Following BEST-CLI and BASIL-2, Do We Better Understand How to "Best" Serve Critical Limb Threatening Ischemia Patients?

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Chronic limb-threatening ischemia (CLTI) is the most severe manifestation of peripheral arterial disease (PAD) including ischemic pain, ulcerations, and/or gangrene representing a major medical and socioeconomic burden on health and social care services worldwide.[1] Recently, 2 randomized controlled landmark trials (RCT), the BEST-CLI (Best Endovascular versus Best Surgical Therapy in Patients with CLTI)[2] and BASIL-2 (Bypass versus Angioplasty for Severe Ischemia of the Leg)[3] studies, were published investigating patient and limb-related outcomes of participants with CLTI who underwent endovascular versus open-surgical treatment. In the BEST-CLI study uniquely, patients were divided into 2 cohorts, those with a single segment of adequate greater saphenous vein for bypass (cohort 1), and those without (cohort 2). Randomization included stratification by clinical presentation (Rutherford-Becker category 4 vs 5/6) and the presence vs absence of significant tibial disease. BASIL-2 compared the clinical effectiveness of a "vein bypass first" or a "best endovascular treatment first" strategy for revascularization of severe ischemia due to infrapopliteal arterial disease. Correction of additional proximal inflow disease was allowed prior to infrapopliteal revascularization.

Since there was a striking paucity of high-level comparative effectiveness evidence on the optimal treatment of patients with CLTI so far, both these landmark trials were awaited with great interest. However, study outcomes are conflicting and therefore worthy of intensive review and in-depth analysis for all medical professions confronted with such patients.

What are the primary endpoint outcomes?

In BASIL-2, after a minimum follow-up of 2 years, the primary outcome (major amputation or death) occurred in 63% of the bypass group and 53% of the best endovascular group, with an adjusted hazard ratio of 1.35 (95% confidence interval CI 1.02-1.80, *P*=.037), in favor of best endovascular treatment. The mortality difference continues throughout the trial rather than only during the peri-operative period, whereas there was no difference in amputation rates.

In BEST-CLI, in cohort 1 at a median 2.7 years of follow-up, a primary outcome event (major adverse limb event or all-cause mortality) occurred in 42.6% in the bypass group and in 57.4% in the endovascular group, hazard ratio 0.68 (95% CI .59-.79; *P*<.001). There were significantly more re-interventions in the endovascular group, and a significantly reduced rate of major amputations with bypass surgery. In cohort 2, a primary outcome event occurred in 42.8% in the surgical group and in 47.7% in the endovascular group, hazard ratio 0.79 (95% CI .58-1.06; *P*=.12) after a median follow-up of 1.6 years. Adverse event rates were similar in both cohorts.

What are similarities between BASIL-2 and BEST-CLI?

Both are prospective randomized controlled studies comparing the safety and effectiveness of bypass surgery with use of an optimal vein and "best" endovascular therapy in patients suffering from critical limb threatening ischemia (CLTI) using a pragmatic approach leaving in particular the decision of best

Table 1. Comparison of key study characteristics comparing BEST-CLI and BASIL-2.

	BEST-CLI cohort 2	BEST-CLI cohort 2	BASIL-2
Primary endpoints	• Composite of major adverse limb events or death from any cause	• Idem	• Amputation-free survival (time to above the ankle) amputation of the trial leg or death from any cause
Main secondary endpoints	• Occurrence of a major adverse limb event at any time or postoperative death within 30 days • Minor reinterventions • Major adverse cardiovascular event (MACE)* • Serious adverse events	• Idem	• Time to death from any cause (overall survival) • Time to major amputation of the trial leg • Time to first major adverse limb event (MALE)** • Time to first major adverse cardiac event (MACE)***
Main inclusion criteria	• CLTI, which was defined as arterial insufficiency of the lower limb with ischemic foot pain at rest, a nonhealing ischemic ulcer, or gangrene, as corroborated by hemodynamic criteria • Life expectancy 2 years • An investigator with expertise in surgical bypass procedures had to agree with another investigator with expertise in endovascular re-vascularization procedures that clinical equipoise existed in the randomization of each patient • Availability of autogenous bypass (single segment of great saphenous vein)	• Idem • Need for an alternative bypass conduit	•CLTI due to atherosclerotic disease and who required an infra-popliteal, with or without an additional more proximal infra-inguinal revascularization procedure •Life expectancy > 6 months •Judged by two consultants (one of whom could undertake infra-popliteal vein bypass and one of whom could undertake infra-popliteal endovascular interventions) to require and be suitable for both infra-popliteal vein bypass and infra-popliteal endovascular intervention •Adequate aortoiliac inflow to support both revascularization strategies
Main exclusion criteria	•Excessive risk associated with open vascular surgery according to the criteria of the American Heart Association and the American College of Cardiology or according to the medical judgment of the investigator	• Idem	• Previous vascular intervention to the target infra-popliteal artery within the previous 12 months • Ischemic pain or tissue loss considered not to be primarily due to atherosclerotic peripheral artery disease
Number of study sites	150		41
Average number of patients per site entire study	12.2		8.4
Intended sample size	1620 participants	480 participants	600 participants
Final sample size	1434 participants	396 participants	345 participants
Power calculation	85%	80%	90% reduced to 80%
Enrollment period	08/2014 – 10/2019	Idem	07/2014 – 11/ 2020

* In BEST CLI, MACE was defined as a composite of myocardial infarction, stroke, or death from any cause.
** MALE = major adverse limb events.
***MACE = major adverse coronary events defined as a composite of myocardial infarction, stroke, or death from any cause.

endovascular therapy to the discretion of the operator. The second similarity is that both studies were terminated early due to slow enrollment and termination of funding.

