Peripheral artery disease (PAD) is a systemic disease associated with impaired limb function, poor quality of life, and increased cardiovascular morbidity. Its incidence has been dramatically increasing over years because of the emergence of an aging society and the increase in the number of patients with atherosclerotic risk factors. The clustering of these risk factors promotes disease development, reportedly leading to the differential location of atherosclerotic lesions in lower extremity arteries. The clinical presentations of PAD include intermittent claudication and chronic limb-threatening ischemia (CLTI). PAD is associated with a high risk of mortality and morbidity from both cardiovascular and limb events. The therapeutic goals for patients with PAD include 1) relief from PAD-related limb symptoms, 2) the prevention of new-onset and the development and recurrence of PAD, and 3) the prevention of concomitant adverse events due to coronary artery disease (CAD) and cerebrovascular disease (CVD; myocardial infarction and stroke). Antithrombotic agents are of several types, and their main role in patients with PAD is to reduce systemic events mainly including cardiovascular and lower extremity-related events. Currently, the efficacy of direct oral anticoagulant (DOAC) is also suggested by recent clinical trials. Although endovascular therapy (EVT) has been the first-line revascularization strategy for symptomatic PAD, whether clinical outcomes after EVT are comparable to those after surgical bypass therapy remains inconclusive.

The clustering of cardiovascular risk factors promotes the disease development. A recent meta-analysis showed a progression to worsening intermittent claudication or chronic limb-threatening ischemia (CLTI) in 21% (12%–29%) over 5 years. A comparison of the characteristics of Japanese and non-Japanese patients with PAD with claudication who underwent drug-coated stent (DCS) therapy revealed that body mass index was lower in Japanese patients than in non-Japanese patients and that dyslipidemia was less frequently observed in Japanese patients than in non-Japanese patients. DM, renal insufficiency including hemodialysis (HD), and tissue loss are more frequently observed in Japanese patients with CLTI than in non-Japanese patients with CLTI.
CLTI. Notably, patients with CLTI who underwent HD account for about half of all CLTI cases in Japan, which is one of the major characteristics of CLTI in Japan. This may be related to the fact that Japan has a lower kidney transplantation rate than other countries, although Japan has a universal health insurance system that allows the initiation of dialysis in all cases resulting in end-stage renal failure, regardless of age. Patients with PAD in Japan are characterized by older age, a lower body weight, a lower prevalence of dyslipidemia, and a higher prevalence of DM and HD compared with those in Europe and North America. Accordingly, the features of symptomatic PAD are different between Japan and other countries.

The location of lesions in lower extremity arteries varies according to accumulating atherosclerotic risk factors. Dyslipidemia and smoking are more likely to cause atherosclerotic lesions in the proximal inflow region, whereas age, diabetes, and renal failure are significantly associated with lesions in the distal outflow region. In particular, as renal function worsens, the incidence of below-the-knee (BTK) arterial disease increases. More peripheral, distal lesions often increase the difficulty of both endovascular and surgical revascularization procedures. Therefore, it is no exaggeration to say that there are a substantial number of PAD cases in Japan that are the most challenging to treat in the world.

In patients with PAD, a clinical assessment of symptoms and physical signs of other atherosclerotic diseases, including CAD, is mandatory, and in cases of clinical suspicion, further tests will be needed. In patients with PAD, 25%–70% of cases have concomitant CAD. The severity and complexity of CAD specifically evaluated with the SYNTAX score are higher in patients with CLTI than in those with claudication. A higher score would be attributed to a higher prevalence of older age, DM, and renal insufficiency in patients with CLTI. Although there is no doubt that the presence of CAD in PAD adversely impacts clinical outcomes compared with the absence of CAD in PAD, previous studies demonstrated that the prognostic impact of the presence of CAD and reduced cardiac contraction appears different between patients with IC and CLTI. The latest European Society of Cardiology (ESC)/European Society for Vascular Surgery (ESVS) 2017 guideline newly recommends screening for presence of heart failure with transthoracic echocardiography and/or natriuretic peptide assessment in patients with symptomatic PADs under class IIa and level C recommendation.

**Clinical Issues of Japanese Patients with CLTI before Revascularization Approach**

The natural course of CLTI without undergoing appropriate intervention is dire, with a high risk for major amputation. Therefore, revascularization should be considered as the first-line therapy for patients with CLTI. There have been several discussions about the decision-making of which revascularization strategies should be selected, either endovascular or surgical revascularization. However, we believe that there are larger issues before referral to vascular specialists.

