The CLI Global Society Multidisciplinary Roundtable Discussion on BEST-CLI: Implications of the Available Data

Moderator/Interviewer: Barry T. Katzen, MD, FACR, FACC, FSIR, President of the CLI Global Society

Roundtable Participants: Walter Dorigo, MD; Anahita Dua, MBCHB, MBA, MSc; Andrew Holden, MBChB, FRANZCR, EBIR, ONZM; Robert Lookstein, MD, MHCDL, FSIR, FAHA, FSVM; Jihad A. Mustapha, MD, FACC, FSCAI; Richard F. Neville, MD, FACS; John H. Rundback, MD, FAHA, FSVM, FSIR; Eric Secemsky, MD, MSc, RPVI, FACC, FAHA, FSCAI, FSVM; Jos C. van den Berg, MD, PhD; Thomas Zeller, MD

The long-awaited results of the BEST-CLI trial were recently published in the *New England Journal of Medicine* and presented at the 2022 American Heart Association Scientific Sessions.[1] This prospective, randomized trial was sponsored by the National Institutes of Health and compared two standard-of-care treatments (surgical bypass and endovascular therapy) for patients at risk of leg amputation due to critical limb ischemia (CLI). BEST-CLI enrolled more than 1800 patients from the United States and abroad. Patients who were deemed adequate candidates for revascularization bypass surgery or endovascular therapy were randomized into the trial. Patients enrolled were randomized to receive bypass surgery or endovascular therapy in two parallel cohorts. Cohort 1 included patients with adequate great saphenous vein (GSV) as a bypass conduit. Cohort 2 included patients who did not have adequate vein conduit available. The initial primary conclusion of the trial reported that patients with good-quality saphenous vein available who were randomized to bypass had a statistically significant reduction in major adverse limb events or death compared with endovascular therapy. This included 65% fewer major reinterventions and 27% fewer amputations. Importantly, the trial demonstrated that both surgical bypass and endovascular intervention can be effective techniques for revascularization, and centers of excellence should offer both modalities.

The initial results have triggered active discussion among the vascular community regarding the design analysis, generalizability, and real-world application of the trial. Subgroup analysis is eagerly awaited. The CLI Global Society supports a multidisciplinary approach to the complex disease of critical limb threatening ischemia (CLTI), with the goal of improving the quality of life of patients with CLTI by reducing mortality and amputation rates, and questions whether this study provides the "last word" in patient management. Today, I am pleased to interview 10 experts on CLTI who bring their varied specialties, experiences, and opinions to the table to help us understand and utilize these results to assist practitioners in making the best choices for our patients.

-Barry Katzen, MD, President of the CLI Global Society

Dr Katzen: What is the key result you take away from the initial results of the BEST-CLI trial?

Dr Dorigo: In my opinion there are two key results. First, open surgical bypass and endovascular treatment are equally effective in preventing amputation in patients with CLTI at the price of a higher percentage of reinterventions among patients in the endovascular group. Second, there is no clear evidence of the superiority of autologous saphenous vein over alternative and prosthetic conduits in the surgical patients.

Dr Dua: The key result is that if there is a decent piece of vein and appropriate targets for a bypass, then a right saphenous vein graft, bypass should be the procedure of choice for this patient population assuming they can handle a surgical intervention.

Dr Holden: The obvious answer to this question is the main conclusion drawn by the authors—patients with CLTI and an adequate GSV had a significantly lower incidence of the primary outcome—a composite of major adverse limb events and death. However, I believe the most important conclusion is that both surgical and endovascular strategies showed similar effectiveness in patient survival and preventing amputation. Endovascular revascularization had a significantly higher rate of reintervention, which, interestingly, did not impact the patients' quality of life (QoL).

Dr Lookstein: The main finding is that technical success for endovascular CLTI cases is only 85% when a broad sample of endovascular operators is sampled. This is clearly a call to action to train more endovascular operators in advanced techniques to improve upon these results.

Dr Mustapha: The key result is that bypass surgery and endovascular revascularization are both effective in preventing major amputation with similar survival rates. The noted increased reintervention rate in the endovascular group did not appear to affect the QoL rating, as demonstrated by a better long-term QoL outcome in the endovascular group.

Dr Neville: I believe that one key result of this trial was its emphasis on a multidisciplinary team approach to CLTI. The investigators spent significant time and effort visiting potential centers and emphasizing the importance of a multidisciplinary approach as part of the study protocol. Of course, the trial also indicates that patients with a saphenous vein as a conduit should strongly be considered for bypass as the first method of revascularization.

