicare adults or all adults, that's question number one. And then question number two, can somebody give me an example of a patient in each of these two categories, one and two, who would present with symptoms, I mean without symptoms, but with signs?

DR. REDBERG: And I just want to say, if you want to put your cards up, I see Dr. Salive and Dr. Zuckerman, who I will recognize next. Dr. Schafer, did you want to address that question?

DR. SCHAFER: So, I'm just stepping in, and I'll ask you guys just to comment.

Some of these diagnostic studies came after 2000 so the majority, and I know some of you know this, of the diagnostic studies, that is before, just to sort that out, but you showed different diagnostic studies, and I believe on that paper we say, maybe up in the upper paragraph, we look at outcomes in the Medicare population, so that's what this would pertain to.

DR. REDBERG: So for adults means for Medicare age.

DR. CAMPOS-OUTCALT: So the second one was, I'd like an example of somebody who presents without symptoms but with signs.

DR. DAVIS: I'm Dr. Davis, from APMA. One of the first, I think you saw the literature, 35 percent are diabetics, diabetics with neuropathic symptoms have no symptoms but have the clinical evidence and it's right there in front of you, and we see that a lot and that's just in one, that's a third of what you're looking at with ALUs.

MS. WISE: So what do you mean when you say right in front of you?

DR. DAVIS: Say again?

MS. WISE: Can you explain what you mean when you say it's right there in front of you?

DR. DAVIS: Well, when you have a venous leg ulcer, when you have an ulceration that you have biopsied and it shows that, again, it's consistent with a venostasis ulcer, you have definitive proof, but the patient says I don't feel anything and the only reason I'm here is because my spouse didn't like the smell in the room, or they saw my socks sticking to my leg, I didn't feel it, I could have seen it, but I ignored it because I didn't feel it, and therefore it is not.

MS. WISE: So we don't see signs until C6?

DR. DAVIS: Say again?

MS. WISE: You don't see signs until C6?

DR. DAVIS: Well, many times in our era, they don't see the signs of it per se, and yet when you look at it clinically, you can see hemosiderosis deposits, you can see the venous leg ulcer, you can see the long-term dermatological effects of venous disease and

yet they still don't feel it, they don't have the itch, they don't have the pain, they don't feel anything along the line, except they can visually see that there's a disruption in the skin at times they're looking, but many times they're not even looking, and I think, I would think that that's a third of what we're looking at.

DR. SEDRAKYAN: Can you state your name for the record?

DR. DAVIS: Yes, Dr. Dan Davis.

DR. CAMPOS-OUTCALT: So just to follow up on this, then, these categories of C0 through C6, I'm having a hard time seeing how that pertains to what we're voting on, then, because, as the questions are worded, because when I think about an asymptomatic patient, this is somebody to which screening usually applies, so that we're looking for disease early on so we can, and is there an intervention at that point in time that can improve the outcome long term, and that's not really what this question asks at all, and I don't really see a lot of difference between the two questions to be honest.

DR. REDBERG: Between the two questions of?

DR. CAMPOS-OUTCALT: Between the questions of people without symptoms but with signs, and separating those two. I'm just not seeing that that's the right question to be asked. We've got early disease and we've got late disease, and we're not asking that question, because to me it's a big difference, should I be treating people with early disease, versus treating someone who is asymptomatic and --

DR. REDBERG: So I think --

DR. SHORTELL: Let me make a quick point of clarification. I think that the much more common scenario and I think the one that the question was designed to pick up is the patient with varicose veins and no pain, no itching, no heaviness, no throbbing. That would be much more emblematic, I think, of this question.

DR. REDBERG: Thanks very much, and we're going to continue the panel discussion, and I think part of the issue is that we are looking at a wide spectrum of disease. So I

think it was one of our first presenters, maybe Dr. Allison, who talked about varicose veins and then venous reflux and -- oh no, maybe it was AHRQ -- venous insufficiency and all of those, and it is, I think, an important distinction.

The examples we just heard was first a venous ulcer but then a varicose vein, and there is a big difference in between a venous ulcer. And I think you're right, that, you know, when we say we want to find something early, it's because, the assumption is that intervening early is better than intervening later. I don't know that we have that data for chronic venous disease because I didn't think we saw that, intervening early was better than intervening later, but I think in terms of focusing on the patient, it is important to separate people who are coming in with symptoms, and I think it's important also to distinguish symptoms that will then improve with something we can offer them, and what would that be.

And again, I felt like that was where the literature was again insufficient in really

helping to decide. My tendency is to think more conservatively before thinking more invasively, and it wasn't clear to me that we have the data to say that any invasive therapies were going to be better, and clearly there were adverse effects. But certainly, I think that's why our questions were divided into with symptoms and without. You know, I think the signs is just a little confusing, because a lot of people have varicose veins, 25 million, I think we heard.

DR. CAMPOS-OUTCALT: Right, but signs could be telangectasia or reticular veins and that's very different, you know, C1 signs are very different than C5 and 6 signs, but they're all included in the same question here.

DR. REDBERG: Dr. Salive, did you have something?

DR. SALIVE: Marcel Salive. So, I guess along those lines, I didn't see any presentation from the evidence report on anything relating to asymptomatics or anything broken out that say, so I haven't felt, you know, I don't feel there's strong evidence to support that, I'll just throw it out there.

Echoing another comment someone made, I did review some of the SVS guidelines and I think, you know, the hard part there was, and I think it's been brought up before, it seemed like the SVS was more generous in how they graded the evidence to me, and maybe I'm wrong, I would like to be convinced or otherwise, because they would make strong -- and I think one of the commenters made this point, that they could make, you know, a strong recommendation based on weak evidence, and there were a few of those in the guidelines. There was very few where there was strong evidence and high, or a strong recommendation and high quality evidence for the treatment.

So the treatment that we're talking about in this, you know, I'm mainly referring here to the varicose vein treatment guideline. That guideline didn't have a lot of high quality evidence in it, and it does go back farther than 2000 so I feel good about that, we are looking at more than just a snapshot.

MS. WISE: Sorry, but I guess my question about the data that goes before 2000 is with the rise in diabetes, how applicable

are those studies to the current population of patients suffering from the disease state.

DR. REDBERG: So we did see data from 2002 to 2015, so I believe we have the current data, and the question is, we didn't see older data.

MS. WISE: Well, we saw the San Diego study which was from the '90s, and that was sort of the baseline data that was laid out in the beginning, and that was from the 1990s. I mean, I wrote down that question, how applicable is that as a baseline to evaluate today's mean Medicare population? Because, you know, again, that study says that African-American women were the least likely to have disease, whereas the data now says that that population presents with the most severe disease, there's some disconnect there. You know, I don't think they wake up with C6, so somewhere along the line they had varicose veins that are being -- you know, I think that we really have to examine what impact diabetes is having on the evolution of this disease state, because it is definitely having a significant impact on the vascular side and I

think that's been acknowledged. Is it having the same potential impacts on the venous side and we're just now starting to see that? I know we know utilization is up but clearly we don't know why. The whole tech assessment says all the evidence is insufficient, but are we even asking the right questions is what I'm latching onto.

DR. REDBERG: There's a lot of cards up, so I'm going to go to Dr. Zuckerman and then I'm just going to go to Lawrence, Lewis, Lewis, Cuyjet, Carr.

And to that, I think we have, I mean the current data, I think we all agree that the data certainly is not robust, you know, most of it was insufficient, and that -- but I think, I mean it's clear to me, not everybody with varicose veins is going to go on and get venous ulcers. I mean, I think varicose veins for a lot of people will remain as varicose veins and not look appealing, but will likely not progress. Dr. Zuckerman.

DR. ZUCKERMAN: Diana Zuckerman. So, I want to support this issue of how discouraging it is to have so little data, but

particularly to emphasize, I mean, if 15 percent of the studies had an average age of 65 and older, that still means like approximately half the patients are under, and that number of patients can clearly change the data, the results so that they may not be relevant at all to the older patients. And even if they're relevant to the patients who are 65, it may not be relevant to the ones who are 75.

So we really desperately need, not just for this but for, you know, all data that MedCAC has to deal with, better data and subgroup analysis for the major Medicare population which is primarily, although not exclusively, 65 and older. And with logistic regressions and other types of analysis, it should be possible to look at even the older group, so it's not just 65 and older, but get a better sense of how age changes outcomes for different treatments, and which treatments are better, more effective, and safer for these different groups of patients.

And given that the doctors want coverage for their patients and the patients want coverage for themselves, and the

companies, device companies want coverage for their devices, it's in all of our interest to get those, to get data that proves what works and what doesn't, and for whom. And registries are going to be nice to have and helpful, but they can't answer all these questions. A randomized clinical trial has certain advantages.

And also, just to say that I hope that the registries in addition to really looking at the data separately for these older patients, will also be looking at specific devices, that there are, you know, different laser devices and different stents and so on, to use the unique device identifiers as they become available, and to have data that are very specific to specific products, because it may very well be that some lasers are great and others not so great.

DR. REDBERG: Dr. Lawrence.

DR. LAWRENCE: Yeah, Peter Lawrence. I've enjoyed the discussion about data and the absence of data and the importance of registries, but I think that I would like to shift the focus a little bit more to

appropriateness, because the reason we're sitting here is the 1,400 percent increase in venous procedures, at least I believe that's part of it. And last year it was similar on lower extremities, a dramatic increase in the number of procedures. And for me it's not about the absence of data although the data could certainly be more robust, it's about the indications and the appropriateness of care.

