Strategies of endovascular intervention for patients with symptomatic lower extremity artery disease

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Received: 1 December 2021 / Accepted: 26 January 2022
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Abstract Peripheral artery disease (PAD) is an obstructive arterial disease of the lower extremities. Due to the aging society and improved diagnostic techniques, the number of patients identified with PAD is increasing. Endovascular treatment (EVT) is a widely accepted interventional management method for diseased lower extremity arteries. Anatomically, the arteries of the lower extremities are divided into three segments: aortoiliac, femoropopliteal, and below-the-knee. The strategies of EVT recommended in the relevant guidelines are different for each segment. During the past 20 years, the indications and strategies of EVT have been evolving owing to the development of devices and improvement of clinical outcomes of EVT. Although it might be challenging to catch up with the evolving EVT strategies, we should develop an optimal EVT strategy for each PAD patient, considering that patient and lesion characteristics would also affect clinical outcomes. In this review, we describe the current knowledge of EVT strategies for each segment. We selected the EVT strategies that are currently performed for a majority of symptomatic PAD patients.

Keywords endovascular treatment, peripheral artery disease, catheter, cardiovascular disease

1. Introduction

Peripheral artery disease (PAD) is an obstructive arterial disease of the lower extremities. PAD sharply increases with age and exposure to major cardiovascular risk factors, including smoking, hypertension, dyslipidemia, and diabetes. It has been reported that 29.7%–53.6% of patients with PAD have coronary artery disease [1, 2]. In addition, patients with PAD have a three- to six-fold increased rate of cardiovascular mortality compared with those without [3–5]. Therefore, risk factor reduction is universally recommended to reduce cardiovascular events in patients with PAD.

The resting ankle-brachial index (ABI), determined using a non-invasive and inexpensive method described below, is recommended by relevant guidelines for the screening and diagnosis of PAD of the lower extremity. The ABI for each leg represents the ratio of the tibial artery systolic pressure above the ankle to the average of the right and left brachial artery pressures. A prospective cohort study of 6880 elderly patients ≥65 years of age monitored over 5 years indicated that patients with ABI <0.90 had a significantly increased risk of death or severe cardiovascular events compared with those with ABI ≥0.90 [6]. PAD is now defined as ABI <0.90, and values from 0.91 to 1.0 are considered borderline abnormal [7].

Patients with PAD may be asymptomatic or present with claudication or chronic limb-threatening ischemia (CLTI). Claudication typically presents as leg cramping with exercise that is relieved by rest. Claudication is the hallmark of atherosclerotic PAD, but only about 10% of patients with PAD experience claudication [8]. CLTI is a clinical syndrome defined by the presence of PAD in combination with rest pain, gangrene, or lower limb ulceration of >2 weeks. CLTI is associated with impaired quality of life, amputation, and even death. All patients with suspected CLTI should be urgently referred to a vascular specialist [9].

The management of patients with PAD is complex and includes modification of risk factors, pharmacological therapy, supervised exercise therapy, arterial recanalization, and surgery. Conservative management with analgesia and primary major amputation may be appropriate in some patients with PAD [10]. However, these management methods are not suitable for most patients with PAD because major amputation continues to result in significant morbidity and
mortality. Indeed, a retrospective analysis of 959 consecutive major amputations performed in 788 patients indicated that the patient survival rates at 1 and 5 years were 69.7% and 34.7%, respectively [11].

Peripheral arterial recanalization, including bypass surgery and endovascular treatment (EVT), is an aggressive treatment for PAD. No data support performing endovascular procedures on patients with PAD for the purpose of preventing progression of claudication symptoms to CLI. Similarly, no data support recanalization in patients with asymptomatic PAD [12]. Therefore, patients at increased risk of PAD should be carefully assessed for the possible presence of claudication, ischemic rest pain, and non-healing wounds [12]. In addition, peripheral arterial recanalization should be limited to patients with symptomatic PAD. EVT for patients with symptomatic PAD has been widely accepted because EVT is less invasive than bypass surgery. The application of EVT has been increasing due to the aging society and improved diagnosis of PAD [13, 14]. In addition, interventional devices have improved over time.

