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REVIEW

Catch Up with the Latest Trend in Vascular Intervention —Chronic Limb-threatening Ischemia Up to Date

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Abstract:
Endovascular treatment for patients with lower extremity artery disease is conducted worldwide due to its efficacy. Many studies have shown durability for patients with intermittent claudication, and various guidelines have shifted to the use of endovascular treatment. However, clinical outcomes in patients with chronic limb-threatening ischemia who undergo endovascular treatment have not been fully investigated. Generally, chronic limb-threatening ischemia cases have complex lesions such as small vessels, severe calcification, poor runoff vessels, chronic total occlusion, and long lesions, which result in poor outcomes. Thus, endovascular treatment for chronic limb-threatening ischemia cases remains challenging, despite the many technical and device advances. In 2019, the Global Vascular Guidelines were proposed for the treatment of patients with chronic limb-threatening ischemia. Here, we review previous guidelines and reports of patients with lower extremity artery disease who underwent endovascular treatment.

Keywords:
chronic limb-threatening ischemia (CLTI), endovascular treatment (EVT), latest trend, lower extremity artery disease (LEAD)

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Introduction

Vascular intervention for patients with lower extremity artery disease is used worldwide due to technical and device advances. Over the last 20 years, devices such as the bare-nitinol stent (BNS), SG, drug-coated balloon (DCB), and drug-eluting stent (DES) have been introduced in endovascular treatment (EVT), and there are many reports of favorable early and long-term outcomes [1-6]. Thus, guidelines generally recommend EVT for patients with aorto-iliac (AI) or femoropopliteal (FP) lesions, except for those with complex lesions [7, 8]. The 2019 Global Vascular Guidelines (GVGs) include recommendations for treatment methods (EVT, surgical reconstruction, conservative treatment, or major amputation) for patients with chronic limb-threatening ischemia (CLTI) [9]. However, lesion complexity (small vessel diameter, long lesion, chronic total occlusion, severe calcification, poor below-the-knee [BTK] or below-the-ankle [BTA] runoff) is a major concern in EVT for CLTI, and results in poorer outcomes compared with patients with intermittent claudication. The purpose of this review is to assess decision-making and outcomes of EVT for CLTI based on previous reports.

Decision-making

Definition of CLTI

Patients with CLTI who are eligible for revascularization should meet one of the following criteria: (1) ischemic rest pain confirmed in a hemodynamic study, (2) diabetic foot ulcer or foot ulcer that has persisted for more than 2 weeks, and (3) gangrene of the crus or toe.

Risk assessment

CLTI is associated with advanced age, multiple comorbidities, frailty, sarcopenia, and malnutrition, and the 2019 GVGs recommend patient risk analysis (hospital mortality and life expectancy) as the first step [9]. Risk stratification tools such as the Vascular Quality Initiative CLTI mortality prediction model, and Surgical reconstruction versus Peripheral INtervention in pAtients with critical limb ischemia

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Table 1. GLASS FP and IP Grades.

	GLASS FP grade		GLASS IP grade
0	Mild or nonsignificant (<50%) stenosis	0	Mild or no significant disease in the primary target artery path
1	• Total length SFA disease <1/3 (<10 cm) • May include single focal CTO (<5 cm) as long as not flush occlusion • Popliteal artery with mild or no significant disease	1	• Mild or no significant disease in the primary target artery path
2	• Total length SFA disease 1/3-2/3 (10-20 cm) • May include CTO totaling 1/3 (<10 cm) but not flush occlusion • Focal popliteal artery stenosis <2 cm, not including trifurcation	2	• Stenosis involving 1/3 total vessel length • May include focal CTO (<3 cm) • Not including TP trunk or tibial vessel origin
3	• Total length SFA disease >2/3 (>20 cm) length • May include any flush occlusion <20 cm or non-flush CTO 10-20 cm long • Short popliteal stenosis 2-5 cm, not involving trifurcation	3	• Disease up to 2/3 vessel length • CTO up to 1/3 length (may include tibial vessel origin but not tibioperoneal trunk)
4	• Total length SFA occlusion >20 cm • Popliteal disease >5 cm or extending into trifurcation • Any popliteal CTO	4	• Diffuse stenosis >2/3 total vessel length • CTO >1/3 vessel length (may include vessel origin) • Any CTO of tibioperoneal trunk if AT is not the target artery

AT: anterior tibial artery; CTO: chronic total occlusion; FP: femoropopliteal; GLASS: Global Limb Anatomic Staging System; IP: infrapopliteal; TP: tibioperoneal