Dr Rundback: The BEST-CLI trial demonstrated that both endovascular therapy and surgical bypass can be effective in properly selected patients with CLTI. Clinical decision making should not be based solely on the effectiveness of each specific treatment modality but needs to include a comprehensive evaluation of physician skillsets, patient anatomy, and co-morbidities. In most cases, BEST-CLI supports a commitment to revascularization rather than primary major amputation in patients with CLTI.

Dr Secemsky: Surgical bypass in selectively chosen patients has a high success rate with low complications. Venous bypass is a superior conduit compared with synthetic grafts, and patients should be screened for suitability if being referred for revascularization, and it should be determined whether they are reasonable surgical candidates willing to undergo a surgical bypass procedure. Endovascular quality differs significantly across sites/specialties and needs further homogenization to improve overall end outcomes.

Dr van den Berg: BEST-CLI is a confirmation that in patients who are fit for surgery and have a proper autogenous vein graft available, surgery is the best treatment option.

Dr Zeller: Bypass surgery and endovascular intervention are similarly effective in preventing major amputation with similar survival rates. The only difference is the need for reintervention favoring the surgical approach. However, this increased reintervention rate does not affect the patients' QoL rating, as shown by a significantly better QoL outcome over time in the endovascular group.

Dr Katzen: What will be the effect of the trial on real-world practice?

Dr Dua: I think the biggest impact will be to bring bypass consideration into endovascular therapy practice in that those who performed endovascular procedures on CLTI have to take a pause and possibly evaluate patients for both vein and operative targets prior to attempting very aggressive recanalization attempts that may obliterate bypass targets.

Dr Holden: The trial certainly serves as an important reminder that preoperative assessment of the GSV is necessary in patients with CLTI who are fit for either surgical or endovascular revascularization. The results will probably have an impact on the strength of societal treatment guidelines for CLTI. I suspect many centers with an endovascular-first approach to CLTI will continue their practice and quote some of the trial limitations to support that decision.

Dr Lookstein: I believe that endovascular experts will continue to practice endovascular and bypass experts will continue to perform bypass. The operator who only dabbles in the care of these patients should re-evaluate their practice and decide whether to refer these patients to endovascular or bypass experts.

Dr Mustapha: As is common in randomized controlled trials (RCTs), the study cohort likely does not represent real-world practice. This is evident with the low rate of enrollment, even at the top enrolling sites. Therefore, at this time, I do not believe real-world practice will change. Patients with adequate vein and distal targets should be evaluated for surgical options. However, the real-world CLTI patient typically presents with multilevel, multivessel disease and multiple comorbidities. There is a known trend toward an endovascular-first approach due to patients' treatment preferences and availability of highly trained endovascular operators with high technical success rates. Surgical or endovascular treatment aside, these are difficult cases and the complex CLTI patient should be referred to a high-volume center with a known rate of technical success.

Dr Neville: Again, I believe the emphasis on the multidisciplinary approach will drive increased communication among providers involved in care of the CLTI patient. In our own institution, there is a wide range of providers involved and this trial will be used to fortify our local guidelines, which were recently implemented. I do believe that this will increase consideration of bypass as opposed to an endovascular-first approach for all patients.

Dr Rundback: For vascular surgeons, I suspect there will be a renewed effort to evaluate patients for intact greater saphenous conduits in consideration of distal bypass as an initial approach for the management of CLTI. For primarily endovascular specialists,

this migration may be somewhat slower until further data from the trial and companion registry are evaluated, particularly regarding optimal patient selection criteria for surgery.

Dr Secemsky: More venous conduit screening will be performed if the patient is a suitable surgical candidate. Hopefully, more multispecialty operator conversations will be had to agree on the best revascularization approach for CLTI patients with anatomy suitable for surgical revascularization.

Dr van den Berg: At this point that is still difficult to say, a lot will depend on subgroup analyses that will be coming out over the next year, and on whether physicians in the field will study the entire paper to get an idea of the applicability of the results in daily practice or will just stick to the "headline" message.

Dr Zeller: Guideline recommendations will be revised in a way no longer recommending an endovascular-first strategy in the treatment of CLTI patients. However, highly trained endovascular centers will not significantly change their revascularization strategies because a primary technical success rate of 85% does not match with acute treatment success rates in those experienced centers even in unselected lesion morphologies. In general, the choice of the revascularization method depends on the quality and expertise of the individual department regardless of the focus on open surgical or endovascular revascularization. In addition, a significant number of patients have their own treatment preferences mainly favoring the less invasive endovascular approach. The study cohort may not represent real-world practice. Even if no screening logs were mandatory in the trial, the annual enrollment rates even in the top enrolling study sites represent only a low single-digit percentage of the treated patient population in real life.