And this is a procedure that shifted from a hospital in an operating room to outpatient surgeries, and now office space. And when it goes to office space, anybody can do it, a psychiatrist can do this procedure and get the same reimbursement as a cardiologist or vascular surgeon.

So my, I was going to ask the question to the two sort of groups that had multiple presentations and/or a consortium of societies, but how important is it, number one, that the ambulatory procedure facility be accredited? Number two, how important is it there be an accredited vascular lab?

I can tell you in my practice that 90 percent of the time when a patient comes to see

me for a second opinion and I repeat the duplex ultrasound which has been done, there is no reflux in a patient who's told that they need six or eight procedures done.

And then the last thing is the specialty, is if we don't have any training in venous disease, and there's several societies that do, or several residencies that do, and no advanced training, then people are getting paid to do procedures that have zero training in the management of venous disease, and it really becomes an economic outpatient model.

And I think that the issue right now, and I wonder if there is a way for -- I know Medicare has addressed it on the inpatient side, and limited certain procedures to certain specialties and certain degrees of training, but until we do that, everybody sitting here can do appropriate procedures, but there's a whole universe of physicians. I work in LA and on the 405 there's the biggest sign I've seen on the 405 advertising these procedures. And when I look up the doctors who are doing them, one is a neurologist who's interested in pain, and the other is a bariatric surgeon. And if

we allow that to happen, I don't think we're ever going to get control of inappropriate procedures and volume.

So I wonder if the one thing that we could do, that MedCAC could advise the CMS, is to somehow link reimbursement for procedure to an accredited vascular lab, accredited outpatient facility, and a physician who has training in the management of venous disease.

DR. REDBERG: So Dr. Lawrence, you didn't think chronic venous disease was a big enough area for us to tackle today, huh? Glad we opened it up to the entire accreditation. I would suggest that's a very important question and we can get to that in the discussion, but our kind of first two voting questions are going to be more on the evidence and the treatment. I would suggest that to me, you said you like talking about evidence, but you want to talk about appropriateness, but to me you need the evidence to talk about appropriateness, although I understand that you're now talking, but I think your implication is that the people who are not particularly specialized in the procedure but

are yet offering it are doing it on non-evidence-based indications.

DR. LAWRENCE: But we're also hearing presentations of data that may be done by people who have no clue as to what they're doing, or they may be nonaccredited, so if a patient has no reflux, then they're not going to get better if they have a procedure if they have light pain.

DR. REDBERG: But that really is in a bigger picture, and I believe CMS takes the position, which is very strongly supported by the AMA, that they do not regulate the practice of medicine, so that's for us, the medical profession to do, you know, to make a decision on whether there should be accreditation, whether only, you know, people trained in the procedure, because you're right, anyone can submit a bill to Medicare and -- but the accreditation issue is really important, but I think it's a little beyond the first two voting questions.

Anyone want to add anything more officially? Okay. Dr. Lewis.

DR. ROGER LEWIS: I'm Roger Lewis.

I'm going to make a comment and while I'm making it, if the AHRQ team and Dr. Henke could stand up, that would be great. My comment is that there were --

DR. REDBERG: Okay, but we're supposed to be on the panel discussion right now, we're done with questions to presenters.

DR. ROGER LEWIS: Okay, I'll just make my comment and they can dispute it later. My first comment is, there were distinctions raised, or concerns raised about the representativeness of RCTs, and a contrast has been drawn between RCTs and registries. To me that's a false choice, and the thing that the chair and others were implying, I just want to make explicit, which is, the way to address this is to do randomized trials that are pragmatic to ensure that the population who ultimately receives these procedures is well represented in the RCTs so that we get the kind of evidence that we need.

So my comment is that, my other comment is that as best I can tell, the evidence basis for improving the outcomes of patients with chronic thrombosis or venous

obstruction except perhaps in cases where there are particular anatomic lesions that caused that obstruction is in fact very weak, and if anybody else on the panel would like to comment on that, that would be helpful to me. My comment is that from what I've heard today, it seems that the evidence of improved outcomes in patients with chronic venous obstruction or thrombotic disease is very weak, perhaps with the exception of patients that have very specific anatomic, for example compression lesions, and if someone could comment on that, that would be great.

DR. REDBERG: That was my understanding as well. Did anyone have a different understanding? Dr. Comerota, did you have a different understanding?

DR. COMEROTA: The question was that the evidence for obstruction is weak?

DR. REDBERG: The evidence for improved outcomes.

DR. COMEROTA: Well, again, it gets to the issue of what's the location of the obstruction and how frequently is it diagnosed. Now obstruction is a very difficult diagnosis

to make with noninvasive techniques, it's exceedingly difficult, very low sensitivity. So then if you look at only anatomic obstructions, they may or may not be hemodynamically significant, and when they do become significant it's usually with exercise, and that's not when we study the patients, we study the patients at rest. So there's an enormous gap right there in how, what capabilities we have to identify obstruction as hemodynamically important.

DR. REDBERG: Dr. Cuyjet.

DR. CUYJET: Just a comment. First of all, I think you summed up the dilemma, the cart before the horse, I think that's what we are dealing with, and I want to expand on Dr. Allison's point.

I think registry data is important. Somebody mentioned the transaortic valve, TAVR data. Three of the hospitals I work with in Long Island are CMS designated TAVR centers, they have very complex valve teams, they're still participants, there's PARTNER I, PARTNER II was published in April, there's 34-R to test a new Medtronic valve that started

recruiting in June. I think we need to get really good registry data and have these studies done at designated centers where the data can be accumulated, we can look at whatever variables we choose to assess outcomes of an intervention, it would be very helpful, but we really don't have that information right now.

DR. REDBERG: But again, there was an RCT before that was FDA approved, and a registry was set up.

DR. CUYJET: Yeah, but that's, the other piece of that is we need to figure out, have a good RCT for the difference. I mean, I don't want to date myself, but in 1975 when I started doing my internship, if you had pain you got a Jobst stocking prescription, end of story as far as the pain was concerned, there was no classification, or you had a vein that needed to be seen in wound care, that was the extent of it. So we could go back maybe another ten years, 1990, look at that data if it's possible, but I think going forward the registry data coupled with RCT data is going to be extremely important in terms of our

recommendations.

DR. REDBERG: Dr. Carr.

DR. CARR: I was just going to mention that in the AHRQ report they did reference at the end the U.K. NICE report, which they have, and I did review it before this, and I think they did a really comprehensive review with very specific recommendations related to referral over probably a wider evidence base, and I just would say as CMS looks at what they derive from this session, that they include the U.K. NICE report as data that should be evaluated, because I think it, I don't want to take any more time but they identify symptoms, they identify referral for wound care, and then they identify a triage along with some, that's very similar to some of the guidelines that we've seen. And at least in my point, I saw that as perhaps a more neutral and extensive evaluation of the literature than some of the registry presentations on their own.

DR. REDBERG: Right, and just a comment on disconnect that people have commented on. I think it's pretty common that guidelines have a more liberal interpretation

of the evidence that are frequently not as rigorous in terms of evidence base as evidence reviews, and I think that's what we're seeing in this case as well.

So, we have about 15 more minutes and seven more people that have cards up, so we can have that much more discussion. Does that mean you're changing your mind? Okay, then I'll just go down the line. Dr. Lewis, and then Dr. Wise and then Dr. Comerota.

DR. SANDRA LEWIS: It seems to me that the big concern here is we don't know the natural history of disease, and at some point perhaps registries are the way to help us with this. We might see this huge percentage of people with venous varicosity but we have no idea what percentage of them or what, if we're going to call them risk factors or associated factors seem to impact this, and at this point it would be very hard to develop appropriate use criteria without understanding the patients that we're dealing with and where we're going with it.

DR. REDBERG: Sandra, I just want to clarify because I think that's an important

point, but you're really saying, because most of our current registries are procedure based, but you're suggesting registry as a way of gathering data, because we in the U.S. as opposed to a lot of the Scandinavian countries don't track people, you know, long-term for outcomes. So you're just saying registries of people with varicose veins unintervened, so we know how they do over years?

DR. SANDRA LEWIS: Yes.

DR. REDBERG: Okay.

DR. SANDRA LEWIS: And then as we look to answer the questions, is symptom control a health outcome, or are health outcomes more infection, disability, I'm not sure where we draw the line, and I think that's going to be an important thing to think about as we vote.

DR. REDBERG: I think symptom control is a health outcome, certainly that's what's important to patients. I think one of the challenges I saw in the data, as I said, was because most of the patient reported outcomes are very subjective, you really do have to have a double blind trial, and none of the data we saw was double blind trials.

DR. SANDRA LEWIS: And we don't have good data on whether there is symptom control.

DR. REDBERG: Right, thank you. Ms. Wise.

MS. WISE: I want to I guess address the issue of the lack of RCTs. I think that as we continue to talk about this issue of heterogeneity, the RCTs that we're talking about just will never exist. There's no way that we can look at all of the different possible interventions in specific, you know, C6, C5, C4, C3 and have enough numbers per one study, because I think that what we have to face is that the cost of doing -- the reason why device trials are so much smaller than drug trials is because one procedure costs you thousands of dollars to do it in a clinical trial. It's not like having someone take an antihypertensive and it costs the drug company a hundred dollars per person per month. In the case of a device trial it costs an industry partner thousands of dollars per patient, so our trials are historically always less than 200 patients, it's very rare.

