

Please note: Dr. van de Hoef has served as a speaker for Philips-Volcano Corporation, St. Jude Medical, and Boston Scientific. Dr. Escaned has served as a speaker for Boston Scientific, Philips-Volcano Corporation, and St. Jude Medical. Dr. Piek has served as a speaker for Philips-Volcano Corporation.

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## 3-Year Outcomes of the OLIVE Registry, a Prospective Multicenter Study of Patients With Critical Limb Ischemia



We read with much interest the recent paper and editorial by Iida et al. (1) and Menard (2), respectively, in *JACC: Cardiovascular Interventions* assessing the mid-term outcomes after endovascular therapy in a prospective multicenter (A Prospective, Multi-Center, Three Year Follow-Up Study on Endovascular Treatment for Infra-Inguinal Vessel in Patients With Critical Limb Ischemia [OLIVE]) registry in 314 patients with chronic limb ischemia (CLI). At 3 years, amputation-free survival, freedom from major adverse limb events, and wound-free survival rates were 55.2%, 84.0%, and 49.6%, respectively. Wound recurrence rate at 3 years was 43.9%. After multivariable analysis, age (hazard ratio [HR]: 1.43,  $p = 0.001$ ), body mass index 18.5 (HR: 2.17,  $p = 0.001$ ), dialysis (HR: 2.91,  $p < 0.001$ ), and Rutherford 6 (HR: 1.64,  $p = 0.047$ ) were identified as predictors of 3-year major amputation or death. Statin use (HR: 0.28,  $p = 0.02$ ), Rutherford 6 (HR: 2.40,  $p = 0.02$ ), straight-line flow to the foot (HR: 0.27,  $p = 0.001$ ), and heart failure (HR: 1.96,  $p = 0.04$ ) were identified as 3-year major adverse limb event predictors. Finally, CLI due to isolated, below-the-knee lesion was a wound recurrence predictor (HR: 4.28,  $p = 0.001$ ). Three-year

survival, freedom from major amputation, and reintervention rates were 63.0%, 87.9%, and 43.2%, respectively.

The authors should be commended for writing this important and timely paper, especially as the research in CLI has reoriented towards optimizing long-term patient outcomes. Long-term patient outcomes beyond limb salvage are critical because large registry studies in peripheral artery disease have shown that suboptimal medical management increases the risk of cardiovascular death, stroke, and myocardial infarction by up to 7-fold at 3 years (3). In this regard, it is striking that in the OLIVE registry, despite a very high incidence of established vascular disease (100%) and cardiovascular disease (21% to 46%), only 26% are on statin therapy, 40% on clopidogrel, and/or 50% on cilostazol. Additionally, there are no data presented on whether the statin use or blood pressure control had been optimized and reached the targets set by the TransAtlantic Inter-Society Consensus (TASC) II guidelines (4). However, the authors should be congratulated for reporting on the degree of optimal medical therapy in their patient subset. In fact, most of the recent prospective studies have focused primarily on endovascular device use/techniques to optimize limb outcomes and have not quantified whether patients received guideline-based optimal medical therapy before or after endovascular intervention (1).

These observations suggest a persistent deficit in the quality of medical care in CLI and have profound implications. First, population-based interventions that improve medical therapy for CLI may have a large impact both on amputation-free survival and reducing the risk of cardiovascular mortality and myocardial infarction. Second, the addition of an optimal medical treatment metric in the assessment of endovascular and/or surgical interventions on CLI will allow for uniform comparisons between different treatment strategies. Furthermore, it is known that the costs of inpatient care in the year before amputation in patients with CLI is more than \$20,000 per patient. This cost varies by 2-fold across hospital referral regions in the United States; much of this difference in cost is driven by the use of revascularization treatments and not related to patient or amputation care. Additionally, there is little evidence that higher spending on vascular care (primarily endovascular care) in the year prior lowers amputation rates. The quality of baseline medical therapy will be important in assessing and comparing the overall quality and cost of vascular care provided by institutions and individual providers (5). This is axiomatic in light of the environment in

which medicine is practiced today with the creation of accountable care organizations and increasing patient/payer scrutiny.

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## REPLY: 3-Year Outcomes of the OLIVE Registry, a Prospective Multicenter Study of Patients with Critical Limb Ischemia



We would like to thank Dr. Philip for his interest in 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 (1) evaluating outcomes of endovascular treatment for infrainguinal vessels in patients with critical limb ischemia (CLI). One issue that was pointed out this time described problems in the current treatments for patients with CLI. We completely agree with Dr. Philip that the quality of baseline medical therapy is extremely important when assessing and comparing the overall quality and cost of vascular care. As noted, we have no evidence that the medical costs associated with revascularization with endovascular therapy actually prevent amputation, whereas the efficacy of optimal medical therapy (OMT) for amputation prevention and prognosis improvement has not been established, either (2). The current guidelines

recommend OMT for peripheral arterial disease (PAD) as follows: 1) antiplatelet therapy; 2) statins; and 3) angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. There is a report that the administration of 2 or more of these agents reduces mortality. However, we should also note the lack of consistency in the provision and adherence of these recommended therapies in PAD patients (3). Some antiplatelet drugs and statins have been reported to improve limb prognosis (2). The OLIVE study demonstrated a low administration rate of statins in the real world. In this study, 52% of subjects were on dialysis, 41% had hyperlipidemia, and the mean body mass index was 22, but the administration rate of statins was as low as 26%. Inadequate drug treatment for PAD and poor adherence of patients have recently been reported (4,5), and it is meaningful that the OLIVE study also revealed that OMT is rarely provided for CLI in actual clinical practice. Among CLI patients in the clinical setting, some presented with hypotension or terminal status of arteriosclerosis with sarcopenia. For these patients facing such a prognosis, both OMT administration and revascularization are controversial. Either way, the evidence level for the role of OMT for CLI is insufficient, and such verification is urgently necessary.

The onset and progression of CLI are strongly correlated with diabetes mellitus and renal failure. Patients with these complications present with a higher prevalence of infrainguinal arterial lesions, which have a high rate of restenosis and reintervention after endovascular therapy. In the OLIVE study, the percentage of subjects with diabetes mellitus and those on dialysis was as high as 71% and 52%, respectively, and approximately 75% had the infra-popliteal arterial lesions, resulting in high rates of restenosis and reintervention (1). In patients with rest pain or ulcers/gangrene who developed a first episode or recurrence, reintervention seemed to be both inevitable and the only option: the medical intervention to prevent major amputations provides only class III guidance in the current guideline. On the other hand, repeated revascularization is an additional financial burden, despite providing only local treatment. A general treatment model, including systemic treatment and social aspects, should be considered in order to improve CLI prognosis as well as medical cost burdens. Even if revascularization is the first-line treatment for CLI, this does not necessarily justify repeated interventions performed within a short period of time.

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