As shown in Figure 1, the arteries of EVT are usually divided into three segments: aortoiliac, femoropopliteal, and below-the-knee. Stents should generally be avoided in bending areas (around the hip and knee joints), such as the common femoral and popliteal arteries. In addition, the sizes of the arteries in each segment are quite different. The diameters of the aortoiliac, femoropopliteal, and below-the-knee arteries are 8–12, 5–7, and 2–4 mm, respectively [15]. Therefore, the anatomical location and extension of arterial lesions have an important impact on EVT options. Patient and lesion characteristics also affect the strategies and outcomes of EVT. In this review, we present a summary of knowledge regarding EVT strategies that are currently performed in most symptomatic PAD patients.

2. EVT for aortoiliac lesions

Case Presentation

A 74-year-old man with a history of hypertension, dyslipidemia, smoking, and old cerebral infarction was admitted to our hospital because of gangrene and severe infection of his left foot. Computed tomographic angiography and angiography showed that the entire iliac artery was occluded from the distal aorta (Figure 2a and 2b). After implantation of bare nitinol stents (BNS), the aortoiliac arteries were successfully recanlized (Figure 2c). The left ABI, which had not been able to be measured at the time of admission because of the low blood pressure of his left foot, was 0.74 after the successful EVT.

Guideline (Bypass or EVT)

The recanalization strategy to be undertaken for PAD patients should be based on evidence and can include EVT, bypass surgery, or both. We summarize the guideline recommendations regarding recanalization strategies for patients with PAD.

In the case of short (<5 cm) lesions of the iliac arteries, EVT provides good long-term patency (>90% over 5 years) with a low risk of complications [16, 17]. The 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society...
for Vascular Surgery (ESVS) (ESC/ESVS-2017-guideline) recommended the endovascular-first strategy for short lesions [18].

Lesions such as obstruction of the entire iliac artery, diffuse lesions, aortoiliac bifurcation lesions, and infrarenal aortoiliac lesions, have been major limitations of aortoiliac EVT. However, as acceptable results of aortoiliac EVT for such complicated lesions have been reported [19, 20], the ESC/ESVS-2017-guideline recommended consideration of the endovascular-first strategy for long lesions, such as bilateral lesions and aortoiliac lesions in patients with severe comorbidities [18].

Although endovascular-first strategies are widely applied for aortoiliac lesions, bypass surgery is still considered for patients with ilio-femoral lesions, and aortic occlusion extends up to the renal arteries [18].

Devices of the aortoiliac EVT

EVT devices that are currently used for most PAD patients with aortoiliac lesions are balloons, BNS, and covered stents. As many studies have indicated that stent implantation improved the clinical outcomes of aortoiliac EVT compared with balloon angioplasty, primary stenting should be considered rather than provisional stenting [16, 18, 21].

Thromboembolism and atrial rupture are severe complications of aortoiliac EVT. EVT for thrombotic lesions and severe calcified lesions is associated with a high risk of such complications. To overcome such complications of aortoiliac EVT, covered stents have been developed with acceptable clinical outcomes reported [22–24].

Japanese evidence of aortoiliac EVT

The clinical outcomes of BNS for aortoiliac lesions of 2601 limbs of 2096 patients have been reported in a real-world setting between January 2005 and December 2009 [19]. In that study, the mean lesion length was 52.9 ± 31.2 mm, and the mean total stent length was 68.1 ± 33.9 mm. Primary patency rates were 92.5%, 82.6%, and 77.5% at 1, 3, and 5 years, respectively. About 5 years later, another clinical study of aortoiliac EVT was performed in Japan. The clinical outcomes of aortoiliac EVT in 1128 limbs of 893 patients were reported in a real-world setting between April 2014 and April 2016 [20]. In that study, the mean total stent length was 82.1 ± 48.5 mm. Primary patency rates were 94.0%, 91.2%, and 89.2% at 1, 2, and 3 years, respectively. Compared with a previous study [19], the initial technical success was higher, despite a higher prevalence of CTO, suggesting the contribution of recent technical advances [20].

