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EDITORIAL COMMENT

Intermediate-Term Results of the OLIVE Registry*

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The report by Iida et al. (1) in this issue of *JACC: Cardiovascular Interventions* on the intermediate results of the OLIVE (A Prospective, Multi-Center, Three-Year Follow-Up Study on Endovascular Treatment for Infra-Inguinal Vessel in Patients With Critical Limb Ischemia) Registry is an informative expansion of an earlier accounting of the 1-year outcomes by the same investigators (2). The study cohort comprised 314 Japanese patients with critical limb ischemia (CLI) who were prospectively followed after undergoing endovascular treatment (EVT). There was an impressive 95% retention of the patients originally enrolled in the registry over the 3 years of the current report. The primary outcome of the study was amputation-free survival, whereas secondary measures included major adverse limb event (MALE), wound-free survival, and wound recurrence. The OLIVE registry restricts its scope to endovascular therapy and has no comparative surgical arm.

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The demographics of the registry cohort reflect the challenging clinical patterns of comorbid disease typically seen in CLI patients. Of particular note were the high rates of diabetes mellitus (71%), renal failure (61%), and hemodialysis (52%) and the low rate of statin use (26%). Nearly 90% of patients had tissue loss, with 15% of patients classified as Rutherford Class 6 and 20% as having multiple wounds. The authors do not explain how almost 20% of the study cohort had a normal baseline ankle brachial index (ABI), and only 6% had an ABI <0.4. This discrepancy between the reported degree of ischemia and the baseline hemodynamic status leaves open the possibility of contamination of the dataset by patients with nonischemic ulcers or wounds, particularly important in light of the focus given to wound healing and recurrence in the study. Patients in the OLIVE registry had disease limited to infrainguinal arteries, although how treatment of common femoral arterial disease was considered was not further elucidated. The surprisingly low rate of patients ambulatory at baseline (12%) highlights both the poor functional status and vulnerability of the study cohort.

The major finding of the registry was a 3-year amputation-free survival rate of 55%, a result comparable to that found in both the surgical and EVT arms of the BASIL (Bypass versus Angioplasty in Severe Ischemia of the Leg) trial (3). Rutherford Class 6 and end-stage renal disease were major predictors of death or major amputation, consistent with an ample literature previously indicating the significant influence of dialysis dependence and the extent of disease on survival and limb salvage. That a low body mass index was also predictive of a poor outcome is a novel and intriguing result. While a breakdown of MALE events was not provided, MALE outcomes were also in the predicted range for this challenging population.

The OLIVE investigators are to be applauded for taking on the challenge of assessing wounds in the registry. Reliably characterizing and tracking ischemic leg wounds is difficult, time-consuming, and fraught with reporter bias, and for these reasons, this important outcome metric is usually missing from CLI studies. Wounds in the OLIVE registry were managed by plastic surgeons and dermatologists; vascular surgeons were conspicuous in

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their absence from the current study. The registry incorporated independent assessment of photographed ulcers within the context of a wound core lab for the first year, while evaluation was less rigorously left to the discretion of participating plastic surgeons thereafter.

The goals of care for CLI are to relieve rest pain and heal wounds, which, if achieved, give the patient the best chance of surviving with a preserved limb. Along with questions about cumulative cost and cost-effectiveness, it is the durability of successful treatment that remains the most important unresolved concern associated with EVT. Is perfusion improved to the degree to heal a small ulcer, a large ulcer, a heel ulcer—and prevent a recurrence of that ulcer or a breakdown of a toe amputation incision? Although the OLIVE registry does not include desirable hemodynamic information or insight into the nature of reinterventions, it does provide relevant and valuable data on ulcer recurrence. Notably, in the described cohort, 43% of patients required a reintervention, and only 41% of those who began the study with an ulcer were alive and without an ulcer 3 years later. In comparison, of those whose presenting symptom was rest pain, 70% were alive without an ulcer at the 3-year follow-up point. Few papers address the impact of different treatment strategies on ulcer healing in CLI patients; one that does, found surgical bypass associated with a 2-fold improvement in wound resolution compared with EVT (4).

