Cyberseminar Transcript

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Series: Spotlight on Evidence Synthesis Program

Session: Cost-effectiveness of Leg Bypass versus Endovascular Therapy for Critical Limb Ischemia

Presenter: Paul Shekelle, MD, MPH, PhD and Melinda Maggard-Gibbons, MD

**Molly:** I would like to give you a rundown of who is joining us today. So we have Dr. Paul Shekelle, he is the director of the ESP Center that did this report in Greater Los Angeles and joining him today we have Dr. Melinda Gibbons, she will be giving the results of the report. And finally, as our operational partner discussions we are grateful to have joining us today, Dr. Jim Edwards. He is the director of Surgical Informatics. And we have Dr. Bill Nylander joining us today and I think I’ve covered just about everybody so with that, I am now going to turn it over to Dr. Paul Shekelle and you should get that pop up now so just go ahead, hit the dropdown menu, and select screen two.

**Dr. Paul Shekelle:**  Hi. We good then Mol?

**Dr. Melinda Gibbons:**  You are good.

**Dr. Paul Shekelle:** Okay. Well thanks very much Molly. I’m Paul Shekelle. I’m a general internist here at the West LA VA and I direct the ESP here, that’s the Evidence Synthesis Program. I’m going to go through just a handful sort of general introductory slides but then I’m going to turn it over to my longstanding colleague, Dr. Melinda Maggard-Gibbons, whose a general surgeon with whom I’ve worked for, gosh, 10 or 15 years now on these kinds of systematic reviews and she will take us through the details of this. Next slide. How do we advance a slide? There we go.

We want to make sure that we acknowledge the operational partners that nominated this topic. It originated when Dr. Gunnar was still the National Director of Surgery. It’s now continued under Dr. Wilson and then we are message synthesis methodologists and so we work on lots of different topics.

And for each topic, we then have to draw in clinical and relevant stake holders to help advise us on the scope of the project and you can see the people here who were part of the technical expert panel of this project. Being a technical expert panelist doesn’t mean that you had to agree with everything we did. That responsibility is ours but these people help advise us on what the scope and what some of the other questions about it should be and, of course, Dr. Edwards from Portland is on the call today and he will be able to fill in people on any of those details.

Next question, again, this is the disclosure. This is our work although we’re being supported by VA it doesn’t necessarily mean that this is official policy of VA and then none of the people who are working on this have any employment consultancies, honoraria, or stock, etc. that would conflict with this. Next slide please.

Just real quickly about the Evidence Synthesis Program. So it’s been around for 12 or 13 years now. We work on evidence based products for Central Office. These are things that are either going to be used to develop clinical policies or implement effective services and support or sometimes to help set research agendas. There’s four of the centers around the country. There’s us, oh I think that’s another slide so I’ll wait for that. At any rate, it’s all led by VA clinicians and we’ve been, this was originally an outshoot but has since grown to be quite a substantial undertaking in its own regard but it was initially an offshoot of the AHRQ Evidence-based Practice Center Program. We are managed by the Coordinating Center in Portland and for any of you who are on the phone who have some idea about some topic that you think there needs to be an evidence report on, then you can go to the program website and suggest a nomination. Those topics are vetted every so often by the Coordinating Center and then certain ones are selected and sent out to the centers around the country for review.

Here’s what I was going to say. So here’s where the other sites are. So there’s one up in Portland, one in Minneapolis, one in Durham, we’re in Los Angeles, and then obviously VACO, and then the Coordinating Center.

Now onward to the meat of this. This is the Cost-effectiveness of the Leg Bypass versus Endovascular Therapy for Critical Limb Ischemia. Next slide.

And now I’m going to turn it over to my colleague, Dr. Melinda Maggard-Gibbons, a general surgeon whose going to take us through sort of the meat of this. So Melinda, take it away.