3. EVT for femoropopliteal lesions

Case Presentation

A 72-year-old woman who was a current smoker was admitted to our hospital because of an unhealed ulcer on her right 4th and 5th toes. Computed tomographic angiography and angiography showed long femoropopliteal CTO (Figure 3a and 3b). After successful balloon angioplasty, DCBs were used for the long femoropopliteal CTO lesion (Figure 3c). Three months after the femoropopliteal EVT, the right foot ulcers had healed.

Guideline (Bypass or EVT)

The Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II), which was published in 2007, recommended that the lesion length of femoropopliteal EVT should be <5 cm [25]. However, as the clinical outcomes of femoropopliteal EVT have improved, the recommendation has been lengthened to <25 cm in the ESC/ESVS-2017-guideline [18].
Although the endovascular-first strategy is widely applied for femoropopliteal lesions, bypass surgery is still considered for patients with long (i.e., ≥25 cm) lesions who are fit for surgery. An autologous vein is available for bypass surgery, with a life expectancy of >2 years [18].

**Devices for femoropopliteal EVT**

EVT devices currently used for most PAD patients with femoropopliteal lesions are balloons, BNS, drug-coated balloons (DCB), drug-eluting stents (DES), and covered stents. Compared with balloon angioplasty, BNS implantation improved the clinical outcomes of femoropopliteal EVT [26–29].

Recently, paclitaxel-eluting devices, including DCB and DES, have become available for use in femoropopliteal lesions. Compared with balloon angioplasty, DCB was found to improve the clinical outcomes of femoropopliteal EVT [30–32]. In addition, compared with BNS, DES improved the clinical outcomes of femoropopliteal EVT [33, 34]. However, the long-term efficacy and safety of paclitaxel devices for femoropopliteal lesions require further investigation. In addition, because paclitaxel is an anti-cancer chemotherapy drug, an increased risk of mortality with the use of paclitaxel devices for patients with PAD has been reported [35]. On the contrary, many reports showing a lower mortality risk associated with paclitaxel devices for PAD patients have also been published. The patient-level meta-analysis of data from 2,581 Japanese cases obtained in RCTs and single-arm studies found no harmful effect on 5-year mortality with the use of paclitaxel devices [36]. After the results of this study were reported, the long-term effect of paclitaxel devices on the mortality of patients with PAD seems less severe in Japan. Immunosuppressant-eluting devices are also being developed to overcome these problems, although this technology is not yet available in Japan.

Heparin-bonded self-expanding covered stent grafts (Viabahn™) are another device for femoropopliteal EVT. Long femoropopliteal lesions are difficult to overcome using femoropopliteal EVT. Indeed, stent implantation for long femoropopliteal lesions increases the risk of loss of patency, stent fracture, and in-stent restenosis [37–39]. In clinical trials in symptomatic PAD patients with long femoropopliteal lesions (approximately 20 cm), Viabahn™ demonstrated significantly improved clinical outcomes compared with BNS [40, 41].

Viabahn™ can also be used as a hemostatic device for vessel perforation. In addition, the length of the Viabahn™ was up to 25 cm. Therefore, Viabahn™ is often used to treat severely calcified and long femoropopliteal lesions. However, the incidence of stent thrombosis, which is a serious adverse outcome of EVT, is significantly higher in Viabahn™ than in BNS [42]. In addition, when branch arteries of the femoropopliteal artery are considered essential for the blood supply to the lower limb, we should avoid covering the branch arteries by Viabahn™.