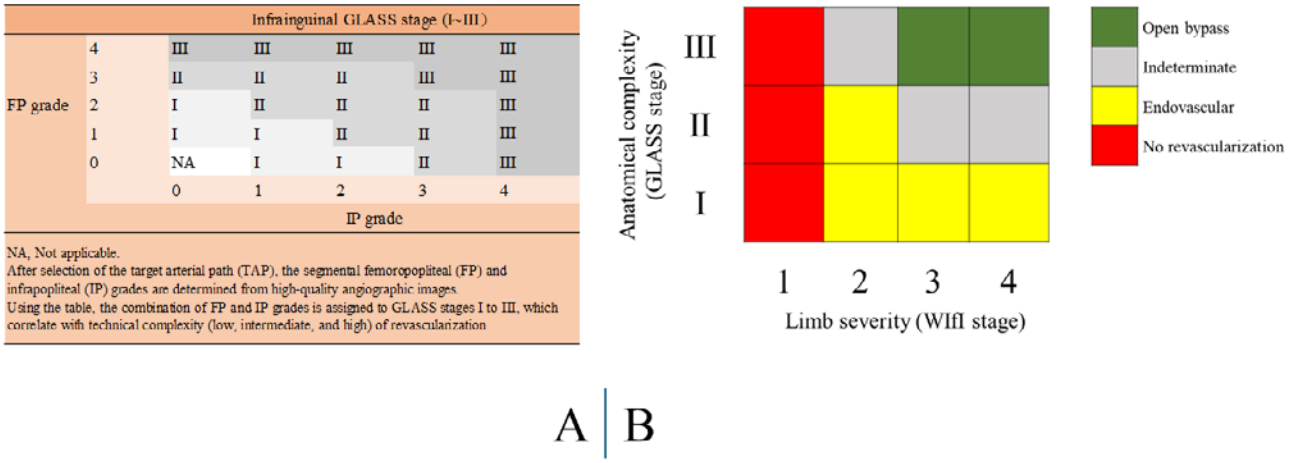


Figure 1. Global Limb Anatomic Staging System (GLASS) femoropopliteal (FP) and infrapopliteal (IP) grades (A). Recommendation of initial revascularization methods in the Global Vascular Guidelines (GVGs) (B).

(SPINACH) have been used for patients with CLTI [10-17]. In 2023, the JAPAN Critical Limb Ischemia Database introduced freely available risk estimation software [18]. The risk in this software is estimated based on a Japanese CLTI cohort, and thus, may be most appropriate for Japanese patients. The GVGs define average-risk cases as those with anticipated periprocedural mortality <5% and anticipated 2-year survival >50% and propose decision-making in average-risk cases based on anatomical complexity and limb severity [9]. The guidelines recommend EVT for high-risk cases (anticipated periprocedural mortality >5% or anticipated 2-year survival <50%) to reduce morbidity.

Evaluation of anatomical complexity

The GVGs propose the use of the Global Limb Anatomic Staging System (GLASS) to evaluate the anticipated target arterial path. The GLASS stage is based on the FP and infrapopliteal (IP) grades and is useful in decision-making for patients with CLTI (**Table 1**, **Fig. 1A**), since the technical success of EVT and limb salvage after EVT are associated with the GLASS stage [19, 20].

Evaluation of limb severity

The GVGs recommend the use of the wound, ischemia, and foot infection (WIfI) classification for evaluation of limb severity [21]. WIfI includes three components (evaluation of tissue loss, ischemia, and foot infection) and can also contribute to the decision-making process. The ischemia grade is determined using the ABI, ankle systolic pressure, transcutaneous oxygen pressure ($TcPO_2$), or skin perfusion

Table 2. Ischemic Grades.

Grade	ABI	Ankle systolic pressure, mmHg	TcPO2, mmHg	SPP, mmHg
0	≥0.80	>100	≥60	≥50
1	0.6 ~ 0.79	70 ~ 100	40 ~ 59	40 ~ 49
2	0.4 ~ 0.59	50 ~ 70	30 ~ 39	30 ~ 39
3	≤0.39	<50	<30	<30

ABI: ankle brachial pressure index; SPP: skin perfusion pressure; TcPO2: transcutaneous oxygen pressure