Dr Dorigo: I do not think it will change the contemporary approach to CLTI patients. Endovascular-skilled physicians will continue to follow the endo-first strategy, having much better results in their everyday practice than those reported in the trial; surgeons devoted to surgical bypass will continue with their open approach supported by the results of the study. Regardless, I think we need to open a serious discussion on the open surgical bypass saphenous vein dogma which is not corroborated by the results of the trial.

Dr Katzen: Will this trial change your own clinical practice?

Dr Holden: No. We currently assess all CLTI patients with extensive non-invasive vascular imaging (magnetic resonance angiography or computed tomography angiography) and those patients with complex vascular occlusive disease considered fit for surgery also undergo duplex ultrasound assessment of superficial veins. A final decision on the revascularization strategy is made with the patient. We also audit our endovascular reintervention rates and achieve significantly lower reintervention rates than those reported in this study.

Dr Lookstein: No.

Dr Mustapha: This trial has not changed the practice in our center. We historically have screened patients for available GSV conduit and refer for bypass surgery when patients are deemed to be good surgical candidates. However, we do struggle with the availability of high-volume surgeons who perform distal bypass surgery in CLTI patients. The bulk of patients referred to our center are complex limb salvage cases who are not good surgical candidates, many of whom have had failed bypass, so options are limited. We continue to see a decrease in the need for revascularization due to the use of drug-coated devices in patients with recurrent stenosis.

Dr Neville: My group currently maps the veins of every patient and performs a risk stratification with medical and/or cardiology evaluation. The trial may not significantly affect our own practice; however, I do believe we will see an increase in bypass referrals.

Dr Rundback: The BEST-CLI data will not substantially change our practice patterns. As experienced endovascular operators, our technical success rates are higher than was reported in the trial, and our clinical results support our endovascular-first approach as providing limb salvage in the most patients. Further, our patient population tends to have very advanced disease not suitable for bypass. In fact, we were early participants in the trial and discontinued participation because less than one in 25 screened patients fulfilled inclusion and exclusion criteria.

Dr Secemsky: The only change for our practice will be that I will probably do more venous mapping. I already refer some patients for surgical bypass and don't expect that number to increase.

Dr van den Berg: The initial reaction (after reading the "headlines") of the vascular surgeons in our multidisciplinary team was to go back to bypass surgery, and this would have been an important change away from our predominantly endovascular-first approach. However, after reading the paper more thoroughly, the conclusion was to not change our approach (where there already was a place for bypass surgery in "fit" patients with a good greater saphenous vein).

Dr Zeller: No. In my institution, we already preselect CLTI patients for bypass-surgery in cases of extreme calcification or recurrent endovascular failure regardless the availability of a useful GSV conduit. Moreover, in my department, more than 90% of all endovascular procedures are performed using drug-coated

devices, which have been shown to result in lower reintervention rates than uncoated devices.

Dr Dorigo: No, it won't. We already tailor our treatment of CLTI patients based on clinical, local, and anatomical criteria.

Dr Dua: I currently hold both endovascular and open procedures in very high esteem and believe totally in the concept of the procedure matching what the patient needs (not putting all patients into one line of thinking), so this trial will not change my practice as I already practice in this fashion.

Dr Katzen: What are the major limitations of the trial?

Dr Lookstein: The major limitation of the trial was the low technical success rate for endovascular. These technical failures drove the findings related to the primary outcome. If the technical success had been improved, the trial would likely have had equivalent outcomes.

Dr Mustapha: A low rate of enrollment and high screen failure rate was seen in this trial and notably is common in many RCTs, especially CLTI trials. Nonetheless, this limits the generalizability of study results, in my opinion. During the long enrollment and follow-up time, endovascular therapy has undergone more changes (ie, drug-coated technology implementation and controversy) while surgical bypass techniques remain consistent.

Dr Neville: Although this was a well-designed and carefully constructed trial, and does deliver prospective randomized data, there are certainly trial limitations. Enrollment was slow and sparse at many centers leading to a problematic application to all "real-world" patients. Exclusion criteria eliminated many patients we treat routinely, such as those with poor medical status, and those who failed recent revascularization; currently 48% of our bypasses are after failed endovascular attempts.