If you noticed, the Varithena trial

was a thousand patients, but that's a drug. So in device trials you're just not going to see that because we don't have the resources to have thousands of patients in an RCT. With that said, I think that putting together, as a number of the clinicians have suggested, very specific information to capture in a uniform way of capturing information, to use it and then develop some very targeted RCTs to frame some very specific questions is a more realistic approach.

But waiting for the day that we're going to design an RCT where we're going to capture 10,000 patients is just, I don't think it's ever going to happen, particularly with technologies that have been on the market for ten or 15 years. So I think that it's important for us to think pragmatically, and I hope CMS is thinking pragmatically about what's the best and most realistic way to capture the evidence that's going to help us understand how best to treat these patients and when to best treat them.

DR. REDBERG: Diana, did you want to comment on that?

DR. ZUCKERMAN: Yeah, thanks. Diana Zuckerman. Yeah, I agree we're never going to have randomized clinical trials with 10,000, but it would be nice to have them with 200. You know, there is just a world of difference. I mean, some of those studies had 43 people, that's just never going to be enough. And yes, it will be necessary to target the groups, and it won't be a huge variety of treatments and a huge variety of conditions, but what we need are some good studies of specific indications and specific products, and comparing them to some of the things that don't cost money such as exercise, or don't cost much money such as exercise, or drugs even, in order to get affordable meaningful outcomes.

DR. REDBERG: Right. The alternative is, you know, spending millions on devices that may not work and may be harmful. It seems worthwhile for us collectively to invest in good data. Doug?

DR. CAMPOS-OUTCALT: Yeah. I don't think we should get hung up on -- I mean, randomized control trials are good and you like to see them, and if they're done correctly give

you high level evidence, if they're done poorly give you lower level evidence. You can have high level evidence with good observational studies, and that's where I would like -- I mean, I agree in many of these we're not going to see randomized control trials, so I'd like to see better observational studies, standard definitions, uniform data collection, control for variables that could be affecting the biases, and that's where I'd like to see some of the efforts be given, let's get some higher quality observational studies which then can lead to high quality evidence.

The grade system does not demand AHRQ randomized control trials to get a high level of evidence or high level of confidence, you can do that with observational studies that are done well, that have large magnitude of effect and are consistent, with consistency between the studies, and to me that's where we ought to be spending some effort here.

DR. REDBERG: Art.

DR. SEDRAKYAN: I'm looking at our voting questions so we get more specific. I mean, it's probably, question one is going to

be the most important and we're probably going to have a lot of discussions if it turns out there is good evidence for intervention, and I think we're asked to vote which ones specifically. So I would focus on question one more, and I'm reading the question. It says for adults with varicose veins and/or with symptoms or signs of chronic venous insufficiency, how confident are you there's sufficient evidence for interventions that improves intermediate health outcomes in patients presenting with symptoms?

Now it goes back, is it with symptoms alone, without signs, or symptoms and signs? I think we need to have a qualifier on --

DR. REDBERG: We're going to vote on those separately, Art.

DR. SEDRAKYAN: But then it says with symptoms but without signs, so I want to make sure that A is with both symptoms and signs.

DR. REDBERG: Okay.

DR. SEDRAKYAN: Because I'm hearing Peter Lawrence's comment on C2, and I'm worried about getting itching and pain, that patient is presenting, and confined to present so it's

paid for, and you obviously have the symptom of vein pain, so I think we need to qualify it here to make it more specific.

DR. REDBERG: Veins are not the symptoms, veins would be the signs.

DR. LAWRENCE: I agree that there's a concern if there's such a range, that you're going from varicose veins to venous ulcers in this question, and there could be strong evidence for one where you believe that there are, and weak evidence for another. When you have to put them all together and mix them, it forces you to sort of go to the midpoint, which is an average, although you might believe in some circumstances this is a five and in others it's a one, and that's the challenge of answering these questions.

DR. REDBERG: So as you know, and we're getting to the vote in just a minute or two, the panel, the voting members will vote and then you can all say why you voted the way you did. It's a very complex area and I think the questions try to address it as best they could. Dr. Comerota, did you want to make a comment.

DR. COMEROTA: Well, it was going to be a followup on the comments about the randomized trial and the difficulty getting patients in because procedures aren't available. If a trial could be designed that is a crossover study so that the patients' reluctance to coming into the trial is diminished, you may be able to get a broader base of patients and get better patient enrollment because after a certain period of time, i.e., six months or a year offering controlled care, whatever that is, they could be offered a procedure if they're not improved. That may be a much more effective way to get the randomized control data that we need offered to a broader base of patients.

DR. REDBERG: You could, you know, for example, in the National Emphysema Treatment Trial, the lung volume reduction surgery was only offered in the context of the trial and that, you know, you could recruit very quickly in a trial like that. That was a CMS-NIH joint effort which I think worked very well in terms of answering the question.

And I think this is a challenging area

because it's not one procedure versus nothing, there are a number of different approaches.

But I think that we have now kind of moved to the voting questions, and so everybody has the voting questions in front of them and Maria is giving out the clickers.

So I am just going to remind you of the scale which is also on the top of your voting questions, but it's a one to five scale, and one means you have low confidence and five means you have high confidence, and I'll read each question.

The first question is actually four questions, because A has two parts and B has two parts, and so we're going to vote them as four questions, and the same for two. Does anyone have any other questions before I read the first question for a vote? Yes, Diana.

DR. ZUCKERMAN: I'm sorry, I have a question about the first question. Because it includes signs or symptoms, and I thought we were distinguishing between them.

DR. REDBERG: It's divided in the A and B part, so in A it's going to be presenting with symptoms. The general header included

both to be more general.

DR. ZUCKERMAN: Okay, sorry about that.

DR. REDBERG: Okay. So I'll read the questions.

MS. ELLIS: Yeah, we're just waiting for the questions to project on the screen.

DR. REDBERG: Okay, I'll read it while we're waiting. For adults with varicose veins and/or other clinical symptoms or signs of chronic venous insufficiency, how confident are you that there is sufficient evidence for an intervention that improves intermediate/near-term health outcomes in patients presenting with symptoms? So again, symptoms are things patients can feel.

So, can they go ahead and vote on that, Maria?

MS. ELLIS: One second.

DR. REDBERG: Okay. Any other comments or questions while we're waiting? Yes, Leslie.

MS. WISE: So when it says improved, what is improving, the signs or the symptoms? I mean, because improving symptoms makes sense,

right, but if a patient has no symptoms or signs, what are we improving?

DR. REDBERG: The intermediate/near-term health outcomes in patients presenting with symptoms. So we're voting on whether there was improvement in health outcomes.

MS. ELLIS: If you would like, I see some panel members have already started voting so if you would like, you can go ahead and select your vote while we're getting this on the screen, and then also have them go down the line and say their votes.

DR. REDBERG: Okay, we can do that. So everyone can go ahead and vote and when we have the votes complete, we can start down the line with why you voted the way you did, and at some point that will catch up.

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

MS. ELLIS: All right, we're waiting on four people to vote, I have five of nine, six of nine. If everyone could just push your vote one more time. I have seven of nine, eight. One more. Okay. The mean was 3.33,

and again, we will show it on the screen. There it is.

DR. REDBERG: Okay. So we can start with Art, and say why you voted.

DR. SEDRAKYAN: I voted four, and the reason I voted four is because the question includes patients who are very likely to benefit from intervention. I'm assuming the range of patients we're talking about from visible signs up to the ulcer in the category, it's hard for me to say no, because certainly, and particularly also taking into account that near-term outcomes can include quality of life measures and confidence and many other items that are psychosocial, and I feel like we didn't differentiate those, so it's hard to say no to this, posed this way for this question.

DR. REDBERG: Doug.

DR. CAMPOS-OUTCALT: I rated three, and as a general rule I tend to be a hard grader and pretty methodologically rigid, and here I just find the data to be too heterogeneous, not well defined. However, I'm still moderately convinced that there's benefit for a defined group of people.

DR. CARR: Jeff Carr. I voted four, similar reasons to the previous two.

DR. CUYJET: Al Cuyjet. I voted a three, being quite literal because it's immediate and near-term health outcomes and the range is very broad so that leaves a lot of leeway.

DR. LAWRENCE: I voted a four rather than a three or a five because I think most patients would improve, but I can come up with one where I think there would be no benefit, which is a patient with deep valvular incompetence and no superficial incompetence who has symptoms, and they will not be helped by any treatment.

DR. ROGER LEWIS: I voted a four, I interpret this as being confident that there was some benefit to some patients who were symptomatic, leaving unanswered the question of who that would be.

MS. ELLIS: I'm sorry, could you please state your name before you say your vote?

DR. ROGER LEWIS: That was Roger Lewis.

DR. SANDRA LEWIS: Sandra Lewis. I voted three for pretty much similar reasons.

DR. SALIVE: Marcel Salive. I voted three for similar reasons.

DR. ZUCKERMAN: Diana Zuckerman. I voted two because of a lack of data on the right age group. I mean, I think there probably are treatments that work, and they work for some people under some circumstances, but I don't have a lot of confidence that it works for this age group.

MS. WISE: Leslie Wise. I voted four for reasons previously stated.

DR. CARMAN: Teresa Carman. I voted four for similar reasons.

DR. COMEROTA: Anthony Comerota. If I were to vote, I would have voted three, because there's I believe robust observational data but the methods of generating the observational data were not well controlled.

DR. REDBERG: Well, I shared, like I said, the lack of confidence in the data applying to Medicare beneficiaries in addition to the heterogeneity, but I don't vote.