**Dr. Melinda Maggard-Gibbons:** Great. Thank you so much Paul. So as Paul mentioned, I am a general surgeon although we did have a number of vascular surgeons involved to help us with this topic and I have been involved with Paul’s team for quite some time working on reviews that cover surgical topics and happy to be here today. So for background, critical limb ischemia is a severe form of peripheral artery disease and it’s marked by ischemic rest pain, tissue loss, or gangrene. So it’s really far on the spectrum on how peripheral artery disease impacts patients. It’s estimated that 1.3% of the U.S. adult population suffers from CLI. It is associated with significant morbidity, mortality, and increased utilization of health care resources. So revascularization really takes two primary forms. It can be surgery or endovascular therapy. The most recent guidelines from the American Cardiology and the American Heart Association do not specify, specifically, which type of therapy they recommend first for patients with CLI. Next slide.

We had two key questions that we set out to answer. The first one among adult patients with CLI, what is the cost effectiveness of leg bypass surgery, also referred to as the open approach, compared to endovascular procedures? And this could include balloon angioplasty, arterial stents, and atherectomy. The second question was, does cost effectiveness of leg bypass surgery compared to endovascular procedures for CLI vary by different patient population setting or time, so short versus long term? Next slide.

A detailed literature flow is shown here on the screen. Our literal search revealed over 4000 references and through our screening process we had 393 references. We ultimately, and he’s going to follow through on this figure, identified 27 studies of original data that met our inclusion criteria. Although of note, some of them were multiple publications on one unique study, for example, perhaps they did different analyses, looked at different time points. And also showing here are the lists of the information, the data variables, that we collected from these different studies. Next slide.

So for key question one, I’m just going to restate it again, among patients with CLI, what is the cost-effectiveness of leg bypass surgery compared to endovascular procedures? And the studies that we used to answer this question included one RCT, this is the BASIL study from the UK, three cost-effectiveness models studies that were published, and 16 observational studies. Next slide.

So for the RCT, I’m going to spend a little extra time on it because it is, tends to be a higher level of evidence. It was a very well designed study with 27 hospital, 452 patients. Primary outcome amputation-free survival and the secondary outcomes all-cause mortality, health related quality of life, and also costs. Next slide.

So the results from this trial showed that there were really no statistically significant differences in amputation free survival and health related quality of life at one year or three years. All-cause mortality favored the surgery first treatment strategy after two years of follow up. Before the two years, there was a nonsignificant difference favoring angioplasty. The table that is shown here is that for the 12 month outcome results that shows just what I referred to. Now of note, there were some other data points that I think are worth noting that aren’t shown on the slide. That patient’s receiving surgery did have a lower immediate failure rate, 3% versus 20%. They had a higher [unintelligible 10:18] morbidity, 57% 41% and a lower 12 month greater intervention rate 18% to 26%. And also worthwhile to mention about this study is that they really only looked at angioplasty and now contemporary endovascular procedures include much more than that and often stents are placed. So it’s just important to remember in thinking of the results of this study and how it applies to what is down contemporarily. Next slide.

So the surgery first management option also was found to have more resource use by patients in the first year but these differences disappeared in the subsequent years. So as shown here in this table, you can see the results for the number of admissions to the hospital and the total days spent in the hospital. These are utilization outcomes that we looked at and you can see here that there were more days spent in the hospital as you would expect for surgery than in the endovascular patients shown here on the second row. This study also looked at cost effectiveness for their patients and they found that the results, the estimates that came up were $184,000 per quality adjusted life year and, of note, this study was done in the UK but they translated the results into U.S. dollars. Next slide.

So for the observational studies, just briefly, about half of them were multi-institutional studies and the other half were single. Most were from U.S. Institutions but there were two from Germany, one was from Australia. Nine had more than 500 patients and six had 500 or less and two of the studies, which is particularly relevant to our presentation today, focused on the VA population and these were from New York and so this graph shows a lot of data points but it has some useful information summarizing the observational studies that were reporting on short term outcome. And so in this slide, EV is representative of endovascular procedures and so what it shows, pictorially, is that most of the estimates favor the endovascular approach over surgery for these short term outcomes that are listed on the far right hand side. But of note, few of these were statistically significant. Next slide.

So for the long-term outcomes and specifically mortality which is shown in yellow and re-intervention which is shown in gray that it looks like these were favoring the treatment with surgery, which is shown pictorially in this slide, and those data estimate points are above the zero line on this graph. Next slide.