What are the differences between the two studies?

Major differences exist regarding patient and interventional characteristics as summarized in **Table 1, Table 2,** and **Table 3**:

Study endpoints. BASIL-2 used a harder, more investigator independent endpoint of *amputation-free survival* defined as time to major (above the ankle) amputation or death of any cause whereas BEST-CLI defined the composite endpoint as *death of any cause* and *major adverse limb event* defined as above ankle amputation of the index limb or a major index-limb re-intervention (new bypass, interposition graft revision, thrombectomy, or thrombolysis). An endovascular procedure such as balloon angioplasty or stenting was not considered to be a major re-intervention, a procedure that is, in most institutions, standard of care for salvaging, eg, a stenotic bypass-graft anastomosis **(Table 1)**.

Patient population. Patient enrollment was stopped in both studies before reaching the per-defined sample size, with BEST-

Table 2. Comparison of key patient characteristics comparing BEST-CLI and BASIL-2.

	BEST-CLI cohort 1	BEST-CLI cohort 2	BASIL-2
Patients who did not undergo any procedure	4.3% / 1.1%	3.6% / 2.0%	8.7% / 1.2%
Cross-over to other revascularization method	3.5% / 0.4%	1.0% / 2.0%	7% / 3.5%
Median age (years)	66.9 / 67.0	68.4 / 68.8	72.4 / 72.5
Male	72% / 71.1%	71.6% / 72.4%	81% / 82%
Diabetes mellitus	72.1% / 71.6%	62.2% / 58.3%	68% / 69%
Mean eGFR (ml/min)	NA	NA	66.5 / 67.6
Chronic hemodialysis	9.4% / 11.8%	12.8% / 10.1%	6% / 3%
Previous stroke	12.8% / 13.9%	19.4% / 12.1%	15% / 20%
Coronary artery disease	42.3% / 44.4%	49.5% / 53.8%	NA
Previous MI	NA	NA	24% / 13%
Previous PCI & CABG	NA	NA	26% / 19%
Previous intervention study leg	5.6% / 5.2%	10.3% / 10.1%	31% / 39%
RBC 4	20.3%/20%	29.4%/30.2%	13% / 11%
RBC 5 (and 6)	79.7%/80%	70.6%/69.8%	87% / 89% (RBC 5 only)
ASA class 3 or 4	80.8%/75.9%	83.5%/80.9%	NA
No. patients completing the trial	560/1434 (39%)	226/396 (57.1%)	212/345 (61.4%)
Screen failures	unknown	unknown	unknown

CABG = coronary artery bypass graft surgery; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; NA = not availabler; PCI = percutaneous coronary intervention; RBC = Rutherford-Becker classification.
For all columns, where 2 data elements are listed, the first figure refers to 'open" and the second to 'endo' (open/endo)

CLI being the much bigger study (cohort 1: 1434 of intended 1620 patients, cohort 2: 396/480 patients enrolled in 150 study sites) compared to BASIL-2 (345/600 patients enrolled in 41 study sites). Patients enrolled in BASIL-2 were older (median age 72.5 years vs 67 and 68.5 years in cohort 1 and 2, respectively), had undergone more previous interventions of the target limb, and seemed to have more frequent cardiac concomitant diseases. Of note, the requested life expectancy had to be at least (only) 6 months in BASIL-2 (not further defined) as compared to 2 years in BEST-CLI (due to reasons other than PAD only) **(Table 2)**.

Study procedure. In BASIL-2, all distal bypass anastomoses were either tibial or pedal, whereas in BEST-CLI, 40% of the grafts were anastomosed onto the popliteal artery. Similarly, in BASIL-2 besides inflow lesion treatment all endovascular procedures did include at least one below-the-knee target vessel, whereas tibial artery intervention was performed in BEST-CLI in 53.2% of cases only, in the remaining cases the femoral-popliteal artery was the single target **(Table 3)**.

What are the consequences of these landmark studies?

Both studies included a highly selected patient cohort. As stated by the authors of the BASIL-2 publication, "clinical experience suggests that few patients with chronic limb-threatening ischemia are deemed suitable and have an optimal vein for infrapopliteal bypass." Moreover, a further limitation of generalizability of the study results is the low acceptance of patients for randomization between an open surgical procedure and an endovascular intervention. The key question is which data apply more to a daily practice patient population.

First, data from BEST-CLI cohort 2 suggest equivalent efficacy of clinical outcomes between bypass surgery in patients without a suitable single great saphenous vein and endovascular therapy.