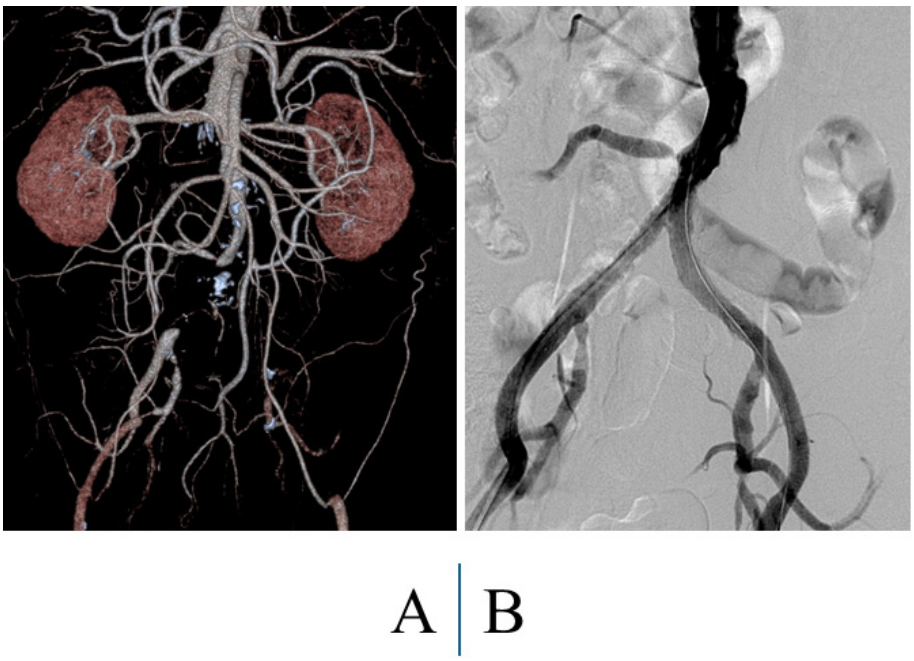


Figure 2. A 73-year-old male presented with bilateral intermittent claudication (200 m). CT revealed aorto-iliac occlusion (A). Completion angiography showed successful revascularization with stenting using the kissing balloon technique (B).

pressure (SPP) (**Table 2**). Most Japanese patients with CLTI have IP lesions, sometimes including a BTA lesion, and ABI does not always reflect the status of ischemia. Thus, there are some patients with severe ischemia who still have ABI in the normal range. Measurement of $TcPO_2$ or SPP is required for these patients. The wound grade or foot infection grade may be determined based on the opinions of the plastic surgeon, dermatologist, wound nurse, or vascular surgeon.

Preferred revascularization

The GVGs provide preferred infrainguinal revascularization strategies for an average-risk patient with an appropriate vein conduit based on the combination of WIfI stage and GLASS (**Fig. 1B**). As mentioned above, the guidelines recommend EVT for high-risk cases.

Recent randomized trials showed different results in preferred revascularization for CLTI patients [22, 23]. The BEST-CLI trial reported the superiority of surgical revascularization in patients with an appropriate autologous vein, compared with EVT [22]. The BASIL 2 trial revealed that the EVT-first strategy was associated with better amputation-free survival compared with the bypass-first strategy [23]. Preferred revascularization for CLTI patients should be fully investigated in the future study.

EVT

AI lesion

Many studies have reported the effectiveness and safety of EVT for AI lesions. The 2016 American Heart Association/American College of Cardiology guidelines, the 2017 European Society of Cardiology/European Society for Vascular Surgery guidelines, and the 2019 GVGs recommend EVT for an AI lesion as first-line treatment [7-9]. In particular, patients with CLTI have more comorbidities, and revascularization with laparotomy should be avoided. Although EVT for a complex aorta lesion such as that in Leriche syndrome remains controversial, there are some reports of the effectiveness and safety of this treatment (**Fig. 2A and B**) [24, 25]. The experience of the EVT team may contribute to technical success and risk reduction in aorta intervention. Thus, Iida et al. [25] found that hospital volume can affect

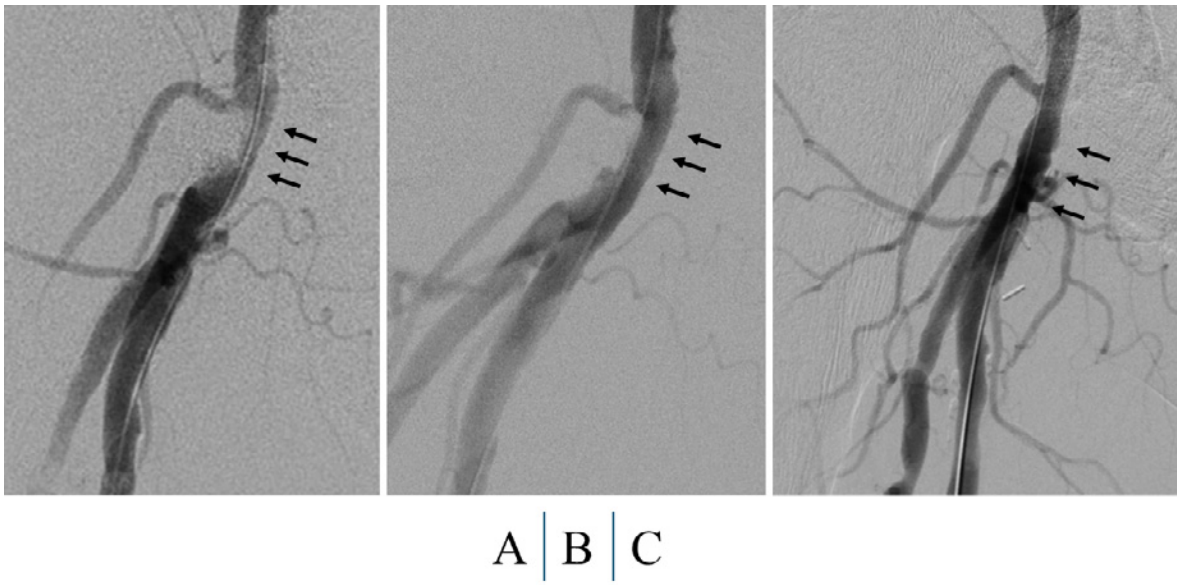


Figure 3. An 86-year-old female with intermittent claudication of the right lower extremity. Angiography revealed significant stenosis of the right common femoral artery (CFA) (black arrow) (A). Completion angiography showed residual stenosis after drug-coated balloon angioplasty (black arrow) (B). After 6 months, the patient had recurrent symptoms and CFA endarterectomy was performed. Angiography showed no significant stenosis of the CFA after endarterectomy (black arrow) (C).

outcomes after AI EVT with stenting since patients treated at high-volume hospitals had a significantly lower 1-year restenosis rate compared to those treated at low-volume hospitals. Decision-making for patients with CLTI with a severe AI lesion requires a thorough discussion among the members of the vascular team.

