Risk Factors for Major Amputation in the Japanese Population
— How Can We Predict and Prevent Lower Limb Loss in Patients With Peripheral Arterial Disease? —

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Currently, there is a rise in ischemic foot ulcer/necrosis lesions because of peripheral arterial disease (PAD), and this is further increasing with the rapid increase in diabetic and dialysis patients and population aging. Lower extremity amputation significantly reduces patients' activities of daily life and quality of life, leading to shortened life prognosis and increased treatment cost. The burden on both patients and society is high. However, awareness of PAD and foot lesions in primary care is somewhat lacking. The need to predict and prevent leg amputation is an urgent global issue that includes Japan. In this issue of the Journal, Higashi and colleagues report their retrospective analysis of a 2-year observational prospective cohort study (4,016 eligible patients at 1,745 clinics in Japan) that evaluated predictors of amputation in diabetic patients undergoing antiplatelet therapy for PAD. Amputation risk was predicted at baseline by a history of lower extremity revascularization (LER)/amputation, chronic kidney disease (CKD), and comorbid cerebrovascular disease (CVD) and coronary artery disease (CAD). In patients with PAD and diabetes (DM), the amputation event rate was highest for those with ankle-brachial pressure index (ABI) <0.40 and progressively decreased at higher ABI cutoffs. The authors’ findings from this large cohort are valuable because they are likely to be representative of patients with PAD and DM who receive antiplatelet therapy in real-world clinical practice in Japan. In addition, they contribute to early detection and preventive risk factor management for ischemic foot lesions and limb amputation (Figure). DM is the strongest risk factor for PAD development and its prevalence in PAD patients in Japan is reported to be 41.2%. Furthermore, 70% of patients with severe lower extremity ischemia in Japan undergoing peripheral revascularization suffer from DM, and half account for dialysis. In diabetic patients, typical symptoms of PAD such as intermittent claudication are not always obvious, 75% are asymptomatic, and some are diagnosed only when there is pain at rest and gangrene appears. This results in a high risk of leg amputation. This is because, compared with non-diabetic patients, PAD in diabetic patients is accompanied by neuropathy, occurs in younger individuals with less sex differences, has increased below-the-knee stenotic/occluded arterial lesions (there are relatively few lesions in the aorto-iliac arteries) and increased multi-level arterial lesions, and has reduced intermittent claudication symptoms because of the narrower range of activity. Higashi et al report that the lower limb amputation event rate of diabetic patients with PAD was 4.43-fold higher than that of patients with PAD alone (i.e., without DM).

Figure. Risk factors for major amputation in patients with peripheral arterial disease (PAD) receiving antiplatelet therapy. ABI, ankle-brachial pressure index; CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cerebrovascular disease; CLTI, chronic limb-threatening ischemia; DM, diabetes mellitus; LER, lower extremity revascularization.
Of note, foot care education for diabetic patients and medical personnel, prevention of onset by regular foot care for high-risk patients, and multidisciplinary treatment of severe foot lesions by team medical care has been shown to reduce leg amputation by 49–85%.4

In the Reduction of Atherothrombosis for Continued Health (REACH) registry, data from approximately 5,000 Japanese cases have been collected. In REACH Japan, 43.8% of PAD patients had a complication of CVD, CAD, or both, and the greater the number of impaired vascular beds, the higher the risk of atherothrombosis events.4 That is, the incidence rate of atherothrombosis for those with CAD or PAD is higher than that for those with CVD alone, and it is even higher for those with all 3 diseases.5 Results were similar for the entire REACH Registry.5 Polyvascular disease has to be treated with sufficient awareness because all cardiovascular events have an increased incidence as the number of diseased lesions increases.7 The development of polyvascular disease is thus directly linked to the patient’s prognosis, and early diagnosis and treatment of each disease is essential.

According to a Japanese survey of both patients and physicians, the implementation rate of preventive foot care for patients with high-risk foot disease was approximately 40%.6 Results of the patient survey also revealed that even for patients receiving foot care, there are few who can manage and evaluate foot blood flow by objective examination. Furthermore, approximately 25% of physicians in the physician survey answered that they did not use any testing equipment when they performed blood flow measurement in the foot. It is suggested that management and evaluation by objective examination are insufficient for assessing the foot blood flow in high-risk patients with PAD/chronic limb-threatening ischemia (CLTI).6 It has been reported that approximately 75% of PAD patients are asymptomatic, and it is often difficult to diagnose patients based on their subjective symptoms alone. In TASC II,9 it is recommended that the ABI should be measured in all patients between the ages of 50 and 70 with cardiovascular risk (especially those who smoke or have DM) or at ≥70 years of age, even if they have no symptoms in the lower extremities. If ABI is ≤0.9, PAD treatment should be administered even if there are no symptoms. According to the medical condition survey in Japan, less than approximately 10% of diabetes internists or nephrologists who take regular care of high-risk patients use the algorithm when they treat foot ulcer and gangrene.8 It has been suggested that medical treatment is likely to be conducted without appropriate guidelines for foot lesions. Considering that there is no standardized algorithm setting and a low recognition of the importance of blood circulation evaluation, it has been suggested that a proportion of CLTI patients might have required leg amputation because of a lack of proper diagnosis and treatment.

In Japan, current screening or lifestyle intervention in clinical practice is still insufficient to prevent leg amputation. Based on the data reported by Higashi et al,10 in addition to antiplatelet drug administration and glycemic control, it is necessary to conduct active measurement of ABI, conduct strict follow-up for patients with comorbid CVD and CAD, CKD, and history of LER/amputation, and create more awareness among clinicians and patients.

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