Okay. I'm going to just read the

second part of the question and not belabor the entire question, because now you're voting on the same group, but now it's in patients without symptoms but with physical signs.

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

MS. ELLIS: We're done.

DR. REDBERG: Okay, and the mean was a two, and should we go down again?

MS. ELLIS: Yes.

DR. REDBERG: Okay, so Art?

DR. SEDRAKYAN: Sedrakyan. This is going to be controversial. I voted three and let me explain why. Not because I believe there's evidence, but because of what we've heard, people who have signs, you know, and don't have symptoms, it's so natural, because they would like to have symptoms to get reimbursed for their therapy, that's what Peter said. So this leaves the category that one of the presenters highlighted, diabetic patients can't feel it, and that made me like uncomfortable, whether this question is going to end up being really controversial. If we were to ascertain that people won't make up

their symptoms to be reimbursed for it, I would certainly vote zero, but the way the question is asked, unfortunately it leaves the room for some issues. So I'm glad it's two still, but I think I'm an outlier.

DR. CAMPOS-OUTCALT: Yeah, I voted a two. I did so because I have slightly less confidence than I had in question 1.a.

DR. CARR: Jeff Carr. I voted three, again for the reason that if someone had signs, i.e., a big ulcer, there's fair evidence or fairly good evidence that compression and some therapies would improve that, so I saw that as something that could be a sign without a symptom that could mandate treatment.

DR. CUYJET: Yeah, I voted two. There's been a lot of discussion about our lack of knowledge of the natural history of the disease and it's a complex, not a single disorder, so if patients are asymptomatic, I don't have any evidence to support interventions.

DR. REDBERG: State your name.

DR. LAWRENCE: I voted a three, moved it down from a four --

DR. REDBERG: That would be Peter Lawrence.

DR. LAWRENCE: Peter Lawrence, sorry. I voted a three, moved it down from a four because I know of patients who have no symptoms but have physical signs such as a healed ulcer C5 or C6, and those with C1 who would not benefit, so I think it's right in the middle because there are some who would and some who wouldn't benefit from this when they have no symptoms.

DR. ROGER LEWIS: Roger Lewis. I voted a two because of the lack of representation of this patient population in the data that were presented.

DR. SANDRA LEWIS: Sandra Lewis. I voted a one because of lack of representation, and just not very confident.

DR. SALIVE: Marcel Salive. I voted a one for the same reasons as the last two speakers.

DR. ZUCKERMAN: Diana Zuckerman. I voted a one. I guess I'm just to say, I would have thought an ulcer in addition to being a sign, would also have some symptoms, but maybe

not. But anyway, I still voted one.

MS. WISE: Leslie Wise. So, I actually also voted a one because I assumed the thing, if it's an ulcer, and I'm not a clinician so maybe this is not for me, but it's hard for me to understand how an ulcer would be a sign but not a symptom, so if it is a sign then I guess I would say it's a three, because you have some physical manifestation and you have to intervene some kind of way. But if it's not a sign, then I would vote one because there's no evidence of what you should do with a patient that comes and has no signs, that they are completely, you know, no sign or symptoms or, oh no, they have signs but no symptoms, right. They're not complaining, it's not a problem, you know, if it doesn't bother you, don't bother it, I guess is what I was thinking, but if it were an ulcer, then yes, I would vote a three.

DR. CARMAN: Teresa Carman. I voted a three for the similar reasons in the case of venous ulcers. There certainly is beneficial data demonstrated, it may not be applicable to all levels of CEAP classifications, but

certainly the severe classifications.

DR. COMEROTA: Anthony Comerota. I voted one. I think the fact that a diabetic patient with an ulcer that has neuropathy, the neuropathy eliminates that as an asymptomatic patient. So to use one pathology to negate another pathology doesn't seem reasonable to me, so I eliminate those patients. The overwhelming majority of patients that this question will refer to are those patients with varicose veins, and in that subset are patients with reticular veins, and I think treating those in an asymptomatic patient will not get you benefit.

DR. REDBERG: Thank you.

DR. SCHAFER: Rita, I'm just going to make a comment. So actually, your last comment was what we were trying to get at, but it's difficult to say asymptomatic because if you've got telangectasia, you know, it's still a sign, so --

DR. REDBERG: It's a sign but it's not a symptom.

DR. SCHAFER: Right.

DR. REDBERG: A symptom is something,

you feel it and you call your doctor, that's why you went in. A sign is something that perhaps your doctor notices when you went in for routine checkup or something else.

DR. SCHAFER: So we were thinking more along, if it's an ulcer, you've got other symptoms whether it's a neuropathy or something, so it does not negate.

SPEAKER: But the question does include chronic venous insufficiency, it's not just varicosity.

DR. REDBERG: So now we're going to go to 1.b which is the same question we just voted on, but instead of intermediate and near-term health outcomes, now we're going to vote on long-term health outcomes in patients presenting with symptoms, and then we'll vote without symptoms. And the question is up there so you have it in front of you.

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

DR. REDBERG: Okay, it says the mean was 2.56, which means we're going to have a discussion about the specific interventions for this one as well, and Art, do you want to start

with why you voted as you did?

DR. SEDRAKYAN: Sure, Art Sedrakyan, I voted three, thinking again, the evidence behind surgery for patients with moderate to advanced disease is well documented and well known, RFA and other things are coming up, so I feel like there's a substantial number of patients who would benefit in the long term from removal or ablation of the veins. So if it were more specific in terms of moderate to severe I would have voted five; if it were stratified by less than moderate, mild disease, I would have voted one, but again, it's a matter of classification.

DR. CAMPOS-OUTCALT: Doug Campos-Outcalt. I voted three, more or less for the same reasons I voted three on 1a, I have moderate confidence and I think research could end up changing much of this.

DR. CARR: Jeff Carr, I voted two, mainly because I thought the strength of the evidence was really insufficient for patient-centered outcomes, so that's why I lowered it. Not that there aren't studies showing technical improvement or hemodynamic changes, but I

thought the missing piece was patient-centered outcomes.

DR. CUYJET: Al Cuyjet, I voted two. I know we used greater than six months, but to me that's a short-term outcome, there were two trials that were cited with followup to two years, but I don't have enough evidence to assess the long-term outcome arbitrarily, and if you make it a year or two, you don't have it.

DR. LAWRENCE: Peter Lawrence. I voted a four because there are patients who get long-term benefit with venous ulcers due to either compression and/or ablation, and it reduces the likelihood of recurrent ulcer. And there are patients on the other end of the spectrum with varicose veins who do not have recurrences and a benefit as far as symptoms, so to me both groups benefit, it's not perfect in the data, but it's a four as far as the range of patients who might benefit from this procedure.

DR. ROGER LEWIS: I'm Roger Lewis, I voted a three for reasons that have already been stated.

DR. SANDRA LEWIS: Sandra Lewis. I voted a three for similar reasons.

DR. SALIVE: Marcel Salive, I voted a two. I felt like this did not have very much data and I was not very confident, and I think other people explained that better than me.

DR. ZUCKERMAN: Diana Zuckerman. I voted a one because the combination of lack of long-term data and lack of any meaningful data on patients such as age group, that combination I thought was pretty devastating, and although one hopes that there's something that works for some people in the long term, I just wasn't confident of who that was and what the evidence was.

MS. WISE: Leslie Wise. I voted a four for reasons previously stated.

DR. CARMAN: Teresa Carman. I voted a three just based on the definition of what long term is and the need for longer-term data.

DR. COMEROTA: Anthony Comerota. I voted a three for reasons previously stated.

DR. REDBERG: Okay. So we'll come to the last part of this multipart question, so the same long-term health outcomes question,

but now it's in patients presenting without symptoms but with signs.

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

DR. REDBERG: Okay, and that was a mean of 1.33.

DR. SEDRAKYAN: Art Sedrakyan, I voted one after clarification from Jyme and again, the previous voting was really because of the inconsistencies in terms of patients' symptoms, what they can present and how to get reimbursed for it, but now that we've clarified that, I'm much more comfortable voting one, so that we make sure that's covered.

DR. CAMPOS-OUTCALT: Doug Campos-Outcalt, and I voted one. The combination of lack of data on patients over 65, lack of information about patients presenting with symptoms, but signs without symptoms, I just couldn't go for it.

DR. CARR: Jeff Carr. I voted one, same as the previous speaker.

DR. CUYJET: Al Cuyjet, I voted a two. Again, the range of symptoms and absence of evidence to support a higher level of

confidence.

DR. LAWRENCE: Peter Lawrence, I voted a three, moved it down from a four for the last one. There are patients without symptoms who have C3, 4 and 5 such as lipodermatosclerosis who could benefit from a procedure even though they're asymptomatic based on randomized trials.

DR. ROGER LEWIS: I'm Roger Lewis. I voted a one based on the lack of data presented that would give confidence, and because there was no option of zero.

DR. SANDRA LEWIS: I'm Sandra Lewis. I voted one for similar reasons, although I didn't think about zero.

DR. SALIVE: Marcel Salive, I was thinking about the imaginary numbers, but voted one.

DR. ZUCKERMAN: Diana Zuckerman, I voted one, same reasons as others have mentioned.

MS. WISE: Leslie Wise, I voted one.

DR. CARMAN: Teresa Carman. I voted one, considering the C1 and C2 disease.

DR. COMEROTA: Anthony Comerota. I

voted one because it's very difficult, again, to have a patient with lipodermatosclerosis and/or ulceration that's asymptomatic. The majority of these patients are going to have minimal disease and they will be undergoing a procedure that has potential risk.