So key question 1 also was addressing the cost data that was available and so for this we found three studies. Again, one which I’ve already mentioned the results from the BASIL trial that is reported here on the top line and then another study from the U.S. which showed the incremental cost-effective ratio of surgery first had $47,000 quality per adjusted life years and for the endovascular of $100,000 per quality and then one study from Germany had somewhat different results where the cost-effective ratio of surgery and endovascular approach were somewhat similar. Of note, these studies didn’t have a lot of high level randomized data’s put into them so it adds to the challenges with actually getting very useful and reliable estimates out. Next slide.

So for key question 2, which is very important, in does the cost-effectiveness of leg bypass surgery compared to endovascular procedures vary by the patient population, setting, or time. So for this, there were three types of studies, if you [unintelligible 16:00], that were included. The RCT provided data for this question as did two of the cost-effectiveness studies, and three as the observational. So we definitely had fewer studies overall that were able to help us answer this question, or questions. Next slide.

So we provide a narrative summary for these and what we’re able to find is that for specifically patients with infrapopliteal disease the endovascular therapy appears to have worse long term outcome, increased short term utilization in the surgery group, but similar utilization between groups over long time horizons. Now for patients with end stage renal disease it appears they had lower costs per year of ambulation with endovascular first approaches as to compared to surgery first. Patients with diabetes had worse outcomes for the composite of reintervention, amputation, or stenosis when treated with endovascular therapy compared to surgery. And lastly for patients with borderline functional status, the cost effectiveness model favored endovascular first approaches over surgery first. Next slide.

So summary of our review. Endovascular therapy has a lower initial length of stay and the strength of evidence of this was high because this was a consistent finding that we were able to note across the study. Endovascular therapy had lower short term mortality. The strength of evidence was somewhat low for this because of the inherent bias to the studies that were available. Surgical therapy had a lower long term mortality and, again, for this the strength of evidence was determined bias to be very low. Cost effectiveness appears to vary by the time horizon where the initial outcomes and utilization tend to favor percutaneous interventions but longer term outcomes tend to favor open revascularization and strength of evidence for this was low. And lastly, endovascular therapy less cost effective than surgery in infrapopliteal disease. Strength of evidence is low. Next slide.

So for similar limitations which I’ve mentioned somewhat throughout the study quality, the one RCT identified has some series limitations in term of the directness and applicability to modern care. The fact that it didn’t have stents and was limited to angioplasty is what I’m referencing. And observational studies have serious limitations with respect to risk of bias which I’ll talk about a little more later but the differences between these groups are apparent. Heterogeneity among the observational studies are relative. Consistent finding was shorter length of stay for patients treated with endovascular therapy and other outcomes were not as consistent. Applicability of findings through the VA population; so we identified two publications from the same institution that were specific to VA populations and it is likely that the applicability of these studies to VA is reasonably good. Costs, however, from non-VA institutions cannot be assumed to be applicable to VA settings. Next slide.

Summary, continued. Studies report short term effectiveness and research utilization favoring endovascular therapy but most were not statistically significant. Long term outcomes were more mixed. Mortality favored surgery although concluding cause-and-effect is not possible since the endovascularly-treated patients did tend to be older and many may have had a shorter life expectancy regardless of therapy. So the clinical effectiveness and research utilization surgery compared to endovascular approach for critical limb ischemia is not known and won’t be known until several ongoing trials report their results and it is likely that findings will vary by time horizon where initial outcome utilization may favor endovascular interventions but long term may favor surgery. So by far and away the largest gap is really the high quality evidence of the differences and outcome for these patients between these procedures. So there are two trials underway which are important to note and the BASIL 2 and then The BEST-CLI. And of note, recently the investigators for The BEST-CLI actually modified their protocol to increase sample size and extend the duration of follow up which really indicates that definitive results from this trial, in particular, are probably not coming any time real soon so it’s important for us to note, but hopeful, that we will have some useful information from these trials and it’s good that they are currently underway. Also too for the VA, VA has a lot of cases and may have some rich data and so that some prospective observational studies could also come out of the VA to help us answer some of these questions. Next slide.