A scaffold was maintained in the femoropopliteal artery after using BNS, DES, or Viabahn™. These scaffold devices improved the clinical outcomes of femoropopliteal EVT. However, restenosis and occlusion of the scaffold are serious problems associated with femoropopliteal EVT. Tosaka et al. [39] reported that occlusion after femoro-

![Figure 3](image-url)
popliteal stenting was an independent predictor of recurrent restenosis and artery occlusion. Indeed, after the scaffold occlusion, lesion elongation is often observed. In addition, it is well known that the plaque and thrombus inside the occluded scaffold are difficult to compress completely with a balloon catheter. The long-term clinical outcomes of DCB are worse than those of scaffold devices. However, the scaffolds do not remain in the femoropopliteal artery after using DCB. In addition, the clinical outcomes of DCB are better than those of balloon angioplasty. Therefore, DCB is currently the most common device for femoropopliteal EVT.

Because of the efficacy and safety of DCB in the treatment of in-stent restenosis of the femoropopliteal lesion [43], the medical insurance of Japan approved the use of DCB for the treatment of in-stent restenosis of the femoropopliteal lesion from October 2021. Consequently, EVT operators can now use scaffold devices more easily for femoropopliteal lesions.

**Japanese evidence of femoropopliteal EVT**

Compared with aortoiliac EVT and below-the-knee EVT, the availability of a variety of devices is one of the features of femoropopliteal EVT. Herein, we summarize the clinical outcomes of femoropopliteal devices.

Clinical outcomes of BNS for femoropopliteal lesions in a real-world setting with 639 limbs in 511 patients were reported by Soga et al. [44]. In that study, the primary patency rates at 1, 3, and 5 years were 79.8%, 66.7%, and 63.1%, respectively. The challenge of femoropopliteal EVT with BNS stenting is the long-term patency and durability of stents, where the artery is very long and mobile. New stent designs have been shown to improve long-term patency. However, the three-year clinical outcomes of INNOVATM and LIFE™ stents with two new designs of BNS have not yet met our current needs [45, 46].

Clinical outcomes of Zilver PTX™, a polymer-free paclitaxel-coated stent, for femoropopliteal lesions in a real-world setting with 797 limbs in 690 patients were reported by Iida et al. [47]. The one-year rate of restenosis was 37%. In addition, it was reported that the risk factors for restenosis of Zilver PTX™ were lesion length of ≥16 cm, external elastic membrane area of ≤27 mm², and minimum stent area of ≤12 mm².

The Japan cohort of 2:1 randomized controlled trial that compared the Eluvia™, a polymer-coated paclitaxel-eluting stent, and Zilver PTX™ was also reported. The mean lesion length was 91.8 ± 38.0 mm for Eluvia™ and 87.4 ± 41.7 mm for Zilver PTX™. At 12 months, the primary patency rates were 90.9% for Eluvia™ and 84.6% for Zilver PTX™ [48].

Ohki et al. reported that the Viabahn™ for complicated femoropopliteal lesions, where the mean lesion length was 21.5 ± 5.8 cm and 65.7% were totally occluded, providing 88% to 92% primary patency at 12 months [49].

**4. EVT for below-the-knee lesions**

**Case Presentation**

A 78-year-old woman who had undergone left femoropopliteal EVT two years previously was admitted to our hospital because of severe rest pain in her left foot. Computed tomographic angiography performed two years before indicated occlusion of the anterior and posterior tibial arteries (Figure 4a). However, angiography showed additional severe stenosis from the distal popliteal artery to the peroneal artery (Figure 4b). After balloon angioplasty of the distal popliteal artery, anterior tibial artery, and peroneal artery (Figure 4c), the remaining pain in her left foot disappeared.

**Guideline (Bypass or EVT)**

The application of recanalization of below-the-knee lesions is limited to patients with PAD and CLTI. In other words, below-the-knee recanalization is aimed at improving symptoms and ulcer healing in patients with PAD and CLTI.