As stated in the TransAtlantic Inter-Society Consensus (TASC) II guidelines, about half of the patients who underwent major BTK or above-the-knee amputations for PAD were asymptomatic 6 months before. In general, some may assume a gradual progression from minor (asymptomatic) to severe (CLTI) symptoms via “moderate” symptoms (claudication); however, CLTI can be developed from asymptomatic status without any claudication. In the SPINACH study, including both patients with CLTI undergoing surgical bypass therapy and those with endovascular therapy (EVT) in Japan, history of intermittent claudication before the onset of CLTI was surveyed. Surprisingly, about half of the patients had no history of intermittent claudication. The risk factors for the lack of claudication history were the presence of DM, HD, and nonambulatory status. Based on this result, if patients have no symptom but with these risk factors, including DM, HD, and nonambulatory status, careful follow-up would be needed with awareness of their high risk of subsequent occurrence of CLTI. The SPINACH study also surveyed the duration between the occurrence of wound and reference to a vascular center. Unexpectedly, wound duration exceeded 1 month in 60% of patients and 3 months (i.e., one season) in 17%. No clinical features were significantly associated with wound duration. Wound duration was independently associated with wound severity evaluated using the Wound, Ischemia, and Foot Infection classification system. A substantial number of patients with CLTI referred to vascular centers had a long wound duration, and these results suggest that a smoother referral process would enable the initiation of optimal treatment before the worsening of the ischemic wound.

**Medical Intervention**

The therapeutic goals for patients with PAD include 1) relief from PAD-related symptoms, 2) the
prevention of on-set and the development and recurrence of PAD, and 3) the prevention of concomitant adverse events due to CAD and CVD (myocardial infarction and stroke)\(^ {21}\). The management of each atherosclerotic risk factor would have an impact on new-onset and the development and recurrence of PAD. Recent guidelines recommend that blood pressure be controlled to less than 140/90 mmHg (less than 130/80 mmHg in patients with DM)\(^ {25-28}\). ACE inhibitors are firstly recommended as antihypertensive drugs, whereas \(\beta\)-blockers are also effective in lowering blood pressure without worsening symptoms\(^ {17}\). The latest ESC 2019 guideline also recommends that LDL cholesterol be controlled to less than 55 mg/dL in patients with PAD\(^ {29}\). In patients with DM, maintaining a glycosylated hemoglobin A1c level of \(< 7\%\) is often recommended\(^ {30-33}\); however, less stringent goals (e.g., hemoglobin A1c level of \(< 8\%)\) may be appropriate for individuals with advanced vascular complications or limited life expectancy\(^ {34}\). Several studies demonstrated that antithrombotic therapy plays a major role in the prevention of concomitant adverse events due to CVD (myocardial infarction and stroke) and the reduction of recurrence after revascularization (EVT/surgical therapy)\(^ {35-37}\). Paradoxically, despite the robust recommendation of medical intervention for patients with PAD, the rate of optimal medical therapy (OMT) treatment (statin + RA antihypertensive + antiplatelet agent) recommended here is clearly lower in patients with PAD than in patients with CVD and CAD\(^ {38}\), and it has been reported that OMT is not sufficiently implemented. The suboptimal prescription of these guideline-direct medical therapies in patients with PAD is associated with multiple factors, including female sex\(^ {39}\).