And so our contact information is provided here with the link to our full reports and also for the Cyberseminar will be available there and we’re happy to answer any questions. And so now I’d like to turn over the presentation to Dr. Jim Edwards, who is the Director of Surgical Informatics for the VA National Surgery Office.

**Dr. Jim Edwards:** Good afternoon. Looks like you can hear me. So I work for the National Surgery Office. I’m a vascular surgeon. I was Chief of Surgery at the Portland VA for many years and I was the one who initially suggested this topic. And I suggested it because the BASIL study was 14, 15 years old and while I knew that there were The BEST CLI and BASIL 2 were going on and I also knew they had been designed five years ago and I was hoping, even though I hadn’t seen it, that there was some literature that might help us determine which strategy was better. And I was particularly interested in trying to figure out if any subgroups might be better treated by one group than the other. And obviously, we didn’t get the answer to those questions which was disappointing but not particularly surprising. It was interesting to me to see that infrapopliteal disease seemed to be better treated with surgery first. I think that was kind of the most interesting thing I saw in this study. But I would like to give the attendees an opportunity to ask questions also.

**Molly:** Thank you kindly. So we do have some questions and, actually, I’d like to turn it over, Dr. Bill Nylander, did you want to speak at all or kick start things, otherwise, I’m happy to go straight to our questions.

**Dr. Bill Nylander:** Well one question I had because I thought this may be the way this study would go but one of the questions is I was looking at the cost analysis and why was the European cost so much cheaper per year? They were down around 3000 euros which is, you know you add 13% but it’s still so much cheaper than how we do it in the U.S. And then the second question to kick off, and this is for Jim, it looked like that if we knew the mortality of the patient that we still may favor endovascular if it was really a short term result we were going after and is there a way to use a mortality calculator in deciding therapy for these patients?

**Dr. Paul Shekelle:** This is Paul Shekelle. Let me go ahead and take the cost-effectiveness question in terms of the dollars and the euros. I mean bottom line is that I don’t think you should read a whole lot into that. Each of these studies is so different in terms of sort of how they accumulate costs and charges, etc., that when we look at these kind of cost-effectiveness studies, we tend to only focus on the differences between the studies so, I mean the differences within the study, so within the study whatever their biases or whatever their dollars or euros or things that they’re counting as costs or not counting as costs are all the same. But across studies those can vary quite a lot so I know it looks bad, you look at one and says it’s a $100,000 and another looks like it’s 3000 euros and you go how can it be that different? It doesn’t mean that they’re actually necessarily doing it 10 x cheaper in any of the European countries. It can also just be how they aggregate things into what they’re counting as costs so don’t put a lot of, don’t read a lot into those differences. Only look at the differences within the study about whether one method or the other method had a higher or lower cost. And I’ll turn it over to Jim for the rest of this.

**Dr. Jim Edwards:** So Bill as I understand your question you were asking about mortality and would the risk calculator perhaps be helpful. Now if you look at the subpopulations that seem to do better or be cheaper, or be less expensive, with endovascular first, it was patient’s with end stage renal disease and those with borderline functional status and both those comorbidities are known to have increased mortality and so it could be that the risk calculator could help you. But infrapopliteal disease is also associated with shorter longevity and that’s, you know there was a trend toward doing better with surgery so it’s a little hard to know. I don’t know exactly how Best and BASIL 2 are looking at overall risk but, hopefully, they will have collected data to do a risk calculation so hopefully those studies will answer that question.

**Dr. Bill Nylander:**  And the follow up is should this study change my practice? And I’m not sure I can come to a conclusion it should change it but what should my practice be?

**Dr. Jim Edwards:**  So I don’t think this study is going to change, should change anybody’s practice. At this point in time we look at the overall patient condition, we look at the anatomy and we make a decision on how we thing the patient will be best treated. I mean I think the field recognizes that endovascular therapy tends to have worse long term results but certainly is easier on the patient and associated with less mortality and so the sickest patients are probably best served with endovascular and the healthier patients may be better served with surgery first but, again, I think it’s just going to be a case-by-case basis at this point in time.