Dr Rundback: Despite the best efforts of the trial and the principal investigators, there are unfortunately substantial limitations which at this time should limit conclusion regarding individual patient care or CLTI treatment policy. I will only touch upon a few of these limitations here. Most notably, only a small minority of patients who were screened were enrolled in BEST-CLI, suggesting that the findings apply only to a limited subset of individuals with this disease. It will be very elucidating to better understand the percentage and reasons for screen failures. Results from the companion registry are also awaited which may provide insight into comparative outcomes in patients not able to participate in BEST-CLI.

Endovascular failure rates were not satisfactory or comparable to other contemporary studies, and it is not clear if operators were comfortable using adjunctive endovascular techniques such as retrograde or pedal access to achieve better technical success. As a practice supportive of tibial atherectomy based upon our own outcomes, there is concern that optimized endovascular strategies that may have introduced a negative bias toward catheter-based therapy were not utilized. The concept that repeat endovascular intervention constitutes a clinical failure does not take into consideration the relative ease, comfort, and reduced morbidity of these procedures vis-à-vis open surgery. The observation of a low percentage of infrapopliteal interventions is particularly notable and not typical of CLTI patients. I'm curious to know what percentage of bypasses were distal bypasses. If this is substantially higher than the percentage of endovascular patients undergoing tibial intervention there is implied bias against endovascular (ie, untreated tibial disease).

Finally, it would be extremely interesting to assess patient reported outcomes for the treatment groups. I suspect that most patients would prefer a primary endovascular strategy if this did not compromise subsequent surgical outcomes.

Dr Secemsky: With most sites enrolling <10 patients, one of the major limitations is that low enrollment hampers generalizability, and the poor endovascular outcomes reported don't reflect modern clinical practice. Likewise, the optimal surgical outcomes also don't reflect clinical practice. Inclusion of major reintervention in the primary endpoint allowed for patients to cross over into surgical bypass group, and since the decision making was not centrally decided, the operator had the discretion to declare the endovascular procedure a failure. Another limitation of this trial that I noticed was the low involvement of other specialties outside of vascular surgery, as well as the discordance between quality of life outcomes (equal for bypass and endo) vs clinical outcomes (surgery was heavily favored).

Dr van den Berg: The trial itself was well designed, and therefore the limitations are few. It is, however, important to look at the general applicability (to all CLTI patients) of the outcomes, and in this respect the findings may prove to be limited.

Dr Zeller: Even if a relevant number of patients had been enrolled, the study was terminated early before reaching the prespecified enrollment goal. This may explain, in particular, the variation in outcome of the primary endpoint in both endovascular groups where a heterogeneous use of endovascular tools (drug-coated vs non-drug coated devices) may have impacted the outcome, in particular, in the endovascular study cohort. In contrast, surgical bypass techniques are more uniform and are therefore not exposed to the same bias risk resulting from an underpowered study. Moreover, due to the high screening failure rate, the study results cannot be generalized.

Dr Dorigo: First of all, one of the major limitations was the exclusion of patients in poor general condition (who in the

real-world practice represent the majority of CLTI patients) and those having a failure of recent previous treatments; second, the extreme heterogeneity in open and endovascular procedures along with the lack of analysis on the basis of different techniques and materials has to be included as a limitation; third, the fact that about 20% of patients in both group withdrew or were lost to follow-up limits the findings, and, finally, the limited number of procedures performed per center per year limits how we can appropriately apply the findings to current practice.

Dr Dua: The biggest limitation of the trial was a very heterogenous mix of endovascular operators. A bypass done in Europe or Asia or Africa or America is done the same way essentially with the same steps to achieve a particular, quantifiable outcome. But if I recanalize an SFA using an endovascular revascularization technique, and my colleague down the street does the same, we can have two very different procedural approaches, so how can one compare outcomes?

Dr Holden: While the investigators of this landmark prospective randomized trial should be congratulated on overcoming many challenges, it is important to contextualize the results by recognizing trial limitations. The trial assumes clinical equipoise between the two treatment arms and, more importantly, assumes the procedural techniques and outcomes don't change during trial recruitment. This is, of course, not the case, particularly in regard to endovascular revascularization. The use of drug-eluting technologies to minimize restenosis was very low (<50% of cases), probably influenced by the paclitaxel controversy. Other endovascular techniques such as atherectomy or intravascular lithotripsy were not utilized to the same degree they would be in many centers today. It is likely that the choice of endovascular strategy (most commonly plain old balloon angioplasty [POBA]) had a direct impact on the very high rates of acute endovascular failure and reintervention seen in this trial. Concerns regarding the slow rate of enrollment in this trial and the low percentage of women enrolled have been well documented and do challenge the applicability of these data to real-world practice. In the endovascular arms of each cohort, the majority of endovascular procedures were performed by vascular surgeons (73%). It is difficult to assess the impact of this specialty imbalance (without more information on operator experience), but in many centers, interventional radiologists and cardiologists have more experience with complex endovascular reintervention, particularly below the knee.