Device selection of AI lesion

The final device used in EVT for an AI lesion is usually a BNS due to its effectiveness. Recently, the use of an SG was approved for this lesion in Japan, and favorable outcomes have been documented [26, 27]. However, the use of an SG for an AI lesion may be limited by the nature of the graft. The Society for Cardiovascular Angiography and Interventions guidelines recommend an SG for the following class I lesions [28]: AI bifurcation; focal CIA lesion; diffuse CIA lesion; moderate to severely calcified focal lesion; and moderate to severely calcified diffuse lesion.

Common femoral artery lesion

In the first randomized controlled trial (RCT) of thromboendarterectomy (TEA) and common femoral artery (CFA) stenting, Gouëffic et al. [29] showed similar durability and a lower complication rate with CFA stenting compared to TEA. However, most CFA lesions have severe calcification, and residual stenosis is a concern after EVT without stenting for these lesions (**Fig. 3A-C**). Stent fracture and difficulty with CFA access are concerns of EVT with stenting. In a large multicenter retrospective study in Japan, TEA had higher primary patency and freedom from target lesion revascularization (TLR) compared to EVT, and EVT-first treatment was only recommended for limited cases with a contraindication for open surgery [30]. In CLTI cases with complex (CFA plus AI or FP) lesions, a hybrid procedure (TEA plus additional AI and/or FP intervention) can be effective and has been recommended [7, 9, 31].

FP lesion

Recommendations in guidelines are gradually shifting to the use of EVT for patients with FP lesions [7, 8]. For example, the 2017 ESC/ESVS guidelines recommend EVT for an FP lesion within 25 cm [9]. Patients with CLTI generally have advanced atherosclerosis and complex SFA lesions, and the lesion complexity is negatively associated with the outcome of EVT for FP lesions [32]. There are six major concerns in EVT for an FP lesion: long lesion, chronic total occlusion (CTO), severe calcification, small reference vessel diameter, popliteal artery involvement, and a poor BTK runoff vessel. Thus, more investigation of EVT for FP lesions in patients with CLTI is required, especially for the selection of the final device.

Device selection

SG

VIABAHN SG (W. L. Gore and Assoc. Inc., Flagstaff, AZ, USA) is approved for FP intervention in Japan. A Japanese multicenter prospective trial showed 2-year primary patency and 5-year freedom from TLR of 79% each, which were favorable compared to other devices [4]. Although a graft can avoid intimal hyperplasia in the stent, which affects the favorable patency, the intima cannot cover the stent due to the graft, which may result in thrombosis. Thus, acute occlusion during the follow-up period is a major concern with an SG (**Fig. 4A and B**). In a series of 1,215 patients undergoing FP intervention with an SG, Ichihashi et al. [33] found thrombosis in 159 patients (13%) at a median of 6.4 months. Given that the occlusion cohort in this study had a longer lesion length (mean 26 cm) and a smaller ref-

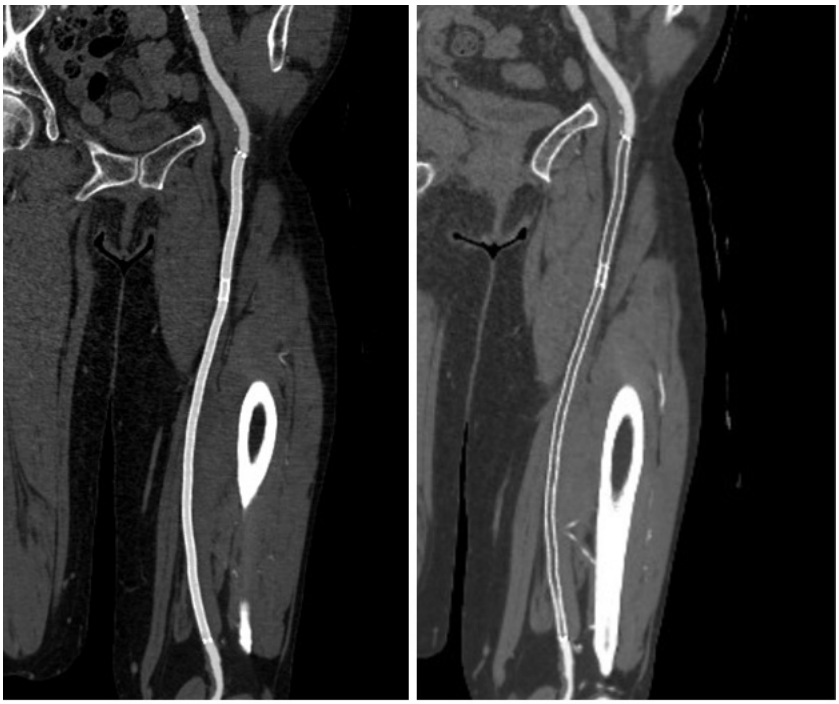


Figure 4. Chronic total occlusion of the SFA in a 77-year-old female who was successfully treated with an SG (A). Acute occlusion occurred in the SG 6 months after the initial procedure (B).