The SCAI expert consensus statement published in 2014 described the indication of below-the-knee EVT only for patients with significant medical comorbidities that limit life expectancy, those with increased surgical risk, those without an adequate distal target for bypass, or those with poor venous conduits [50]. In addition, because the clinical outcomes of bypass surgery for below-the-knee lesions were better than those of EVT, ESC/ESVS-2017-guideline recommended bypass surgery using a saphenous vein graft [18, 51].

Accurate staging of limb threat severity is fundamental to the management of CLTI. The wounds, ischemia, and foot infection (WIF) classification is a widely used amputation risk stratification of CLTI [52]. The Global Vascular Guidelines (GVG), focusing on the management of CLTI, were published in 2019. GVG proposed that patient risk, limb severity, and anatomic complexity (PLAN) are the three keys to evidence-based revascularization. GVG also proposed a new global anatomic staging system (GLASS), which involves defining a preferred target artery path and then estimating limb-based patency, resulting in three stages of complexity for intervention [9].

**Devices for below-the-knee EVT**

Balloon angioplasty is the current standard method for below-the-knee EVT. However, the efficacy of balloon angioplasty for below-the-knee lesions is limited by high restenosis rates [53, 54]. In addition, compared with aortoiliac and femoropopliteal lesions, the term until recurrence of restenosis after balloon angioplasty for below-the-knee lesions is short. Indeed, at 12 months, restenosis after balloon angioplasty for the aortoiliac and femoropopliteal
lesions was 17% to 24% and 31.7% to 63.3%, respectively [18, 21, 26–29]. However, only three months later, restenosis of balloon angioplasty for below-the-knee lesions was observed in 73% of patients [55]. Several studies on the efficacy and safety of BMS, DCB, and DES for below-the-knee lesions have been reported [50, 56, 57]. However, compared with balloon angioplasty, these new technologies were not able to demonstrate a dramatic improvement in the clinical outcomes of below-the-knee EVT for patients with CLTI.

Japanese evidence of below-the-knee EVT

A comparison of the clinical outcomes of bypass surgery and EVT for below-the-knee lesions in CLTI patients was reported by Mills et al. [52]. Between January 2012 and March 2013, 197 patients with bypass and 351 EVT patients were enrolled in the study. Compared with bypass surgery, the 3-year amputation-free survival rate after EVT was not different. The factors that favor EVT were non-adherence to cardiovascular risk management, hemoglobin level of <10 g/dL, diabetes, renal failure, and contralateral major amputation. In addition, the factors favoring bypass surgery were W-3 and fl-2/3 of the WIfI classification, history of minor amputation, prior recanalization after CLTI onset, and bilateral CLTI [58].

A methodology to improve the outcome of below-the-knee balloon angioplasty is the current clinical need. Fujihara et al. reported the safety and efficacy of intravascular-ultrasound-guided balloon angioplasty for below-the-knee lesions. Compared with angiography-guided procedures, the mean balloon size for intravascular ultrasound-guided procedures was significantly larger, and the wound healing rate was significantly better [15].

5. Conclusion

We reviewed the current knowledge about EVT strategies utilized for most symptomatic PAD patients. Device development for EVT has clearly improved the clinical outcomes of EVT, resulting in the expansion of EVT indications. Moreover, EVT technologies are still being developed. However, all EVT devices have both advantages and disadvantages in treating the lower extremity arteries in PAD patients. In addition, EVT strategies and outcomes are affected by patient and lesion characteristics. It is necessary to consider and perform the ideal EVT strategies that have the maximum benefit and minimum risk for each PAD patient.

Conflict of interest The authors have no conflicts of interest to declare.

Acknowledgements We would like to thank Masao Tanaka, MD, PhD, and FACS for critical review of the manuscript and Editage (www.editage.jp) for English language editing.

Funding Sources This work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
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