Reinterventions were adjudicated by an independent multidisciplinary clinical events committee. It will be interesting to see how many of the endovascular reinterventions were deemed by the committee not to be clinically driven. I suspect this will be a low number because this is difficult to objectively determine with direct information including clinical assessment, ankle-brachial index and duplex ultrasound.

Dr Katzen: Can you address bias especially regarding patient enrollment and intervention?

Dr Mustapha: Again, the low rate of enrollment, even at high-volume centers, introduces major bias and limits the generalizability of the results. The high rate (50%) of endovascular procedures that were performed with POBA alone is likely the reason for the high reintervention rate in the endovascular group. POBA alone, albeit the current gold standard due to lack of RCTs in this area, is not the typical approach in high volume endovascular CLTI centers. 86% of the enrolling investigators were vascular surgeons and 75% of the endovascular procedures were performed by vascular surgeons and not those who specialize in endovascular alone. One may ask if choice of therapy (POBA) or operator skill contributed to the low technical success rate in the endovascular group.

Dr Neville: As mentioned previously, a low enrollment rate per site can statistically lead to an element of bias. The exclusion of patients at excessive risk for bypass or with a limited life expectancy and those with prior failed interventions may bias the results as applied to the so-called real-world patient.

Dr Rundback: While there were no intentional biases, the study had notable exclusions which resulted in a bias toward surgical bypass. Patients with excessive risk for surgical bypass or limited life expectancy were not included. Patients with recent prior open or endovascular intervention within 3 months were excluded. Crucially, BEST-CLI did not assess comparative outcomes in the large population of CLTI patients with Rutherford 6 disease, absence of a distal surgical target or dense arterial calcification.

Dr Secemsky: The trial cannot necessarily overcome who was selected for enrollment. What is most important is understanding who was not included, what percentage the "BEST-CLI" patient group represents the community of the CLTI population, and, from there, trying to understand if the outcome rates observed in the trial are reproducible in real world practice.

Dr van den Berg: There is definitely bias related to patient enrollment, using selection criteria that were already mentioned (patients with a good surgical risk profile and available GSV). An additional bias was probably also introduced by the high technical failure rate in the endo group, that translated in a high major reintervention rate (of 15.3% and 20% in the respective cohorts). With a higher technical success rate of the endovascular arm, the results would have looked different.

Dr Zeller: First, the low enrollment rate per study site (compared with the annual operating volume) represents a major bias in terms generalizability of the study results. Second, as already mentioned, the number of endovascular procedures using

drug-coated devices in the BEST-CLI trial was low considering that 50% of the endovascular procedures were performed with POBA alone, which is, in most lesions, an insufficient treatment regarding durability of the procedure. This treatment modality must be considered a major factor driving a large number of repeat procedures in this group. One reason for the high POBA alone rate may be that drug-coated balloons are not available for below-the-knee (BTK) treatment in the United States, and the use of drug-eluting stents is not yet standard of care. As most of the patients were enrolled in the US, the question remains if the study results can be translated to other countries. In my personal practice, only a minority of dedicated BTK lesions of CLTI patients are treated with POBA alone, no lesion above the BTK level.

Third, 86% of investigators who enrolled in BEST-CLI were vascular surgeons and 75% of endovascular procedures were performed by vascular surgeons. This low rate of genuine endovascular specialists (radiologists, cardiologists, angiologists) represents the major bias of the study. It is hard to believe that a vascular surgeon who is doing both open surgical and endovascular procedures has the same endovascular skills compared to an operator who has specialized to only endovascular techniques. At least in my institution, no vascular surgeon has comparable endovascular qualifications as the endovascular team of my department. The low technical success rate and the high POBA-only rate could be the consequence of the high proportion of surgeons performing endovascular procedures in the trial.

Dr Dua: This can be addressed during trial design to ensure you have a diverse mix of patients who are randomized by a third party.

Dr Holden: Selection bias is an obvious concern in this trial, impacting the patient enrollment. Investigators with expertise in surgical bypass and endovascular revascularization had to agree that there was equipoise between the treatment options. This is extremely difficult and is influenced by factors such as lesion location (above or below knee), length and complexity (calcium, chronic total occlusion). It is even more challenging to establish equipoise in single operator sites!