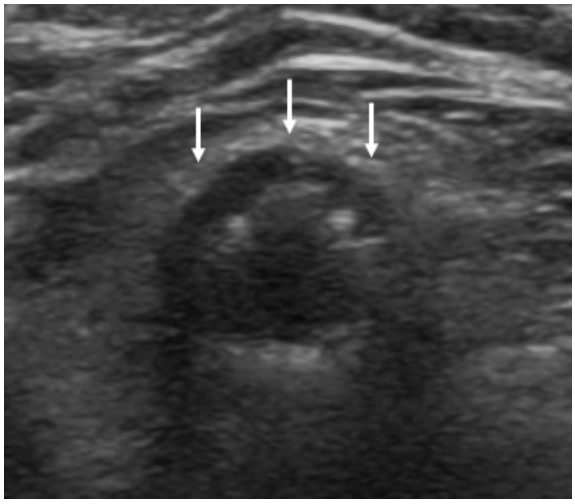


Figure 5. Aneurysmal degeneration around a drug-eluting stent (DES) in an 86-year-old male undergoing SFA angioplasty (white arrow).

erence vessel diameter (mean 5.0 mm), and that 79% had CTO and 50% had popliteal artery involvement, the results suggest that SG implantation for patients with CLTI may be inappropriate, due to the complexity of FP lesions.

DES

Eluvia DES (Boston Scientific, Marlborough, MA, USA) and Zilver PTX stent (Cook Medical, Bloomington, IN, USA) are approved in Japan. Iida et al. [34] found 2-year primary patency of 89% and 80% in Eluvia and Zilver PTX stent cases, respectively, and these rates were higher than in BNS cases. In a series of 1,204 cases undergoing EVT with an Eluvia DES, stent thrombosis occurred in only 3.3% of 1-year follow-ups, which was lower than the real-world SG series mentioned above [5]. However, in a series of 288 patients with Eluvia DES, Shimizu et al. [35] reported thrombosis in 25 cases (9%). Maintaining the release of paclitaxel from the Eluvia DES can avoid intimal hyperplasia in the stent, which affects patency, but the intima cannot cover the stent wall, as for an SG. Further investigation is needed to determine if the uncovered stent wall of the DES may cause thrombosis in patients with CLTI with a complex FP lesion. Aneurysmal degeneration also affects the maintenance of paclitaxel release in a DES (**Fig. 5**), and such degeneration has been observed in 16.8% of patients [5]. Therefore, there is a need to assess the clinical significance of aneurysmal degeneration after DES implantation in a future study.

BNS

Many types of BNS for FP lesions have been introduced in the last 20 years. There are reports of acceptable outcomes with a BNS, but primary patency and freedom from TLR may be lower compared to contemporary devices (SG and DES) [36]. This lower patency in BNS cases may be related to higher in-stent restenosis due to intimal hyperplasia (**Fig. 6**). Recently, an inter-woven nitinol stent (Supera stent; Abbott Vascular, Chicago, IL, USA) and a helical centreline nitinol stent (BioMimics 3D self-expanding nitinol stent;

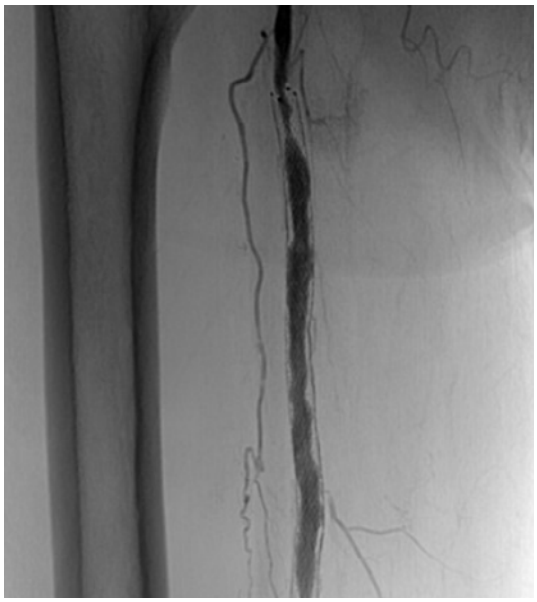


Figure 6. Intra-stent restenosis (ISR) 24 months after SFA angioplasty with a bare-nitinol stent in a 78-year-old male.