DR. REDBERG: Thank you. So, that was very helpful. We now have a discussion, and so two of the four votes had answers that were 2.5 or greater, indicating intermediate confidence or better, and they were both the intermediate outcomes with symptoms and the long-term outcomes in patients presenting with symptoms.

So now in particular for the people that voted higher numbers on those, can you state what the specific intervention is that you had in mind when you gave it high confidence or intermediate to high confidence, and what the associated beneficial outcome was that you had in mind?

DR. CARR: Which one are we doing first?

DR. REDBERG: Well, we'll do intermediate/near-term health outcomes for patients presenting with symptoms, so for, you

know, we voted intermediate to high confidence as a committee, so what specifically, because we all said this was a big group, so you know, was there a specific intervention and a specific benefit that you had in mind when you cast a vote? Yes, Doug?

DR. CAMPOS-OUTCALT: I had in mind compression and endovascular, endovenous procedures, several of which were mentioned, and the outcome being mostly patient oriented, less pain and higher quality of life.

DR. REDBERG: So you thought that the data was convincing, or at least intermediate to you, that compression therapy was beneficial for patients on the outcome of pain.

And Jeff, you agreed with that?

DR. CARR: Yeah, I agree with that, mainly on the compression on the higher CEAP class lesions, that there was sufficient evidence that some therapies would improve patient outcomes.

DR. REDBERG: Any particular patient outcome?

DR. CARR: Decreased pain, wound healing, decreased recurrence of ulcer.

DR. CUYJET: Al Cuyjet. I agree with both the above, and again, for me what I see most typically is pain relief.

DR. REDBERG: For compression?

DR. CUYJET: And/or an intervention such as endovenous laser ablation or radiofrequency ablation.

DR. LAWRENCE: Peter Lawrence. In my experience, compression for patients in the C2 category does virtually nothing, and patients always deny, they try it and it doesn't work, but I think at the higher levels, as was pointed out, that compression works, but --

DR. REDBERG: When you say it works, what are you thinking it improves?

DR. LAWRENCE: Well, in each category, so for edema it controls edema. It depends on -- for the progression of lipodermatosclerosis it improves that with compression. And for patients with venous ulcers using compression, or C5, it prevents recurrence. In other words, compression is good in virtually any category.

DR. REDBERG: For venous ulcers?

DR. LAWRENCE: For anything from 2 to 5, I mean after 2, 3, 4 or 5, compression at

some point, whether it's for dose, or a short or long stretch depending on what it is, there will be a treatment which will help those patients.

But also, there are interventions for every one of them, C2 to C6. If you have a venous ulcer and gross reflux of the superficial system, that patient will heal that ulcer more rapidly or it will not recur if they have ablation of the superficial system. So to me in this group of symptomatic, 2 to 6 benefit from superficial ablation.

DR. ROGER LEWIS: Roger Lewis. My rationale was virtually identical to Dr. Carr's.

DR. SANDRA LEWIS: Sandra Lewis. My rationale was similar to the previous two.

DR. SALIVE: Marcel Salive. I was more of a Doug Campos-Outcalt viewpoint, but basically on compression and endovascular procedures.

DR. ZUCKERMAN: Diana Zuckerman. Yeah, I just wish we had seen some data on the compression compared to placebo, that would have been really helpful.

MS. WISE: So, I think my reading of the tech assessment as well as the NICE tech assessment that was done last year, definitely showed that the endovascular procedures provide some clinical benefit. I will say, though, that the question around compression and the evidence, I know I've heard it said a lot here today that compression should be used, but there are significant questions in the evidence around compression, particularly the need to identify whether the person suffers also from arterial disease. And so like for the NICE guidelines, they don't recommend compression anymore, so I think that that's something that wasn't really addressed in the tech assessment that AHRQ did, and I think it's an issue that needs to be looked at more significantly, so I don't think the evidence was strong in terms of for compression, because it raised those questions and they weren't really addressed.

DR. REDBERG: Thank you, Leslie.

DR. CARMAN: Teresa Carman, and I agree with comments made by Dr. Lawrence regarding compression as well as endovenous procedures for the higher grade, C3 through C6

disease.

DR. COMEROTA: And I would agree with C3 through C6.

DR. REDBERG: I'll just comment, I find it interesting that you're all using this anatomic classification when we're supposed to be commenting on patients with symptoms and I think, to me it's still a little disconnect there.

DR. CARR: But I guess point of information, I thought we clarified that, that just because you had a peripheral neuropathy and you had signs, that we could assume that they had symptoms and signs, but just because you couldn't feel it, that wouldn't exclude you from being in the signs and symptoms class, but I guess it's up to interpretations.

DR. COMEROTA: Rita, were we talking about 1a, question 1a?

DR. REDBERG: We were talking about 1a, although I want to suggest that, unless people have different --

DR. COMEROTA: So they had symptoms, 1a is symptoms?

DR. REDBERG: That's what I said, the

question was with symptoms, but everyone was talking in your answers about CEAP classification, which to me is signs on physical exam.

DR. COMEROTA: Well, it's a more severe physical presentation in a symptomatic patient. If you have a mild physical presentation in a symptomatic patient, we don't have much confidence that interventions will improve.

DR. SEDRAKYAN: Agreed, that's also what I had in mind, severe disease in terms of signs and also symptoms, that's what I had in mind, but I also have combination therapy, not any particular one, but successive therapies or combination therapies.

DR. LAWRENCE: Peter Lawrence. The reason all but C1 is being mentioned here is because in the STEM it says varicose veins are a chronic venous insufficiency, that means C2 to C6 by definition, so all patients, so venous ulcers are part of chronic venous insufficiency, so no one is excluded except for either patients with no veins or telangectasia, so that's why I think we're all referring to

C2, 3, 4, 5, 6. In other words, the STEM basically says C2 to 6, varicose veins are C2 --

DR. REDBERG: I can read what it says.

DR. LAWRENCE: So that's why we're all saying CEAP.

DR. REDBERG: The next part of the question is on the long-term health outcomes. I don't know that we have to go through it again unless you thought differently, that there were different answers, interventions you had in mind for long-term health outcomes than the short term. Did anyone have different interventions or outcomes in mind?

MS. WISE: I think that the evidence suggests that, and I know that it wasn't statistically significant, but it does suggest that the endovenous treatments work better than sclerotherapy.

DR. SEDRAKYAN: But this is long term, so we don't have much long-term evidence.

DR. REDBERG: Okay. The second part of the discussion is considering the heterogeneity of the Medicare population, discuss for which subgroups of the Medicare

population the evidence demonstrates likely benefit, or which subjects are not likely to benefit from interventions. Roger?

DR. ROGER LEWIS: I'm Roger Lewis. I didn't see any evidence presented or in the literature I was able to review to be able to answer that question either way.

DR. REDBERG: Yeah, I agree that there was a dearth of evidence in the Medicare population and on subgroups, particularly as Sandra noted, it did have more women than men which we don't generally see in cardiology studies, but the results aren't broken out by sex, and so we don't know how women did compared to men. There was nothing on race ethnicity as Leslie noted, and there was certainly maybe differences there as well, and we really had very little data in patients over 65 with comorbidities, which is the Medicare population.

MS. WISE: Right, so they said they could come back, maybe not today, but will that analysis end up being published in the final report?

DR. REDBERG: We'll get back to you on

that. Okay. If there's no other comments, we can go on to question two. So for adults with chronic venous thrombosis and venous obstruction, including individuals with postthrombotic syndrome, how confident are you that there is sufficient evidence for an intervention that improves intermediate/near-term health outcomes in patients presenting with symptoms? And again, I believe we're thinking about the Medicare population.

MS. WISE: I have a question and just wanted clarification. Are we talking lower extremity only here? Yes?

DR. REDBERG: Yes.

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

DR. REDBERG: Okay. So the mean was 2.11, and now we can talk about why we voted.

DR. SEDRAKYAN: I voted one. I just didn't see much presented on effectiveness of these therapies for this population of patients. Still, I mean, I see that this is a serious condition that requires therapy, but I just couldn't understand which therapy and what

is the evidence right now, so I was a bit confused. But at the same time I see the severity of the problem and something needs to be done, we can't take a nihilistic approach that it's an incurable situation here, but I still voted one.

DR. CAMPOS-OUTCALT: Campos-Outcalt. I voted two, and had similar reservations.

DR. CARR: Jeff Carr. I voted three with, you know, immediate symptom relief for proximal disease.

DR. CUYJET: Al Cuyjet. I voted three and I'm actually leaning into the evidence, because it states it's chronic in patients with symptoms, which implies progression, and one of the parameters it's looking at is functional capacity in these patients, so I give it a three, borderline.

DR. LAWRENCE: Peter Lawrence. I voted a three because I believe there are several large observational trials that have looked at the outcomes in patients with chronic venous stenosis obstruction, showing that there's an improvement in either symptoms of leg swelling or symptoms of heaviness, or

healing of ulcers. So based on that, although I don't think the evidence is great, which is the reason I left it as a three, I still think there's enough evidence to justify the procedure.

DR. ROGER LEWIS: Roger Lewis. I voted a two. In my mind there is a distinction between the patients with an obvious source of venous obstruction versus a patient with postthrombotic syndrome. I thought the evidence was a little stronger for those with venous obstruction and weaker for those with postthrombotic syndrome and that averaged to a two.

DR. SANDRA LEWIS: Sandra Lewis. I voted one for concerns that there just was not a great deal of evidence to support it, even though it's a serious problem.