Since the mechanism of event occurrence is different among cardiovascular and limb-related events, understanding antithrombotic agents with different efficacies is needed; however, their specific indications remain unclear. Two placebo-controlled randomized trials in asymptomatic patients with PAD demonstrated that a single antiplatelet therapy had no beneficial effect in reducing ischemic cardiovascular and limb-related events\(^ {40, 41}\). On the other hands, in patients with symptomatic PAD, the strongest evidence on secondary prevention in favor of aspirin to protect against major cardiovascular events (MACE) was reported\(^ {42}\). The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events trial demonstrated that clopidogrel was superior to aspirin in a subgroup of patients with PAD, with significant reductions in CV mortality and MACE, without any increasing risk of bleeding events\(^ {39}\). To date, the superiority of dual antiplatelet therapy (DAPT) to single antiplatelet therapy in CV risk reduction in patients with PAD has not been proved. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, Avoidance trial demonstrated that DAPT with clopidogrel plus aspirin versus aspirin alone did not reduce MACE\(^ {43}\). Observational studies on antithrombotic therapies in real-world populations have demonstrated an association between DAPT and a lower risk of MACE and mortality in symptomatic PAD compared with aspirin monotherapy\(^ {44}\). DAPT is currently considered for patients undergoing EVT for coronary intervention. DAPT is generally recommended for at least 1 month after EVT, irrespective of the device type (bare-metal stent and drug-eluting stent (DES))\(^ {35}\). In the Zilver PTX trial comparing provisional DCS to bare-metal stents, DAPT was mandated for 2 months\(^ {38}\). In the IMPERIAL randomized trial comparing Zilver PTX versus Eluvia DES, DAPT was again mandated for 2 months\(^ {46}\). In the treatment of angioplasty with or without drug coating, at least 1-month DAPT is mandated for preventing risk of acute occlusion and thereafter can be switched to single antiplatelet therapy, which is its main advantage as an endovascular device. However, in real-world practice, the duration of DAPT is individually determined by procedural complexity. Long stenting is often followed by a longer period of DAPT; but no specific evidence is available. In the field of surgical bypass therapy, the Clopidogrel and Acetylsalicylic Acid in Bypass Surgery for Peripheral Arterial Disease study demonstrated that DAPT therapy compared with SAPT therapy after surgical peripheral revascularization had no beneficial effect on the composite of graft occlusion, revascularization, amputation, or death and significantly increased the risk of moderate or severe bleeding\(^ {37}\). Anticoagulation has been prospectively tested after surgical and endovascular intervention for symptomatic PAD. The VOYGER-PAD trial evaluated whether additional DOAC would reduce cardiovascular and limb-related events after endovascular or surgical treatment. Approximately, two-thirds of patients were endovascularly treated, whereas the reaming one-third was surgically treated. The clinical presentations were claudication and CLTI in 77% and 23%, respectively. Compared with aspirin alone, additional low-dose rivaroxaban significantly reduced the composite endpoint of lower extremity (acute limb ischemia and major amputation of the lower extremity) and systemic (myocardial infarction, ischemic stroke, and cardiovascular death) events\(^ {46}\). In particular, acute arterial occlusion was significantly reduced. Previously, the VANQUISH study evaluated the relationship between vessel patency and P2Y12
reaction unit (PRU) values, a marker of the resistance on P2Y12 inhibition (antiplatelet effect), after the stent-grafting of patients with symptomatic PAD presenting femoropopliteal artery lesions. The study also found no relationship between PRU values and vessel patency47), suggesting that the effect of antiplatelet therapy would have a small, if any, influence on vessel patency. Clinical attention is shifting from the intensification of antiplatelet therapy to the introduction of DOACs. Antithrombotic drug selection is mainly determined by the condition of each patient with PAD. In the short to intermediate term after revascularization, major adverse limb event (MALE) more commonly occurred than MACE, and the risk should be more cautiously followed. In the long-term, the risk of MALE would be attenuated, but patients would be subject to a continuous risk of MACE. Antiplatelet therapy selection should be driven by the tradeoff of ischemic and bleeding risks in patients with PAD as a chronic atherosclerotic disease.

**When and How to Consider Revascularization for Patients with PAD**

1) **Indication of Revascularization in Patients with PAD**

Patients with intermittent claudication will be an absolute indication for revascularization only when the symptom is refractory to pharmacotherapy and exercise therapy. In contrast, revascularization is the first-line treatment in patients with CLTI for their limb salvage17, 21, 22). In principle, asymptomatic patients should not be indicated for revascularization. However, in clinical practice, to date, either endovascular or surgical intervention is allowed in patients with anastomotic stenosis after surgical bypass therapy, even if they are asymptomatic217). A recent clinical study reported that planned-EVT, i.e., performing TLR every two months regardless of SPP values until complete wound healing was obtained, shortened the time to wound healing in patients undergoing BTK-EVT for CLTI presenting tissue loss.48 Reintervention has been generally indicated for recurrent symptom or delayed wound healing accompanied by the “presence of restenosis with hemodynamically changes.” Planned-EVT strategy is a novel approach that would potentially improve clinical outcomes.

2) **Stratification of Anatomical Severity in Patients with PAD**

The classification of anatomical severity in patients with PAD plays an important role in the selection of revascularization methods. It has been categorized based on the expected technical success and long-term patency of EVT. Until now, the TASC 2000 and TASC II classifications have been commonly used to evaluate the severity of the disease22, 49); however, the ESC/ESVS 2017 no longer described the TASC-based selection of revascularization methods17). More recently, the global vascular guideline (GVG), specialized for the treatment of CLTI, proposed the GLASS classification by simultaneously evaluating the femoropopliteal and infrapopliteal arterial segments17).

In aortoiliac lesions, the TASC II classification is somewhat complicated and is not always easy to use in clinical practice. The Observational Prospective Multicenter Registry Study on Outcomes of Peripheral Arterial Disease Patients Treated by Angioplasty Therapy for Aortoiliac Artery registry, which was conducted at 64 centers in Japan to clarify the clinical outcomes of aortoiliac EVT in real-world practice, showed that the presence of concomitant femoropopliteal lesion and minimum stent diameter were significantly associated with 1-year restenosis, whereas the TASC II classification was not50). In femoropopliteal lesions, the TASC II classification mainly stratified lesions by their length and the presence of chronic total occlusion (CTO); however, previous studies have shown that anatomical characteristics other than lesion length and CTO were significantly associated with loss of patency. The IntraVascular Ultrasound-Supported Endovascular Therapy in Superficial Femoral Artery Disease Prospective multicenter registry study proposed a novel angiographic risk score consisting of distal reference vessel diameter, lesion length, and CTO, which is significantly and independently associated with the 12-month restenosis risk after EVT51). Regarding BTK and below-the-ankle (BTA) lesions, a single-center, retrospective study showed that BTK arterial calcification and poor BTA runoff were significantly associated with delayed wound healing, whereas the GLASS classification was not52). Further investigation will be needed to validate GLASS predicting clinical outcomes.

