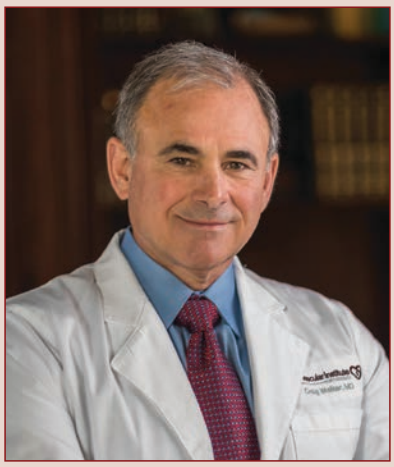
BEST-CLI Deep Dive II



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Hello and welcome to the December 2022 edition of *Vascular Disease Management*. This month we continue our discussion of the BEST-CLI randomized control trial comparing surgery-first with (cohort 1) or without (cohort 2) an adequate venous conduit vs endovascular-first treatment in patients with chronic limb-threatening ischemia (CLTI).[1]

First, to reiterate the major point of last month's editorial, the exceedingly high rate of technical failure in the endovascular therapy arm (15.3%) vs the surgical arm (1.7%) in cohort 1 accounts for nearly the entire difference between groups for the primary endpoint (since failed initial revascularization inevitably leads to subsequent revascularization attempts). This difference results in the early and constant separation in the Kaplan Meier curves observed for the primary endpoint for cohort 1.

A highly perplexing aspect of the excessive technical failure rate for endovascular treatment in the study is that these patients were highly selected and do not represent a real-world cohort of CLTI patients (who often have very poor or no outflow vessels). Given the required adequate outflow for bypass, technical failure utilizing endovascular approaches should have been much lower than contemporary all-comer CLTI studies.

A second important observation regarding the primary outcome was that the overall event rates between endovascular cohort 1 and 2 should have been similar; yet the observed primary event rate for cohort 1 was 10% higher than cohort 2. Given there was no difference between treatment performed in the 2 endovascular cohorts, there should not have been the wide disparity observed.

Third, I would like to reiterate a concern regarding "best" endovascular therapies available. Multiple studies have demonstrated that drug-eluting technologies improve restenosis and decrease reintervention.[2] Yet, the rate of drug-eluting device use was around 25% in the 2 cohorts. This was explained in the manuscript as being due to concerns regarding the safety of these devices stemming from the now-debunked Katsanos controversy regarding mortality in drug-eluting devices during the period of enrollment.[3] However, this publication did not appear until December 2018 and therefore should only have affected the last year of trial enrollment (enrollment in BEST-CLI was from August 2014 to October 2019).

My fourth major criticism of the study is the excessive missingness and loss to follow-up, which in my opinion basically invalidates the results. One glance at the study consort diagram tells of the severe problems with the execution of this trial and highlights concerns for underlying selection bias. One extreme example is the following excerpt from the consort diagram: "1 (patient) was erroneously assigned to the endovascular arm (post randomization) after death had occurred." May I ask, is it a coincidence that the dead patient was assigned to the endovascular arm?

Table 1. Randomization issues with BEST-CLI: Patient numbers.

	Cohort 1		Cohort 2		Grand total
	Surgery	Endo	Surgery	Endo	
Underwent alternate therapy than randomized	25	3	2	4	
Did not have any procedure	31	8	7	4	
Withdrew	94	60	24	10	
Lost to follow-up	68	64	12	14	
Total	218	135	45	32	**430**

Furthermore, the excessive missingness and loss to follow-up does not consider the large number of patients who either did not undergo any procedure despite randomization or underwent a different procedure than assigned by randomization (**Table 1**). In the surgical arm of cohort 1,

nearly 10% of randomized patients either did not undergo a procedure or underwent endovascular procedures despite being randomized to surgery. **Overall, 24.2% (447 out of 1847) of patients post randomization had an issue with inclusion, follow-up, missingness, or data integrity (430 from Table 1 plus 17 who were excluded due to data integrity issues)**.

My trepidation with BEST-CLI is that this deeply flawed, highly publicized manuscript will result in guideline changes without the compensatory high-quality data. For me to consider accepting this trial result, I would request several things from the study group: (1) a sensitivity analysis of only those patients with technically successful procedures using both per protocol and intent-to-treat analyses; (2) presentation of data regarding procedure times, frequency of alternate access, frequency of intravascular imaging, and description of chronic total occlusion intervention techniques employed (to assure modern endovascular techniques were utilized); (3) follow-up data for the high number of patients who were lost to follow-up or excluded due to easily rectifiable data integrity issues (ie, missing demographic data); and (4) data regarding interventional volumes of the participating operators to demonstrate adequate competence in endovascular procedures.

In conclusion, the BEST-CLI trial primary outcome that bypass-first with an adequate venous conduit is superior to an endovascular-first approach cannot be incorporated into clinical guidelines without addressing significant concerns with trial design, execution, data integrity, and biases. We must demand higher-quality data for our patients, with studies matching the current modern standards of clinical trials to answer important questions such as the one posed in BEST-CLI. Further studies must be performed to adequately understand surgery-first vs endovascular-first approaches in CLTI, but for now we are stuck with the status quo. ■

REFERENCES

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