More difficult to understand is the different outcome between cohort 1 in the BEST-CLI trial and the BASIL-2 study population. The better outcome of the endovascular cohort in BASIL-2 is driven by a significant lower mortality rate throughout the entire follow-up period whereas in BEST-CLI the benefit of vein bypass surgery was a reduced major re-intervention and major amputation rate. Interestingly, despite these higher major event rates in the endovascular cohort, patient satisfaction was similar in both study cohorts regarding quality of life measures. It is unclear how much the exclusion of patients with "excessive risk associated with open vascular surgery" may have contributed to

Table 3. Comparison of key outcome characteristics comparing BEST-CLI and BASIL-2.

	BEST-CLI Cohort 1	BEST-CLI Cohort 2	BASIL-2
Bypass location			
Femoro-popliteal	40%	47.9%	1%
Femoro-popliteal AK	NA	NA	0%
Femoro-popliteal BK	NA	NA	1%
Femoro-BTK	35.7%	37.4%	59%
Popliteal-BTK	15.7%	8.4%	40%
Endovascular techniques			
Balloon angioplasty	52.7%	47.2%	60%
Atherectomy	13.6%	15.4%	0%
Drug-coated balloon	27.8%	25.1%	0%
Bare-metal stent	39.3%	43.1%	10%
Drug-eluting stent	24.2%	21.5%	0%
Stent graft	8.6%	12.8%	0%
Technical success	98.3% / 84.7%	100%/80.6%	96% / 80%
All cause death	33% / 37.6%	25.9% / 24.1%	53% / 45%
Major amputation (above ankle)	10.4%/14.9%	15.2%/14.1%	20%/18%
AK amputation	NA	NA	NA
BK amputation	NA	NA	NA
Amputation free survival	43.3%/52.4%	41.1%/38.2%	37%/47%
Cross-over intervention during FU	NA	NA	27% / 19%
Reintervention**	9.2% / 33.1%	14.2%/25.6%	5% / 19%

AK = above knee; BK = below knee; BTK = below the knee; FU = follow-up; NA = not available
**** reintervention: 'major' for BEST-CLI, 'not-specified' for BASIL 2

the similar mortality rates seen in the open and endovascular arms in both cohorts in the BEST-CLI trial. Considering death as the most serious possible event one could argue, BASIL-2 being the more relevant study favoring the endovascular first strategy. However, are both study populations comparable besides presenting with CLTI?

It seems as if the BASIL-2 study population represents a higher risk patient population as compared to BEST-CLI as demonstrated by the highest all-cause death rate of the 3 cohorts (open vs. endo BASIL-2: 53% / 45%, BEST-CLI cohort 1: 33% / 37.6% and cohort 2: 25.9% / 24.1%). Reasons for this high mortality rate may be that BASIL-2 patients are older, they seem to have a higher prevalence of clinically relevant coronary heart disease, and, in particular, they have a more distally located disease anatomy.

Although there were differences in specialty performing the endovascular techniques (in BEST-CLI, 73% of the endo-procedures were performed by vascular surgeons, while in BASIL-2 84% were performed by interventional radiologists) it can be seen (**Table 3**) that technical success rates were in a similar range.

Opposite to BEST-CLI, re-intervention rates in BASIL-2 do not differ between both revascularization strategies. A reason for this may be a higher redo rate for tibial bypass surgery as compared to a distal popliteal artery anastomosis. Whereas BASIL-2 enrolled exclusively lesion anatomies requiring tibial bypass anastomoses, only 60% of the venous bypass in BEST-CLI had a tibial bypass anastomosis. It would be interesting to see upcoming sub-cohort analyses of BEST-CLI regarding major re-intervention rates comparing popliteal and tibial distal bypass targets. Another factor that may have influenced the differences in outcomes is the fact that BEST-CLI included patients with RBC 4-6 (Rutherford-Becker classification), while RBC 6 patients were not included in BASIL-2.

What has become clear from both studies is that medical therapy is sub-optimal in the majority of patients, and therefore it is necessary to strive for reduction of excess cardiovascular mortality by performing a proper cardiovascular diagnostic

work-up and optimization of secondary prevention (by establishing optimal medical therapy).

It has to be kept in mind that the results of both these studies are only valid when the technical success rates in an institution are comparable to those achieved in BEST-CLI and BASIL-2. This is especially true for (distal) bypass surgery, and therefore internal auditing/credentialing should be considered when applying the results in a local practice (cf, carotid endarterectomy, and stenting).

Conclusion

The bottom line is, if a patient is suitable for both revascularization strategies, technical revascularization success is higher with bypass surgery independent of the bypass material. Besides this, on mid-term, patients seem to benefit from both treatment strategies. Open surgery and endovascular intervention should be considered as complementary treatment options. The treatment offered to an individual patient should be tailored to the patient's needs and the available operator expertise in a given vascular center.

Both BEST-CLI and BASIL-2 have generated a wealth of data that can already be implemented in choosing the optimal treatment modalities for patients with CLTI. The planned individual patient data driven pooled analysis of both studies (both trial investigators entered into a data sharing agreement), will provide probably a more granular view that will allow further fine-tuning.

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