DR. SALIVE: Marcel Salive. I felt this was a two, and there was need for replication to have any stronger feeling than that.

DR. ZUCKERMAN: Diana Zuckerman. I voted for a two, I think a little bit of wishful thinking there, there's something

somewhere, I'm just not sure where the data are to prove that.

MS. WISE: Leslie Wise. I voted a one for reasons previously stated.

DR. CARMAN: Teresa Carman. I voted a three for reasons similar to Dr. Lawrence. I do agree that we have fairly strong observational data.

DR. COMEROTA: Anthony Comerota. I voted a three. If we focus on the iliofemoral system and the iliac veins instead of the infrainguinal system, there probably are stronger data there in my personal experience in patients, especially with postthrombotic obstruction, they have remarkable improvement.

DR. REDBERG: Are you thinking of a particular intervention?

DR. COMEROTA: Particularly venous stenting, yes.

DR. REDBERG: And the improvement would be in what outcome?

DR. COMEROTA: Pain and edema, and if a patient presented with ulceration, the speed of healing of ulcers once obstruction is relieved is remarkably different because their

compartment pressures are significantly reduced. And then the prevention of recurrence is substantial, but there's not lots of data out there.

DR. REDBERG: So it's still a limitation, okay.

So the second part of that same question is now in patients, and again intermediate and near-term health outcomes, in patients presenting without symptoms but with signs.

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

DR. REDBERG: Okay, it's 1.44, and we can --

DR. SEDRAKYAN: Art Sedrakyan, I voted again one. To me it doesn't make any difference between the first question and this question, it's the same considerations.

DR. CAMPOS-OUTCALT: Campos-Outcalt. I voted a two or, I'm sorry, I voted a one, and I even had more trouble seeing a patient without symptoms but having signs here, and I just don't think that was addressed at all in anything we have.

DR. CARR: Jeff Carr, I voted a two, similar reasons.

DR. CUYJET: Al Cuyjet. I voted a two, again for similar reasons.

DR. LAWRENCE: Peter Lawrence. I voted a two because I think there's one group of patients who benefit and that's those patients with unilateral, a swollen leg that's asymptomatic, and have a proximal vein stenosis which is May-Thurner syndrome.

DR. ROGER LEWIS: Roger Lewis. I voted a one because of the lack of data that were presented.

DR. SANDRA LEWIS: Sandra Lewis. I voted a two for similar reasons.

DR. SALIVE: Marcel Salive. I voted one for similar reasons.

DR. ZUCKERMAN: Diana Zuckerman. I voted a one for lack of data.

MS. WISE: So, I think I confused symptoms and signs again, so I'm going to say a two. If a swollen leg is a sign and not a symptom, then I would say a two.

DR. CARMAN: Teresa Carman. I voted a two, similar reasons.

DR. COMEROTA: Anthony Comerota. I voted a one. Respectfully, with what Dr. Lawrence said, I still, most of my patients with edema have symptoms of leg heaviness, so that removes that group as asymptomatic, and it's very difficult to make an asymptomatic patient thinner.

DR. REDBERG: That's true. Okay. So the same question, but now we're going to address long-term health outcomes, and the first vote will be long-term health outcomes in patients presenting with symptoms, and again, it's chronic venous thrombosis and venous obstruction.

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

DR. REDBERG: Okay. So it's a mean of 1.56 and we can, again, have a little discussion.

DR. SEDRAKYAN: Art Sedrakyan. We can't be, you can't give a higher score than for intermediate or near-term outcomes, it's worse than even intermediate outcomes, the evidence out there. But I really would like us later on to talk about the subgroup effects

that keep coming up, that some of us are voting higher because of those subgroup effects, and I wish it would be at least observational data on the subgroup effects in the studies that have been presented, it would have helped.

DR. CAMPOS-OUTCALT: Campos-Outcalt. I voted a two for the same reason that I voted a two for 2a.

DR. CARR: Jeff Carr. I voted a one because I saw very little long-term outcome data, insufficient data to vote higher.

DR. CUYJET: Al Cuyjet, I voted a two. Again, the conundrum's twofold, definition of long term, and what we've heard about comorbidities, I don't know how you define long-term health outcomes when I haven't heard any evidence to support improvements.

DR. LAWRENCE: Peter Lawrence, and I voted a three because in the category (a), which was with symptoms, that's for immediate results, and we were close to that in our average. And for long-term results, the stent patency in most series is close to a hundred percent, so it doesn't get worse, and I think it does some initial treatment, but also has

important long-term effects such as maintaining ulcer healing and maintaining the lack of a swollen leg.

DR. ROGER LEWIS: Roger Lewis. I voted a one because of the lack of data, especially patient-centered outcomes that would apply to this question.

DR. SANDRA LEWIS: Sandra Lewis. I voted a two because of the possibility for ongoing ulcer healing, which may take longer than that immediate short term.

DR. SALIVE: Marcel Salive. I voted a one for lack of evidence.

DR. ZUCKERMAN: Diana Zuckerman. I voted a one for lack of evidence.

MS. WISE: Leslie Wise. I voted a one.

DR. CARMAN: Teresa Carman. I voted a three along the same lines as Dr. Lawrence. We know that even though we didn't see the data presented here, the stent durability is certainly demonstrated in the literature and I think these patients do have good long-term outcomes.

DR. COMEROTA: Anthony Comerota. I

voted a three for the same reasons of Dr. Carman and Dr. Lawrence.

DR. REDBERG: Okay. Now we get to the fun part of having additional discussion topics.

MS. ELLIS: We have one more.

DR. REDBERG: Oh, I'm sorry about that. So the last vote is the same question on long-term outcomes, but now it's in patients without symptoms but with signs.

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

DR. REDBERG: Okay, and it's a low confidence vote, this is our lowest one, of 1.22. Did you want to make any additional comments about your votes?

DR. SEDRAKYAN: Same reasoning as before.

DR. CAMPOS-OUTCALT: Campos-Outcalt, I voted a one.

DR. CARR: Jeff Carr, a one.

DR. CUYJET: Al Cuyjet, two.

DR. LAWRENCE: Peter Lawrence, two for the same reasons, that things don't change in certain procedures for proximal disease.

DR. ROGER LEWIS: Roger Lewis, one, same reasons.

DR. SANDRA LEWIS: Sandra Lewis, one, same reasons.

DR. SALIVE: Marcel Salive, one.

DR. ZUCKERMAN: Diana Zuckerman, one.

MS. WISE: Leslie Wise, one.

DR. CARMAN: Teresa Carman, two.

DR. COMEROTA: Anthony Comerota, one, and I would just add that there are large, substantial observational studies that show incidental obstruction of the iliac vein in patients that are asymptomatic, and have CT scans for other reasons, and they do not warrant intervention.

DR. REDBERG: Interesting point. Okay.

Now, we can get to that discussion I was so anxious to get to, I missed the last part of the question. And this is one that I think we have had already some pretty rich discussion on and heard from the presenters, on what are the evidence gaps in venous disease that haven't been previously or sufficiently addressed.

And just to reflect back, I think what I've heard from you is we don't really know the natural history, which I think is an important question. Certainly when I read the evidence review, I think one of the things I was struck by was the comment that we have a much higher rate of chronic venous disease, particularly varicose veins in the U.S. than in other countries, and the suggestion that there were lifestyle or cultural factors that were different, we have higher rates of obesity and we have higher rates of sedentary lifestyle, and how was that related. But again, you know, is it a -- so I think knowing the natural history is important, and certainly the risk factors.

I think we've also talked about the heterogeneous nature of the data that we do have, the lack of sort of generalizability to the Medicare population because of the inclusions and exclusions in the data that is currently there, the lack of older patients, the lack of data by sex, race and age even within the Medicare population, because we now have a Medicare population that goes from 65

but well up into the 90s.

And then finally, as I noted, I think for any procedure based trial it's important to have, or any trials, to have a double blind, because of the placebo effect, particularly because we're looking at patient related outcomes.

But are there other evidence gaps, then? Jeff.

DR. CARR: I would like to just say that as a strong proponent of randomized control trials, and since this is Medicare, the experience with both transcatheter aortic valves, lung reduction and lung cancer screening, I think is informative, because CMS required the trial to demonstrate benefit before payment. However, in the situation related to these procedures, my understanding is that many of them are being paid without a randomized control trial, so the facts on the ground are significantly different than those other situations.

I think that the example of requiring structured elements by CMS for reimbursement for procedures is a precedent, such as the

required patient shared decision-making visit before enrolling in lung cancer screening, is a model that could be used to require coordinated elements to be obtained before paying for these procedures, especially based on the TEC assessment that shows largely with the best of insufficient evidence that we have, that they have similar albeit unknown outcomes. And I would just encourage us to collect or mandate those type visits where we collect the key variables that would be needed to help plan a trial.

MS. WISE: I wanted to make a point of clarification, though, so --

DR. REDBERG: Please state your name.

MS. WISE: Leslie Wise. There are RCTs on these interventions so that part is not correct, there are RCTs on laser, there are RCTs on RF, RCTs do exist. They just found that there was not enough of that evidence, so that's why I'm saying that becomes a challenge, of when is it the right trial. So since there are RCTs and they haven't answered the questions we should have answered, having the structured data point that was spoken of

earlier might be the best way to supplement the evidence that already exists, and then from there figure out if there are other very targeted questions that could be answered by additional RCTs. But I just want to make sure that, you know, there is not the impression that there are no RCTs, because there are.

