Peripheral artery disease (PAD), secondary to atherosclerotic occlusive disease of the aorto-iliac, femoropopliteal, and/or infra-popliteal arteries, affects over 200 million people worldwide with an estimated annual incidence of 220 to 3,500 cases per 1 million persons.\(^1\) Chronic limb threatening ischemia (CLTI), also known as critical limb ischemia, is a more severe form of PAD. It is defined as ischemic pain in the foot while a person is at rest with pain lasting two or more weeks, non-healing wounds, or gangrene that is attributable to objectively proven arterial occlusive disease.\(^2\) The majority of CLTI patients have infrainguinal disease. CLTI patients are at risk for two significant sequelae. First, the reduction of blood-flow into the lower extremity increases the rate of amputation without proper vascular restoration therapy. Second, the presence of CLTI is indicative of a systemic atherosclerotic burden. While CLTI affects about 10% of PAD patients, it is a mortal illness. The major amputation rate in CLTI patients is as high as 40% at 6 months. At one year after presentation, there is a mortality rate of 20% to 25% in the first year after presentation, mainly with cardiovascular events.\(^3\) One report showed that all-cause mortality rate in CLTI patients reaches up to 70% at five years after presentation. That rate seems to exceed that of colorectal cancer, breast cancer, stroke, and coronary artery disease.\(^4\)

The analysis regarding which prognostic factors would affect the clinical outcomes after endovascular treatment (EVT) becomes more compelling, when taking into account the multiple severe comorbidities in CLTI patients. They are typically elderly and have a high prevalence of diabetes, hypertension, dyslipidemia, or renal insufficiency, all of which increase the risk of fatal vascular events, such as myocardial infarction or ischemic stroke.

To that end, in this issue of *Korean Circulation Journal*, Cha et al.\(^5\) provide informative data of long-term clinical outcomes and prognostic factors in patients with CLTI after EVT. The authors are to be commended for presenting a large and well-designed observational study within a multi-center observational study with retrospective and prospective cohorts of patients with lower extremity artery disease treated with endovascular therapy from the Korean Vascular Intervention Society (K-VIS) Endovascular Therapy in Lower Limb Artery.
Diseases (ELLA) registry. Among the overall cohort, about 30% of CLTI patients underwent amputation surgery, and major adverse limb events (MALEs) occurred in 39% within 5 years after EVT. The hazard rate of major amputation is the highest in the first 6 months and remained low afterwards. However, the fact that the incidence of minor amputation (8.9%) is much higher than those of major amputation (4.2%) is promising, taking into consideration that major amputation is related to high mortality and morbidity and high secondary intervention rates. The high amputation rate at the first year shows the importance of early revascularization strategies to decrease the amputation risk in the long term. The incidences of death and myocardial infarction are 3.0% and 0.4%, respectively.

The clinical outcomes in this study seem to be better rather than those of previous studies. According to a Dutch national registry data, for example, five year all cause and cardiovascular mortality rates for patients with CLTI are 57% and 29%, respectively. OLIVE registry in Japan shows that the rates of amputation-free survival and freedom from MALE are 55.2% and 84.0% at 3 years, respectively. They also showed that the highest hazard rates were observed during the first 6 months for both major amputation or death and MALE. It seems to be obvious that wound healing status after EVT during the first 6 months strongly affect the long-term clinical outcome.

Over the last 20 years, the interventional treatment of CLTI has changed significantly with endovascular revascularization replacing surgical bypass as the dominant treatment strategy. The introduction of multi-disciplinary approaches to limb salvage increases the chances of successfully healing an ulcer, subsequently preventing wound recurrence or amputation. On the other hand, treatment modalities in the present study include several novel endovascular approaches and devices which have been released on the market, such as directional or rotational atherectomy, covered stent-graft, drug-eluting stent, and drug-eluting balloon. Although the clinical results with these methods were not analyzed in the current study, the better clinical prognosis with those methods are expected in future reports. The number of patients with non-revascularisable or so called no option CLTI in the past will be decreased.

Similar to all other registries, there are certain limitations that have been mentioned by the authors. Generally, the prevalence of CLTI is 10% among persons with known PAD. However, there are 30% of CLTI patients in the K-VIS ELLA registry, which is not consistent with global incidences. Additionally, cigarette smoking is associated with a marked increased risk for peripheral atherosclerosis, and 70–90% of patients with CLTI are either current or ex-smokers. One report showed that cardiovascular-related mortality in the smoking group is more than 50%, three times that of the nonsmoking group at the 10 year follow up. In this study, current or ex-smokers were associated with improved amputation free survival in both the univariate and multivariate analyses. The author explained these paradoxical results, well. It might occur in the process of exclusion to maintain statistical independence of the samples and thereby reduce bias. If the K-VIS ELLA registry becomes more reliable and trustworthy, this registry data need to show similar clinical results in other vascular registries, when it comes to the strong risk factors of cardiovascular events.

In conclusion, the present study provides contemporary long-term follow-up data for CLTI patients with EVT. Even though numerous approaches have significantly evolved over the past decades, the amputation free survival rate of 69.8% and the rate of freedom from MALE of 61% underscore the poor prospects for those patients.
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