In both trial cohorts, the percentage of tibial or pedal artery procedures in the endovascular group was lower than expected for a CLTI patient population (381 or 30% of 1250 procedures in Cohort 1; 86 or 26% of 333 procedures in Cohort 2). In most centers, over 50% of CLTI endovascular interventions would include tibial or pedal intervention. This illustrates how highly selected the patients in this trial were, despite 66% of all patients having "substantial infrapopliteal artery involvement" as quoted in the *New England Journal of Medicine* publication.

Concerns regarding operator bias have been discussed above, particularly around the specialty imbalance and dominance of POBA in the endovascular arms.

Dr Lookstein: Only healthy patients were enrolled that were deemed good surgical risk. Few women and underrepresented minorities were represented in this trial.

Dr Katzen: Will the results of the trial increase the use of bypass at your center?

Dr Neville: I believe the trial will lead to an even further increase in the use of bypass in our system. We have a large and diverse group of providers treating CLTI patients, many who have advocated an endovascular-first approach regardless of indications, arterial anatomy, or prior attempts at endovascular therapy. This prospective, randomized trial supplies data to emphasize the role for bypass in the current environment and enhance cooperation and communication.

Dr Rundback: In our center, this will not change the use of bypass for the endovascular specialists or surgeons with whom we work closely.

Dr Secemsky: Probably not. Our surgeons also perform endovascular revascularization but still do a lot of bypass procedures. I will probably not refer more than I do already.

Dr van den Berg: Probably not, although a more thorough scrutiny of whether patients have a good surgical risk will be done more frequently in patients with available GSV, and this may lead to a minor increase.

Dr Zeller: No. Due to the reasons already mentioned, and also due to the limited surgical resources in my institution (even though we are a university hospital).

Dr Dorigo: No, as already mentioned, we tailor our treatment of CLTI patients according to clinical, local and anatomical criteria. Moreover, in those patients who were probably excluded from the trial due to their general conditions, we still prefer an endo-first attempt.

Dr Dua: We already practice the way that BEST-CLI results have supported, so we are going to continue to practice in a way which aligns with this RCT.

Dr Holden: No, for the reasons given previously.

Dr Lookstein: Likely not.

Dr Mustapha: No, it will not, due to reasons I previously mentioned.

Dr Katzen: Do you plan to change how patients with CLTI are evaluated for surgical risk and availability of saphenous vein conduit prior to intervention?

Dr Rundback: In our practice, we already routinely assessed the adequacy of the GSV in actual or physiologically younger patients with less complex patterns of disease in order to obtain better informed consent. Similarly, we commonly evaluate the GSV following (early) endovascular failures to assess further treatment option. These practice patterns likely will not change.

Dr Secemsky: I may do more venous mapping as I don't do much as is. Outside of that, I will discuss with each patient and only refer for those for surgical convo if they are great candidates and also willing to undergo surgery.

Dr van den Berg: A more thorough scrutiny of whether patients have a good surgical risk profile will be done more frequently in patients with available GSV.

Dr Zeller: No, because it is already our standard of practice that patients potentially planned for bypass surgery undergo a vein mapping program along with a cardiologic evaluation.

Dr Dorigo: No, we don't.

Dr Dua: In our vascular surgery practice we send patients for vein mapping to determine what type of conduit we have available and have conversations about bypass from the beginning. This will not change in our practice, as we already perform in a best practice fashion in line with these study results.

Dr Holden: No, as discussed previously, this already happens in patients deemed suitable for surgical bypass.

Dr Lookstein: We have always screened patients for saphenous vein conduit and we will continue to do so.

Dr Mustapha: Our centers already perform vein mapping in patients who are otherwise deemed surgical candidates.

Dr Neville: No. Our practice already performs vein mapping in all prospective revascularization patients, and we are aggressive with risk assessment prior to any intervention both for risk stratification, perioperative management, and to impact longer-term cardiovascular morbidity and mortality. Hopefully, our purely endovascular colleagues will begin saphenous vein mapping prior to intervention.

Dr Katzen: Given that surgical and endovascular revascularization approaches were comparable in Cohort 2, is an endovascular-first approach still best for patients without saphenous vein as conduit? Is there true equipoise in this scenario?

Dr Secemsky: Yes, endovascular should be used if there are no veins. Data do not report how many complications or readmissions these patients had. We should think about the whole picture for the patient, and a more morbid procedure without greater clinical benefit should not be frontline.