DR. REDBERG: And I think we got that in the evidence review, but it was more a concern with the quality of the RCTs, the heterogeneity of endpoints, the lack of blinding, you know.

MS. WISE: Which is what I was saying earlier, with the wide range of patients, the wide range of the disease, etiology, you know, I mean, there are just so much variability, it would be hard to have the perfect RCT.

DR. REDBERG: That's just a suggestion, and it gets a little bit into our discussion question five, but sort of a coverage with evidence development approach sort of, has been certainly a successful model, but it's hard to do that if it is available outside of the clinical trial as we learned with the PFO occluders, which took forever to

recruit, but for a trial where you have to be participating in a clinical trial in order to be reimbursed, the recruitment is much quicker and then we have evidence much quicker.

I saw Doug, Art, and then Peter, and then Diana.

DR. CAMPOS-OUTCALT: Yeah, so I'd like to see a larger number of observational studies with standardized definitions and data collection. And I also think that there's very few comparative effectiveness trials which then goes to my next point, which is cost effectiveness. I would like -- to me there's potentially a wide variation here on cost effectiveness that could have a lot of implications for Medicare.

DR. SEDRAKYAN: Art Sedrakyan. I would like to comment, I mean, we already voted today that there is an intervention that can help with these patients, particularly question one, so I think for that question, it's too late probably to think about a large pragmatic trial, what would be the comparator? And technology to me proliferated, there is a lot of technologies out there now, and with the UDI

coming up, there's going to be even differences between the different technologies. So I think for that question to me, we need to focus now on the comparative effectiveness in terms of improvement over time as a cycle for improving technology, which will in turn improve our confidence that this is a good intervention, the interventions are improving in helping patients.

So from that perspective, I think we also need to focus on quality of doing these therapies, and making sure it's not done inappropriately by people who are not well trained, which will in turn also improve the effectiveness margins for technologies, and that's why I believe that a quality registry concept that we're thinking about, many of us thinking, the VQI example or other registries, is really a very good mechanism to incorporate the changing technology evolution.

And like the example of orthopedic devices that you alluded to, Rita, where there are very good quality registries that you see overseas in the U.K. and Australia where they track outlier performance for technologies. I

think we would be able to improve over time and focus on best, those technologies that are providing best outcomes.

And I think it's similar to what you alluded to also for metal-on-metal implants. If we were to do a trial from the outset, it was very needed because it was a totally new technology coming up, but then subsequent evolution with ASR could have been captured already in a setting like a registry. So I think we need that somehow like the metal-on-metal example, we saw that opportunity for question one.

And now it's at least, we have to do that comprehensive all-inclusive registry, anything that's a multiple registry, they have to collaborate, share the data, harmonize the data elements, and be able to link it up with CMS claims, particularly for the CMS population, to look at their longer-term outcomes that we care about. That's another gap in my head, five years and beyond, three years and beyond. Maybe we can't collect directly the data, but registry linkage has been shown to be a good mechanism to look also

at what happens to patients over time.

Repeat procedures that I particularly, I would like to learn more about, because certainly these add costs, so through linkage studies we can do a lot more in terms of long-term outcomes. But before that, it has to be a high quality registry in place at least collecting reasonable baseline data to allow us to do those comparative studies.

So for question two, I certainly believe there is still a need for a large pragmatic clinical trial like the lung volume reduction in coverage with evidence development in the trial. So again, CMS recommendation to include patients into the registry for question one could help us to keep this and make this a hundred percent participation nationwide, so I really would like to see that.

But for the second one, in a trial I think is a better route, because we do really need more evidence now for effectiveness. A registry is not a good mechanism to establish initial effectiveness, it's really for subsequent evolution that it is good at, so we can't be substituting one and replacing the

other, it's never that kind of perspective to registries.

DR. REDBERG: Peter, and then Diana.

DR. LAWRENCE: Yes. Just with regard to question two, it really is a mixture of two diseases which is, one is postthrombotic, the intraluminal chronic thrombus, and the other is the extrinsic compression like May-Thurner. And I think that we talked a lot about the difficulty with prospective randomized trials and to me the May-Thurner, since there are new devices that are being developed and haven't quite yet been released, it's a great opportunity for a prospective randomized trial. The legs are never at risk of limb loss, or virtually never with May-Thurner, and it's an elective procedure and it would be easy, as Dr. Comerota said, to do a crossover trial so everybody gets treated, and have two arms. And I think that that would be a great proposal, is that before reimbursing for the new stents, that they go through some sort of a prospective randomized trial, because I think that that's one that could really be pulled off and would give them good information.

DR. REDBERG: Thank you. Diana.

DR. ZUCKERMAN: I think in terms of evidence gaps, just about everything is an evidence gap for people over 65, so I think that any study would probably be helpful, but I wanted to start out with the diagnostic part because we still don't know what's the best way to diagnose these various illnesses, are clinical exams as good or almost as good, and for which kind of patients. And as Leslie mentioned, maybe there's going to be differences in terms of which patients come in because of what's obvious signs for them, so for whom would clinical exams be sufficient and for whom wouldn't it be, and are there some patients where even after clinical exam seems to show they're okay, they still need a test for some reason? We don't have any good information even on diagnosis, the best way to diagnose, so that seemed like a good place to start.

As well as figuring out, you know, especially for the patients with the most serious disease, what do they need, what's going to work for them, what's going to work

for them in the short term, what's going to work for them in the long term, and how does that change when you're 65 versus when you're 75 or 85?

DR. REDBERG: Thank you. Roger, did you want to comment on that? Teresa, Dr. Carman?

DR. CARMAN: Teresa Carman. So I was, I just want to make one comment on the registries versus maybe meaningful use in gathering data from the EMR. The registries are great because they are going to allow us to evaluate procedures, procedural outcomes and potentially repeat procedures, depending on if it's the same practitioner or the same region that it's collected from. But we're a mobile population, unlike some of the European data that can be gathered because they're not quite as, you know, inner mobile. But I do think the meaningful use data and the EMR abilities as we move more towards the electronic records is a great place to get some of that natural history data to help us better evaluate some of the medical management data that's lacking, and certainly a strong consideration that should be

encouraged.

MS. WISE: Something else. This is Leslie Wise. Based on the additional topics, I know that CMS generally doesn't cover for screening, but I think that with respect to the population in terms of disparity, because these populations seem to be asymptomatic or without symptoms until they have advanced disease, and you see this on the arterial side as well as the venous side, that there might be some consideration of if they appear with one version of vascular disease or if they have arterial disease, then maybe they should be screened for venous disease, or vice versa, but I think there has to be some screening mechanism in place for the populations that we know are out there but tend to be asymptomatic until they have very advanced disease.

DR. REDBERG: As you know, the principle of screening is that early detection is better, and I think we have to have that data that, you know, what would be the advantage of early detection, what would we do differently, how would we advise and would people be better off, because there has been a

lot of, a lot more faith in the power of early detection and there has been evidence of benefit, and actually we're getting more and more that there's a lot of harms with detection, and I think that's why we're very symptom-driven and outcome-driven, because we really, you know, when we start, as I think Dr. Comerota said, it's hard to make an asymptomatic person feel better, and that's what you're doing with screening.

MS. WISE: Well, I mean, I think it's easy for us to say that, but the data on arterial disease is just deplorable. African-American men, five times the national average being amputated, African-American women three times the national average. I don't buy that they just show up needing to be amputated. And the guidelines say when people's legs turn red for PAD, and I think looking at the CEAP classifications, the visual nature of the CEAP signs that are visual is a problem, and when I hear the data that says seven percent of African-American women is the lowest group to be identified with varicose veins, but yet they show up with the most severe disease at the end

sums up somebody's missing something. And so you know, I don't know if you interview, start to interview those people with advanced disease, there's a sign somewhere.

And you know, I used the example the last time I was here during PAD, there was a time when they said that women showed up with heart attacks and they didn't have symptoms, right, we all remember that, women were asymptomatic. Now we know that women always had symptoms, they were just different than what was in the study.

So you know, it's something that we have to, if we're going to do better in these populations we have to begin to figure out how to screen them better, because it can't be by what we're using today.

DR. REDBERG: And I still, I'm all for doing things that have benefits to patients and, you know, certainly in things to prevent. I don't think we've seen any data that screening for chronic venous disease is going to improve outcomes, and I would have a lot of hesitation about endorsing that. I think that what we've seen is we don't know a lot about

the natural history, we don't know a lot about the treatments and what's better and what isn't, and that we need to be gathering a lot more data and start looking more closely and figure out what to do. We've seen that there are a lot of procedures being done, but we haven't seen a lot of data on benefit for those procedures and patient-related outcomes.

Peter, did you want to get back to the accreditation issue?

DR. LAWRENCE: I think that appropriateness is really the key to management of venous disease. Well trained people use appropriate diagnostic techniques that are standardized in accredited labs, and do procedures where there's some sort of a quality measure, are the keys for doing the right thing for our patients. And right now in an office-based practice you don't have to do any of those things and you still get reimbursed, and that's why we see this is like a growth industry for some people who have had no training and have no expertise in venous disease.

So until we correct that problem, we

can have all the prospective trials and great registries, we could have great practice guidelines, but if people aren't following them then we're wasting our time, and I think it's about time for CMS to recognize that the world has shifted from inpatient to sometimes ambulatory and now outpatient, and we have to have the same quality standards in an office space as we have anyplace else. It doesn't mean you put people out of business who are doing good quality work, but you get rid of some of the charlatans who have driven up the volume of venous procedures up to, you know, what is in a two-year period, is something like a 1,400 percent increase.