Veryan Medical Ltd., Horsham, UK) have been introduced in Japan as next-generation BNSs. Garcia et al. [6] showed the durability of the inter-woven nitinol stent for 36 months in a series of 325 cases undergoing EVT. This stent has strong resistance to external pressure, which may be helpful for a lesion involving the popliteal artery in patients with CLTI. In a series of 507 patients with CLTI, Rammos et al. [37] found that the BioMimics 3D stent gave favorable outcomes, and a future RCT is needed to confirm the non-inferiority or superiority of this stent compared to existing alternatives.

DCB

IN.PACT Admiral (Medtronic Plc, Dublin, Ireland), Lutonix DCB (Lutonix, Inc., a subsidiary of C. R. Bard, New Hope, MN, USA), and Ranger DCB (Boston Scientific, Marlborough, MA, USA) are approved in Japan. Many studies have reported favorable outcomes of DCB angioplasty [1, 38, 39], and Hata et al. [40] showed the durability of DCB angioplasty in a series of 927 CLTI cases (789 DCB vs. 138 non-DCB). The primary patency and freedom from TLR in DCB cases may be lower than in contemporary stenting (DES or SG) cases, but the rate of acute thrombosis using a DCB is lower than in stenting. Thus, a DCB-first strategy has gradually become used in patients with CLTI undergoing FP interventions, but there are remaining concerns with DCB angioplasty, as described in the following sections.

Vessel preparation

Bailout stenting (i.e., stenting after DCB angioplasty) is not approved under the Japanese insurance system, and appropriate pre-dilatation before DCB is essential for avoiding the need for stenting. The keys to vessel preparation are intraluminal wiring and appropriate selection of a balloon (diameter and length) based on imaging such as intravascular ultrasound (IVUS), optical frequency domain imaging, and optical coherence tomography. In a series of 469 DCB angioplasty cases, Toyoshima et al. [41] found that intraluminal DCB angioplasty was superior to subintimal DCB angioplasty, with significantly higher freedom from restenosis. In a large prospective multicenter DCB study, the use of IVUS reduced 1-year restenosis in univariate analysis [30]. A discrepancy in vessel diameter of about 1 mm between IVUS and angiography has been noted by Iida et al. [42], but the use of IVUS may provide adequate dilatation to maintain patency [43]. Semi-compliant, non-compliant, and high-pressure balloons have been introduced for FP interventions, and further studies of the selection of balloon type and the inflation time are needed.

Dissection after pre-dilatation and DCB angioplasty

The major issue in DCB angioplasty is residual dissection after the procedure, with Soga et al. [32] finding that 66.6% of FP lesions had residual dissection after DCB angioplasty in a Japanese multicenter registry of 3165 EVT cases. Vessel dissection after SFA angioplasty is divided into six types (A-F) in the modified version of the coronary artery classification of the National Heart, Lung, and Blood Institute [44, 45]. Generally, bailout or provisional (i.e., stenting after pre-dilatation) stenting is not needed for FP lesions with lower-grade dissection (types A-C). (**Fig. 7**). However, there is limited knowledge of hemodynamics at a residual dissection after DCB angioplasty and further investigation of hemodynamic assessment after DCB angioplasty is required [46, 47].

Prognosis after DCB angioplasty

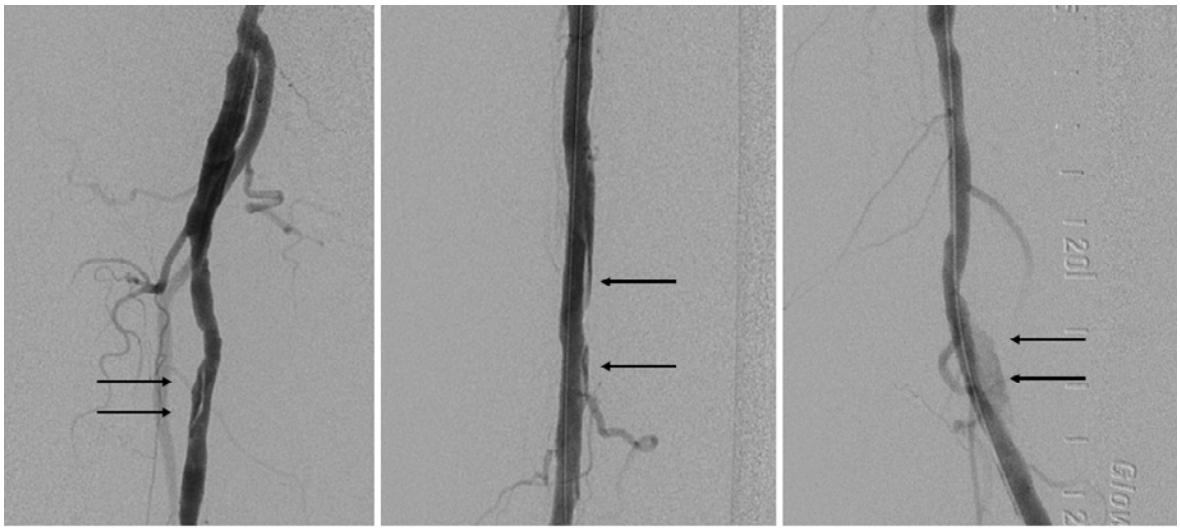
In a 2018 meta-analysis of 28 RCTs with 4663 patients, Katsanos et al. [48] found an increased mortality risk with the use of paclitaxel-coated balloons and stents in the FP artery of the lower limbs. This finding led to many discussions worldwide, but the FDA finally concluded that there was no relationship of mortality with the use of paclitaxel, and this concern has been resolved.