Dr van den Berg: Given the fact that in Cohort 2 the technical success rate in the endovascular arm was even lower than in Cohort 1 (80%), in a center that can achieve an endovascular success rate better than 80% the endovascular approach should be the first choice when a good GSV is not available. We also need to keep in mind that in Cohort 2 the patients were still considered good surgical risk, which as is well known, is not a frequent finding in this CLTI population.

Dr Zeller: As the BEST-CLI study was not powered for a comparison of the primary endpoint of Cohort 2, we cannot be sure that prosthetic bypass is as good as endovascular therapy. Nevertheless, if anatomical conditions are not favoring an endovascular approach as first line strategy, or if no endovascular expertise is available, a prosthetic bypass is a valuable option in CLTI patients.

Dr Dorigo: The result that should give pause for thought, rather than the comparison between open and endovascular surgery in group 2, is the comparison between vein bypass and prosthetic bypass in the two groups. The concept that without an adequate (and the trial furthermore does not clarify what is meant with adequate) saphenous vein segment, the surgical bypass has a significantly higher rate of failure, should be at least re-evaluated.

Dr Dua: If a patient does not have saphenous vein and the target is BTK, then indeed an attempt at angiography and endovascular treatment does make sense as a first-line strategy.

Dr Holden: I don't think there is true equipoise in the scenario described—patients with CLTI without a GSV conduit. In many patients, an endovascular approach with modern techniques can achieve revascularization at least durable enough to achieve wound healing and prevent amputation. In some cases, particularly those with lengthy occlusions and calcification, a surgical bypass (such as composite vein graft) is likely to achieve superior results. We currently don't have high-level evidence to support that decision making.

Dr Mustapha: I do not believe there was true equipoise described. I believe an endovascular approach should be attempted if patient does not have adequate vein.

Dr Neville: We do not have data-based equipoise for those patients without saphenous conduit, Cohort 2, and will continue to treat these patients on an individual basis. This means offering surgical bypass as the first approach given certain indications; large volume tissue loss when flap closure and/or robust perfusion is required as well as in the setting of long segment, calcific

tibial occlusive disease. It was interesting to note that in Cohort 2, outcomes with prosthetic bypass were similar to those with vein bypass. This is in keeping with data we have previously published using our distal vein patch technique and a heparin-bonded PTFE graft. Anastomotic adjunct techniques have greatly improved the results of prosthetic bypass. Therefore, we offer prosthetic bypass to those patients without saphenous conduit who have the appropriate indication; large volume tissue loss, extensive calcific tibial occlusive disease, and certainly after failed endovascular therapy.

Dr Rundback: We will continue to offer primary endovascular therapy as a first choice for any patient with a known compromised surgical conduit.

Dr Katzen: What additional subgroup analysis do you believe to be important?

Dr van den Berg: A comparison of the groups leaving out the technical failures in both arms. This comparison would eliminate the bias that was caused by a high technical failure rate in the 'endo arm' and a high technical success rate in the surgical arm. I think it is of utmost importance to anyone who wants to implement the results of BEST-CLI in his/her practice in favor of bypass should have the same, extremely good results with surgical bypass as those seen in the surgical arm in the BEST-CLI trial. If this is not the case, the equation of course changes dramatically. Auditing of a center's surgical and endovascular results is therefore extremely important in order to make the right choice for the patient.

Dr Zeller: One of two key questions remaining after the study is why did the prosthetic bypass group have results that were as good as the saphenous vein group? And second, why did the endovascular group of Cohort 2 have results that were better than the one of Cohort 1? In particular, the difference in outcomes between both endovascular arms deserves further evaluation considering that the baseline characteristics of Cohort 1 and 2 did not differ significantly.

Dr Dorigo: As reported previously, I think that a deep analysis of the results based on the materials and of the techniques, in both groups, is necessary. The large difference between endovascular results in both groups should be clarified, and the "poor" results of autologous vein as well.

Dr Dua: I think subgroup analysis within the endovascular group, looking at anticoagulation post op, wound healing care, and the type of endovascular procedure would be important to examine.

Dr Holden: Subgroup analysis based on lesion characteristics will be important (lesion length, location, complexity). It is likely that the numbers will be too small to assess outcomes based on specialty background in the endovascular group, but this would also be interesting.

Dr Lookstein: Successful endovascular versus successful bypass.

Dr Mustapha: I believe the question of why the endovascular group of Cohort 2 showed better outcome than the endovascular group of Cohort 1 since the baseline characteristics did not differ.