And when you look at where it's being done, it's invariably being done in an office and it's often being done by people who have no training and they aren't using accredited labs, and they don't have an accredited venous center. So that's something that I think is extremely important, although all the stuff we have talked about today is really important, and getting evidence at a very high level, but this is the most basic level of what you would

want as a patient, and most patients have no clue when they go see a physician in an office what their background is, what their specialty is, what their expertise, whether they're using an accredited lab, they don't have knowledge of any of that, and then that doctor gets paid just the same as somebody who has had a lot of training and does things correctly.

So I think appropriateness is probably the most important thing that could be dealt with in managing patients with venous insufficiency.

DR. REDBERG: Appropriateness, which is a little separate than accreditation.

DR. LAWRENCE: Well, the way you get to appropriateness is by first of all, you've got to do, you've got to have a place to examine. We don't collect data on those people, so appropriateness is the key, but the only way to figure out whether it's appropriate is to do quality measures.

DR. REDBERG: So, are you suggesting something like appropriate use criteria?

DR. LAWRENCE: Well, I think that that, sure, but then it has to be enforced, you

have to make sure that you, if you have appropriate use for a noninvasive vascular lab, most insurance companies have a minimum diameter and they have a degree of reflux, and they have for an ablation, for example, of a saphenous vein, if it's not done in an accredited lab, then you have no idea whether that information is accurate that's being submitted to CMS. So it requires accreditation to do, to me, of individuals, or training, and appropriate accreditation of centers and vascular labs to get to the issues of quality and appropriate care.

DR. REDBERG: Sure, and the same things could be said about imaging too, radiology?

DR. LAWRENCE: Oh, they could be said about a lot of things, but they don't have an increase of 1,400 percent in two years.

DR. REDBERG: Oh, they do, but, Marcel.

DR. SALIVE: So, I think the same thing did happen with bariatric surgery, and maybe that centers of excellence model could be looked at for this as one approach. I know it

was used a lot for a while and then it was dropped by CMS, but it had its usefulness for bariatric surgery.

The other point I wanted to make on the advanced research gaps was I think, maybe it got lost in the shuffle, but I thought it was a good point in the TA that said to study more strategic approaches to the venous disease, and it's similar perhaps to how NICE looked at it, I'm not sure, I didn't have time to read NICE in depth, but I think taking a strategic approach with some steps in it could be, you could do trials of strategies and compare strategies, and if they're distinct enough you can tell, you know, if one is better than the other. And it may, you know, it doesn't have -- you know, it has pros and cons, but I think ultimately it's good for improving the practice and improving the health outcomes, and knowing what actually works.

DR. REDBERG: Dr. Lewis and then Dr. Comerota.

DR. ROGER LEWIS: So one question for the chair, are we interested only in question three, or any of the questions?

DR. REDBERG: I think we're now at three, four and five.

DR. ROGER LEWIS: Okay. So, I just didn't want to be out of order. With respect to the venous disease disparities, my personal practice is in a county hospital that serves a medically indigent population, and observationally it appears to me that there's tremendous disparities in the detection of disease for which we actually agreed as a group, there probably are therapies that affect at lease proximate outcomes. And so I would simply make the point that moving forward, anything CMS can do to ensure that we collect data in a way that allows us to address disparity in access of Medicare beneficiaries to the kinds of care that allows these syndromes to be detected would be great.

Then for question number five, to me this just begs for a form of coverage that mandates comparative effectiveness data acquisition in a way which there are randomization of treatment strategies, and I think the point about treatment strategies is critically important, because ultimately we

want to help physicians know how to pick the right treatment approaches or sequence of treatments, or conditional treatments conditioned on a response to prior treatments for patients that fall into different groups that receive Medicare coverage, and the current state of the evidence makes it in my mind completely clear that that's not going to happen through a gentle organic process given the cart is not only so far before the horse, it's running down a steep hill faster and faster, and the horse has given up and left. So I think that this is something in which CMS needs to think about strategies that can be quite coercive in encouraging the kinds of data collection that will allow us ultimately to know which treatment strategies for which patients.

DR. REDBERG: Dr. Comerota.

DR. COMEROTA: Thank you, Anthony Comerota. Evidence gaps and disparities are what I'm going to address. What we were asked to evaluate on our panel today was symptoms versus no symptoms, and it's been my observation that if we could quantify the

severity of symptoms, patients with a correctable lesion that have severe symptoms are more likely to enjoy the benefits of that procedure versus patients who have very mild symptoms, and yet we see large numbers of those patients treated in various segments of the United States.

And perhaps we ought to begin to quantify the severity of symptoms and link it to outcomes, and then the need to correlate quality of life with outcome instruments such as venous clinical severity score, and we've heard today a consensus of the importance of quality of life, but we also should have some objective measure not unlike the venous clinical severity score integrated in our pre and post-procedure evaluation.

And then and it's already been stated, within the Medicare population, we should begin to develop databases on what's the difference in outcome in the patients that are 65 to 75, versus those that are either over 75 or over 80, and there may be remarkable differences within the Medicare population.

DR. SEDRAKYAN: Any other comments?

Okay. Can you comment about volume of claims data for addressing some of the gaps, CMS claims data, and how much information can we really obtain from claims right now, and whether there are studies, and maybe this can go back to the TA, are there any studies using claims, and what are the codes that could help us at least identify general classes or categories of therapies offered to CMS Medicare beneficiaries?

DR. VEMULAPALLI: Dr. Vemulapalli. I can just comment on the claims data question. We did not see a single study with linked claims data in the analysis that we evaluated.

DR. SEDRAKYAN: So claims alone also is not there?

DR. VEMULAPALLI: No.

DR. O'DONNELL: O'Donnell again. There is a study using Medicare claims data and looking at the complications of endovenous ablation which was, because of the size of the patients studied, it was very helpful in, because you've got a rare event like a blood clot extending into the femoral vein, you have the black swan phenomenon so you need a large

amount of data, and this claims data analysis was very helpful, and I think that's a very good place to go.

DR. SEDRAKYAN: Thank you. In terms of laterality of the disease, is that a challenge in terms of research for registry type of investigations, anyone would like to comment? Linked studies, is this going to be an issue?

MS. WISE: So, I'm not aware of one in the U.S., but the U.K. did do, NICE did a meta-analysis last year in 2015, and they did go to their claims data, which they then modeled out over five years, and it's published, and it says that endovenous ablation technologies are the most cost effective method for treating chronic venous insufficiency. But again, that's the model, it's not, the claims data doesn't actually go out that far, but they did model it and they do indicate it as the most effective. It wasn't included in the review, I don't think, but it was published late last year by Knight, so I think that is the only thing that exists today where it's linked together.

DR. LAWRENCE: Peter Lawrence. Even though it hasn't been published, I believe that the RUC committees that determine reimbursement have collected a lot of this. We've seen it presented at national meetings looking at shifts in practice, inpatient to outpatient to office based, and the severity of the venous disease and the types of procedures, both by CPT and ICD-9, but that's been used to argue for or against changes in reimbursement.

So I think that the data is available, it's just that it's not in a published form, but if it would be useful to the committee, I believe that the RUC committee has a fair amount of that, and that's been the basis for some of their concerns about whether this falls into, venous disease falls into the high risk category because there is such a dramatic reimbursement that something needs to be looked into not only by CMS and MedCAC, but by reimbursement.

DR. REDBERG: Diana, you have the last comments and then we're going to wrap up.

DR. ZUCKERMAN: I just want to say for the claims data and the electronic medical

records data more generally, the hope of including unique device identifiers can really make a big difference because it isn't just, you know, how well each type of device works but the specific devices, and not just the different companies with their different models, and the fact that these devices change over time, so that a device that might seem to have a very good outcome one year, maybe the next year the outcome is going to be better or worse because of changes that were made.

So I think that's a really important role for CMS to play, to encourage that kind of specific information about specific kinds of devices that would be used for diagnostics and for treatment.

DR. SEDRAKYAN: One more gap in knowledge. I mean, I think the evidence that I would like to see is related to treating bilateral disease and how often one side is treated followed by the other side versus simultaneous therapy, and what are the risks for simultaneous therapy, both sides? And I think that would be very helpful in terms of not only outcomes but also cost effectiveness

of these therapies.

DR. REDBERG: Having said that, does anyone have anything else they felt they didn't get to say? Okay.

On behalf of CMS and MedCAC, I just want to thank everyone, thank the presenters for all of your work in preparing the evidence review and for all of your comments, they were really helpful in I think giving us a very broad perspective. I think the committee really did an amazing job of being very thoughtful and systematic, and hopefully this was helpful to CMS in helping to guide, you know, the field going forward for chronic venous disease, and I think we have some ideas that were certainly applicable to other issues so, interesting times.

Lori, did you have any other comments.

MS. ASHBY: Yes, I just have one quick thing that I wanted to remind people of, or just in general, and that is that the technology assessment is currently out for public comment, the comment period closes next Friday, July 29th. You can access it via the AHRQ website or you can access it on our

website, there's a TA link there, so we encourage you to take that opportunity if you wish to do so.

And just to follow up on what Dr. Redberg said, I just wanted to thank everybody for their participation and their input in today's meeting. It was a great meeting, we have a lot of valuable material to work with as we move forward, and thanks again for everything, and have a safe trip home. Thank you.

DR. REDBERG: And the shuttle is here.

(Meeting adjourned at 4:14 p.m.)