3) **Revascularization Strategy (Surgical or Endovascular Approach)**

1) **Revascularization for Aortoiliac Lesions**

According to the ESC/ESVS 2017 guidelines, surgical therapy should be considered for aortic occlusion extending up to renal arteries (class IIa and level C recommendations), whereas hybrid therapy combining iliac stenting and femoral endarterectomy or bypass should be considered for iliofemoral occlusive lesions (class IIa and level C recommendations17). As for endovascular techniques in the treatment of
II. Revascularization for Femoropopliteal Lesions

The ESC/ESVS 2017 guidelines and GVG 2019 also stated that surgical bypass therapy using autologous veins is the first-line treatment for complex femoropopliteal lesions (class I and level A recommendations)\(^{17, 21}\), whereas the definition of “complex lesion” has been repeatedly modified because of the improvement of the technical and long-term success of EVT, thanks to the rapid development of endovascular devices\(^{17, 21, 22, 49}\). Selecting an appropriate device during EVT is clinically important because lesion characteristics considerably vary from case to case. Traditionally, lesion length has been the strongest predictor for loss of patency\(^{55}\) if the endovascular approach is selected. However, the latest devices, including drug-coated balloon (DCB), DES, interwoven stent, and stent-graft, could nullify this notion, and the main driving factor for device selection would be the presence or absence of severe calcification\(^{48, 56-58}\). Fig. 1 summarizes our treatment algorithm in FP lesions. Lesions without severe calcification are generally treated with DCB or DES. DES is often chosen over DCB when there is severe dissection defined as grade C or greater after predilatation. On the other hand, lesions with severe calcification defined as peripheral arterial calcium scoring system of grade 3 or 4 or with calcified nodule are generally treated with interwoven stent or stent-graft. After aggressive vessel preparation, the use of an interwoven stent would be considered if lesions are not perforated but successfully opened. Stent-graft should be applied to lesions with unsuccessful vessel preparation, including vessel perforation or early recoil after aggressive vessel preparation. In the future, when peripheral-specific rotational atherectomy is clinically available in Japan, our treatment algorithm will be concomitantly changed\(^{59}\).

III. Revascularization for BTK Lesions

Revascularization for BTK lesions is strictly limited to patients with CLTI. The anatomical severity of BTK lesions is stratified by a new classification proposed by the GVG, where the target arterial path is determined by the angiosome concept\(^{20}\). Similar to FP lesions, surgical bypass therapy using autologous veins is the gold standard for BTK revascularization,
because long-term patency after EVT using plain angioplasty for BTK lesions is extremely dire. BTK lesions are generally complicated with small vessel diameter and severe calcification; plain balloon angioplasty, which is the only device available in Japan, would result in suboptimal outcomes. The current guidelines have recommended whether an endovascular or surgical revascularization in patients with CLTI is determined by the presence of usable autologous veins and/or life expectancy. Several studies have recently demonstrated that restenosis rate was reduced by the use of antirestenotic devices, including DCB and DES, in the BTK era. These devices will be expected to improve clinical outcomes.

**IV. Revascularization for BTA Lesions**

There is a lack of evidence in this area, and although a severity classification has been newly reported in the GVG, whether the classification is clinically useful or not has not been fully investigated. To date, severe conditions of BTA lesions have been clinically useful or not has not been fully investigated. EVT of PAD. Evidence in the field of this disease remains insufficient compared with CAD and CVD. We believe that patient outcomes will be improved by risk modification, antithrombotic drug selection, and intervention before referral to a cardiovascular center. In addition, continuing to discuss whether EVT or surgical bypass should be used is necessary. We hope that patient outcomes will improve through the accumulation of new evidence.

**Summary**

In this article, we summarize the epidemiology, pharmacology, and EVT of PAD. Evidence in the field of this disease remains insufficient compared with CAD and CVD. We believe that patient outcomes will be improved by risk modification, antithrombotic drug selection, and intervention before referral to a cardiovascular center. In addition, continuing to discuss whether EVT or surgical bypass should be used is necessary. We hope that patient outcomes will improve through the accumulation of new evidence.

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