Dr Neville: As with any well-done clinical study, the BEST-CLI trial raises more questions than it definitively answers. Although the initial results are helpful, I look forward to subgroup analysis including quality of life data as well as further analysis of the endovascular techniques utilized in both groups and further information regarding Cohort 2, especially regarding the prosthetic bypasses performed.

Dr Rundback: Comparisons by age (<75 versus older), chronic kidney disease, diabetes mellitus, number of runoff and revascularized arteries, with and without optimized medical therapy (statin/antiplatelet at least), with and without use of other important cardiovascular medications (Xa inhibitors, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, vasodilators), baseline Rutherford and wound, ischemia, and foot infection scores, and wound healing….to name a few.

Dr Secemsky: Endovascular outcome rates by center and specialty and proportion of crossover patients (endovascular to surgery) and major reinterventions by site.

Dr Katzen: Do you believe the QoL results to be as important as major amputation of the lower extremity and reintervention?

Dr Zeller: QoL is the second-most relevant study endpoint for the individual patient, the most important one is survival rate. Major limb events, in particular major amputation and reintervention, are effectors of QoL. Therefore, amputation and reintervention should affect the outcome of QoL surveys. In the BEST-CLI study, driven by the higher reintervention rate, QoL survey outcomes should be expected to be inferior for the endovascular cohort. However, the study shows the opposite outcome, namely, that for the individual patient, a reintervention procedure seems not to be an important event regarding quality of life.

Dr Dorigo: I absolutely do.

Dr Dua: Yes, absolutely, QoL is a fundamentally important aspect in this patient population.

Dr Holden: QoL is a different parameter to major adverse limb events and reintervention, but no less important. It helps

contextualize those findings. For example, it is highly likely that a major adverse limb event will directly impact on QoL, but it is interesting that endovascular reintervention did not.

Dr Lookstein: Yes.

Dr Mustapha: Yes, I do believe QoL to be as important as major adverse limb events and reintervention. However, of interest, the study did not show that reintervention procedures decreased a patient's QoL.

Dr Neville: Yes, and I look forward to future subgroup analysis regarding quality of life (which is an increasingly important metric) and other data. This trial will continue to generate important information to help guide our care.

Dr Rundback: Yes. Patient-reported outcomes and preferences are key elements of shared decision making and therefore important drivers of management.

Dr Secemsky: These results are critical and should be at the forefront in addition to major adverse limb events. Clearly more reinterventions didn't take away from the QoL benefit. It is all about the patient in the end.

Dr van den Berg: In the end, the QoL is what counts most for the patient, and should therefore be one of the most important endpoints.

Dr Katzen: Do you think the results of this trial will foster further collaboration in a multidisciplinary approach to the patient with CLTI?

Dr Dorigo: Hopefully, it should.

Dr Dua: Yes, I believe that each group has something powerful to offer and frankly the patients get the absolute best care when everyone brings their "A game."

Dr Holden: I hope so, although the imbalance of disciplines in the endovascular group is not helpful in that regard.

Dr Lookstein: Hopefully, it should.

Dr Mustapha: I certainly hope so as both surgical and endovascular approaches bring something valuable to patients with peripheral arterial disease and CLTI. We must not forget that a true multidisciplinary approach to the patient with CLTI must include wound care, podiatry, and patient-specific specialties relating to that individual patient's comorbidities (ie, endocrine, nephrology, infectious disease, etc)

Dr Neville: Absolutely, this is one of the major benefits of this trial. Given that the trial demonstrated that bypass and endovascular therapy are both effective in preventing amputation in patients with CLTI, the trial strongly supports a multidisciplinary approach to the complex patient population.

Dr Rundback: I fear that this trial may result in greater divisiveness amongst vascular specialists, with surgeons claiming that they are now the best or most-qualified individuals to treat patients with CLTI since they can potentially offer all forms of therapy. This would be a fundamental misinterpretation of the study.

Dr Secemsky: I really hope so. If this trial was about making multidisciplinary decisions about patients, including the decision to randomize, and who should perform the revascularization procedure, then this should be how we discuss patients in clinical practice.

Dr van den Berg: It is my strong belief that the best way to treat patients with CLTI is in a multidisciplinary team. As Frank Veith has stated in his book, *The Medical Jungle*, "if appropriate skills are not available to one or another member of the team caring for the patient, the procedure should not be performed." This works in both directions. A vascular surgeon without appropriate endovascular skills should reach out to a more proficient colleague (surgeon, radiologist, or cardiologist), just like an interventional radiologist or interventional cardiologist should have a low threshold to seek support from a vascular surgeon.

Reference

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