Tissue injury caused by paclitaxel

Whether paclitaxel can cause tissue injury in the lower extremity is controversial. In a meta-analysis of DCB RCTs, Katsanos et al. [49] found a heightened risk of major amputation after the use of a paclitaxel-coated balloon in the peripheral arteries, and speculated that "downstream showers of cytotoxic solid state paclitaxel material combined with its long-lasting tissue residence remains the most likely hypothesis for the herein noted increased risk of amputation" [49]. In an animal study, the use of a DCB caused fibrinoid necrosis in distal tissues, and distal embolic materials increased as the paclitaxel dose increased [50]. However, in a series of 927 CLTI cases, Hata et al. [40] found that DCB therapy did not lead to delayed wound healing. Thus, the concern about tissue injury due to paclitaxel remains unresolved.

Future of DCB angioplasty

As mentioned above, only three paclitaxel devices have been approved in Japan, and the appropriate paclitaxel dose (high vs. low) in DCB angioplasty is unclear [51, 52]. Favorable outcomes have been found for other paclitaxel devices or sirolimus devices such as Luminor (iVascular, Vas-



A | B | C

Figure 7. Completion angiography after drug-coated balloon angioplasty showing grade A (A), grade B (B), and grade C (C) dissections in SFA lesions (black arrows).

Table 3. GLASS IM Modifier.

	Infra-malleolar/pedal descriptor
P0	Target artery crosses ankle in foot, with intact pedal arch
P1	Target artery crosses ankle in foot; absent or severely diseased pedal arch
P2	No target artery crossing ankle into foot

GLASS: Global Limb Anatomic Staging System; IM: infra-malleolar

cular, S.L.U., Barcelona, Spain), TCD-17187 (Terumo Corp., Tokyo, Japan), and SELUTION SLR DCB (MedAlliance SA, Nyon, Switzerland) [53-55]. TCD-17187 is a domestically produced DCB. Further studies are needed to evaluate the selection of the DCB (high-dose paclitaxel vs. low-dose paclitaxel vs. sirolimus device) for patients with CLTI.

Summary of FP interventions

In patients with CLTI with complex FP lesions, DCB angioplasty may be the first-line treatment. Selection of the stenting device in a case with flow-limiting dissection or vessel recoil after DCB angioplasty requires further investigation.

IP lesions

Most CLTI patients have IP lesions due to comorbidity (diabetes and chronic kidney disease). Thus, IP intervention is required for most CLTI cases. DCB and stenting angioplasty are not approved for IP lesions in Japan, and thus, only balloon angioplasty can be performed. However, the use of this method for IP lesions has lower technical success and higher restenosis.

Techniques for IP intervention

IP lesions in patients with CLTI often have severe calcification and are long lesions with CTO, a small vessel diameter, and poor BTA runoff. These factors make technical success more difficult. In particular, a BTA lesion is strongly associated with outcomes [56, 57]. The GVGs propose the GLASS infra-malleolar (IM) modifier for BTA runoff (**Table 3**), but this modifier does not affect the recommendation for the initial revascularization method in the GVGs [9]. The basic principle in selecting a target vessel for EVT for IP lesions is to recanalize the vessel that is anatomically easiest to treat (in-line flow to the foot). In-line flow to the foot is the basic approach in EVT for IP lesions, but it is often insufficient to avoid major amputation and achieve wound healing. The angiosome concept, which considers the blood flow-dominated zone to which the wound location belongs, has been suggested to avoid major amputation and increase wound healing, but this concept remains controversial [25, 58]. Recently, woundosome concept has been introduced, which indicates the significance of arterial flow for wounds. Even in the case of indirect revascularization (non-angiosomal revascularization), adequate blood flow through the collateral source may heal an ischemic wound [59]. Iida et al. [60] reported in a prospective series of 440 CLTI patients undergoing IP revascularization that revascularization establishing in-line flow to the wound was positively associated with wound healing, while revascularization based on angiosome concept was not associated with wound healing.

The wire may not cross through the antegrade approach (from the CFA), and in such cases, a retrograde approach