As the authors acknowledge, there are flaws in the current study, some unique and some common to all registries of this nature. The completeness of the database in the absence of an objective auditing mechanism, and hence the degree to which it reflects real-world practice, remains unknown. The absence of a surgical comparator may or may not reflect a bias toward EVT for all patients regardless of the anatomic pattern and initial clinical presentation, thereby limiting its usefulness to those whose practice patterns differ. The unavailability of endovascular techniques typically used in North American practice to OLIVE investigators (e.g., stenting as a bailout option in the event of a suboptimal tibial balloon angioplasty result) will likely and reasonably be cited as a contributing factor in the high rates of reintervention and ulcer recurrence seen. Taken together, however, the shift in results from 1 to 3 years highlights the critical importance of longer term data in accurately judging the best treatment for complicated CLI patients. Despite the collective limitations, the OLIVE registry appears to be a well-constructed dataset that which adds needed information beyond the short-term window that currently limits much of the existing literature on CLI patients receiving EVT.

The BEST-CLI (Best Endovascular vs. Best Surgical Therapy in Patients With Critical Limb Ischemia) study, a randomized, controlled trial currently underway in the United States and Canada (5), will hopefully shed additional much-needed light on the treatment results of CLI patients. In the BEST-CLI study, 2,100 patients in more than 120 centers will be randomized to either open surgical bypass or EVT. Nearly 800 investigators from all disciplines that treat CLI in North America are participating. Patients will be followed for more than 2 years, and a comprehensive cost-effectiveness analysis will provide a more complete context for the financial impact of specific care rendered. Functional outcomes will also be carefully studied in an effort to more fully understand the effect of treatment on quality of life and performance. As in the current study, both initial and recurrent wounds will be tracked and adjudicated.

There have been increasing and appropriate calls for a more cooperative approach to CLI care, modeled on the highly successful construct that has become the current standard for the treatment of cancer in the United States. In such a model, a range of collaborating specialists with unique skill sets—endovascular, surgical, podiatric, medical, diabetic, plastic surgical—will demonstrate a willingness to move beyond care rendered in isolation and at times shadowed by specialty self-interest to that driven solely by the best interests of the patient. This will require those with lingering resistance to EVT to be open to its evolving role. Just as significantly, it would require those who offer percutaneous treatment with little awareness or consideration of the ongoing importance of surgical therapy to be willing to partner with their surgical colleagues. Defining the proper role of both surgical treatment and EVT can only come from rigorous accounting of results, favorable or otherwise, from additional investigations, inclusive of institutional experience, well-formulated registries, and randomized, controlled trials such as BASIL-2, BASIL-3, and BEST-CLI trials.

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REFERENCES

1. Iida O, Nakamura M, Yamauchi Y, et al. 3-year outcomes of the OLIVE registry, a prospective multicenter study of patients with critical limb ischemia: A Prospective, Multi-Center, Three-Year Follow-Up Study on Endovascular Treatment for Infra-Inguinal Vessel in Patients With Critical Limb Ischemia. J Am Coll Cardiol Intv 2015;8:1493–502.

2. Iida O, Nakamura M, Yamauchi Y, et al., OLIVE Investigators. Endovascular treatment for infrainguinal vessels in patients with critical limb ischemia: OLIVE registry, a prospective, multicenter study in Japan with 12 month follow-up. Circ Cardiovasc Interv 2013;6:68–76.

3. Bradbury AW, Adam DJ, Bell J, et al. Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial: analysis of amputation free and overall survival by treatment received. J Vasc Surg 2010;51:18S–31.

4. Neville RF, Steinberg J, Babrowicz J, et al. A comparison of endovascular revascularization and bypass in regards to healing rates of ischemic wounds. J Vasc Surg 2010;51:11–12S.

5. Farber A, Rosenfield K, Menard MT. The BEST-CLI trial: a multidisciplinary effort to assess which therapy is best for patients with critical limb ischemia. Tech Vasc Interv Radiol 2014;17:221–4.

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