**Dr. Paul Shekelle:**  And if I can just jump in there as well. So, again, I’m a general internist, I don’t work in this area but I do do a lot of evidence reviews across a large number of topics and when you see stuff like this, or in other kinds of situations where the observational there haven’t been a lot of trials, the trials that are ongoing are extending and going on to further, you know, to go out further and to enroll more patients in order to accrue more end points. You see this kind of stuff in the observational studies. In other places where we’ve reviewed this literature what it generally means is that it’s a pretty close call. It’s not going to be a slam dunk one way or the other and there’s going to be a lot of nuance in terms of trying to pick out subgroups that might do better one way or the other but that overall it’s going to probably come down to, you know, individual judgements made by the providers given the patient, given the patient’s particular comorbidities, given the patient’s particular values, given what the patient’s hoping to get out of this. That’s probably what’s going to end up driving this.

**Molly:** Thank you very much for that input. Bill did you have another one or should I move onto any audience Q&A?

**Dr. Bill Nylander:** I would move on.

**Molly:** Thank you. So for our attendees if you joined us after the top of the hour and are looking to submit a question or comment just use the Go To Webinar control panel located on the right hand side of your screen, down towards the bottom is a question section. Just click the arrow next to the word question that expands the dialogue box and you can then submit your question or comment there. So the first one that came in they are wondering A) Has this report been published and is okay for distribution outside the VHA? Yes it is. And, as you can see on the screen, there is a web address where you can view the entire report and it is posted on the web so it is accessible outside the VA. And the, let me get to this real quick, looks like the second part they are wondering if this has been recorded and will be made available? Yes. This session has been recorded and it will be posted in our online archive catalogue along with a copy of the handouts and soon a transcript will follow as well so you’ll receive a follow up email about two days from now with the link leading to that recording and feel free to pass that along to anyone you feel might be interested. While we wait for any further comments or questions to come in, we can give people an opportunity to make any concluding comments they’d like in no particular order, Dr. Shekelle, we can begin with you.

**Dr. Paul Shekelle:**  I think I sort of already gave my concluding comment before I accidentally disconnected myself from the phone and other than to say, you know, keep watching the journals, all right? There is going to be new evidence that’s gonna come out on this. I have done a lot more work in the cardiovascular area and I suspect that this is going to go down the same lines as cardiovascular and that there’s going to be elements of anatomy and elements of comorbidity which are going to dictate one or the other but that for a large group in the middle, it’s going to be an individual choice.

**Molly:** Thank you. And Dr. Maggard-Gibbons, did you want to give any concluding comments?

**Dr. Melinda Maggard-Gibbons:**  Yeah just to follow up, I think that this is a really important population of patients and procedures that we still need answered. They’re very costly procedures and there significance, you know, comorbidity and mortality with them and also without doing the procedures so just really hopeful about the two ongoing trials will help give us some additional insight and particularly into the sub-groups of population so that we can answer the question that was posed, you know, what should be done in practice with a patient that is seen in the office? So that’s my hope in that we will have some more information to guide us on that.

**Molly:** Thank you and Bill and Jim I can give you the final say if one of you guys wants to kick it off.

**Dr. Jim Edwards:** So this is Jim I just wanted to thank Dr. Gibbons and Dr. Shekelle and Evidence this program for doing this analysis and for the presentation.

**Molly:** Thank you. Bill, did you want to leave us with any concluding thoughts?

**Dr. Bill Nylander:** No. I do think it’s an important study so even though it didn’t reach a lot of conclusions the field does know that this is the state of the art where we are and if that you are confused about what to do that’s important to understand that the literature doesn’t exactly say what we should do. So and the other thing is, we’ll help to distribute this and put it on our call and for our minutes so it can be distributed throughout surgery.

**Molly:** Excellent. We truly appreciate the further dissemination of this report. Wonderful. Well, there are no further pending questions or comments from the audience except for somebody wrote in saying thank you for the report. So, with that, I do want to thank you all very much for joining us today and I want to, of course, want to thank our attendees for joining us and, as I mentioned, you’ll receive a follow up email with a link to the recording. And stick around just one second while I close out the session and you will be redirected to a feedback survey where you can provide us the answers to just a few questions and we do look very closely at your responses. So thank you once again everyone for joining us and have a great rest of the day. Thank you all.

**Dr. Bill Nylander:** Yup. Bye-bye now.