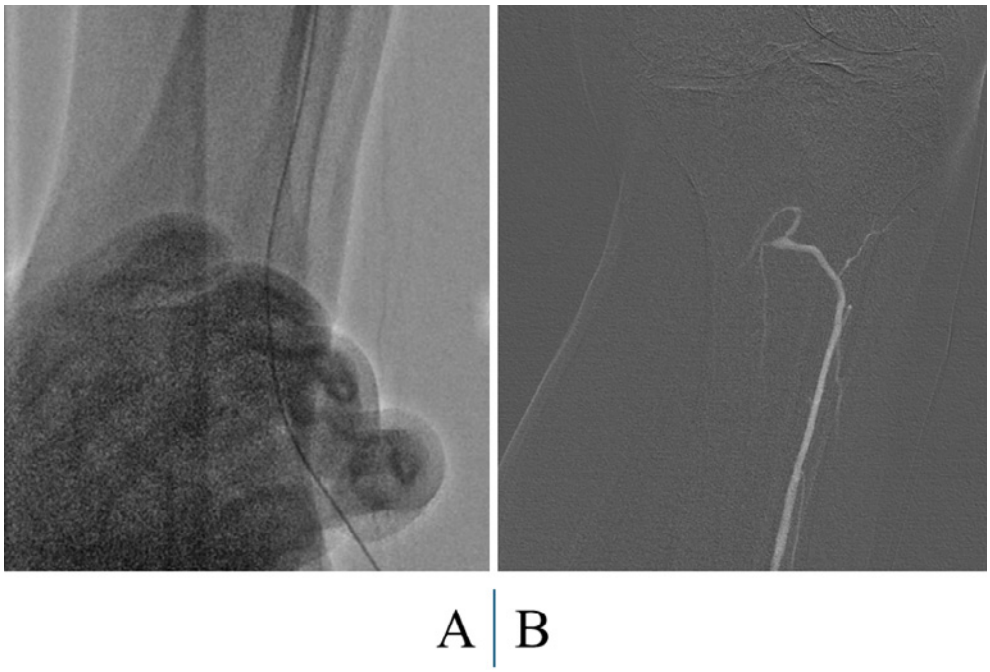


Figure 8. Distal puncture from the dorsalis pedis artery (A) and retrograde angiography of the anterior tibial artery (B).

(so-called "distal puncture") may be appropriate (**Fig. 8**) [61]. However, the puncture site in the retrograde approach is often consistent with the distal anastomosis site of bypass surgery, and thus, careful consideration of the distal puncture site is needed. EVT for a multivessel IP lesion also remains controversial [62-64]. There are reports of higher wound healing in multivessel revascularization cases, but these methods require a prolonged procedure time, the use of more contrast media, and greater radiation exposure. There is limited knowledge of EVT for IM lesions [65, 66]. A meta-analysis showed that additional BTA angioplasty is safe and feasible, with a 92% pooled limb salvage rate at 12 months [66]. However, a BTA vessel has a smaller diameter compared with that of the tibial artery, resulting in lower patency and higher TLR. These findings suggest the need to investigate multivessel and BTA angioplasty in future studies.

Recently, the efficacy of percutaneous deep venous arterialization (pDVA) has been reported for CLTI patients with no option (poor BTA runoff). pDVA might be a last resort for the CLTI patients with poor BTA runoff [67].

Follow-up

As mentioned above, balloon angioplasty alone is approved for intervention for an IP lesion in Japan, resulting in lower primary patency and higher TLR. Until complete wound healing is achieved, additional EVT for an IP lesion may be needed. In real-world practice, restenosis often occurs after IP intervention, and the timing and indication for re-intervention should be discussed with a plastic surgeon or dermatologist, with reference to factors such as wound status, hemodynamic assessment, and nutritional assessment. Additionally, it should be kept in mind that revascularization alone cannot cure ischemic ulcers in patients with CLTI, and team medicine through collaboration with a vascular surgeon, plastic surgeon, dermatologist, wound nurse, nutritionist, physical therapist, and pharmacist is required for CLTI management [68]. In addition to revascularization, wound management, nutrition assessment and support, and appropriate medical therapy are important to achieve complete wound healing and to avoid recurrent ulcers. The GVGs propose a multidisciplinary team approach for CLTI to prevent unnecessary amputation, with the statement that "teams can improve processes, time to intervention, and outcome" [9].

Newly devices for IP lesion

As above mentioned, DCB or stenting for IP lesions cannot be conducted under the Japanese insurance system. The IN.PACT DEEP trial did not show the long-term superiority of tibial artery revascularization with DCB in CLTI patients compared with balloon angioplasty [69]. The DES BTK Vascular Stent System vs PTA in Subjects With Critical Limb Ischemia (SAVAL) trial also did not show the durability of the nitinol DES for IP lesions compared with balloon angioplasty [70]. While the LIFE-BTK trial revealed that the use of a drug-eluting resorbable scaffold for IP lesions in CLTI patients was superior to balloon angioplasty [71]. Continued innovation for IP lesions in CLTI patients is needed.

Conclusions

EVT for lower extremity arterial disease is now performed worldwide due to its efficacy, technical advances, and introduction of new devices. However, the indication for EVT, selection of the final device, and follow-up method are not still standardized in CLTI cases. This may be due to the

complexity of the lesion (severe calcification, long lesion, CTO, small vessel, and poor runoff vessel) and these issues need to be resolved in future studies.

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Conflict of Interest: None

Author Contribution: Taira Kobayashi designed the study; Taira Kobayashi performed the experiments and analyzed the data; Taira Kobayashi provided critical reagents; Taira Kobayashi supervised the experiments.

IRB: This research has been approved by the institutional review board of the authors' affiliated institutions (approval number: 24-43).

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