

8th Asian PAD Workshop

Diabetic Complications and PAD

February 18–19th, 2017 in Busan, Korea

Chairpersons

Day 1—Dr. Moon Kyu Lee (Seoul, Korea)

Dr. Yu Zhao (Chongqing, China)

Day 2—Dr. Hiroshi Shigematsu (Tokyo, Japan)

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The 8th Asian PAD Workshop builds on the progress and achievements made at the previous medical education workshops held across Asia. The latest edition focused on diabetic complications and PAD (peripheral arterial disease) exploring the nature and management of these complications. PAD incidence and prevalence continues to grow at an alarming rate in Asia and diabetes mellitus (DM) is a critical factor in its onset. Screening patients with DM for early PAD diagnosis is essential to identify those at high risk for progressive cardiac and cerebral pathogenesis. Five distinguished speakers invited from Thailand, China, Indonesia, Korea and Japan provided an excellent opportunity to provide in-depth discussions on diverse topics including identifying risk factors, medical therapies such as beraprost for PAD in DM, and surgical techniques for patients with diabetic foot (DF) to salvage limbs and improve patient functioning and health-related quality of life (HRQoL). Case studies were presented along with clinical study data indicating the benefits of early detection and individualised medical and surgical management. Raising awareness of PAD, its consequences and links with DM and DF remains critical to encourage early diagnosis and intervention to prevent disease progression and achieve the best patient outcomes possible.

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Day 1: Diabetic Complications and PAD

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Opening Address: Progress of the Asian PAD Workshop

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The Asian PAD workshop provides a platform for valuable discussions amongst healthcare professionals concerning the prevalence, diagnostic approaches, and management of patients with PAD, especially those with diabetes.

Japan is experiencing rapid ageing, at a faster speed than any other developed country, with almost a quarter of the population being ≥ 65 years old in 2013.¹⁾ Malignancy is known to be the most common cause of death (31%) in the Japanese population, closely followed by cardiovascular disease at 29%.²⁾ Most Asian countries are now high or middle income and ischemic heart disease and cerebrovascular disease have become the most common cause of death. However, diabetes resulting in PAD has also become a main cause of death in many countries.³⁾

Independent factors for PAD confer a high risk of myocardial infarction (MI) and stroke even with no previous history of these events. The principle risk factors are male aged ≥ 65 years or female aged ≥ 70 years, currently smoking > 15 cigarettes/day, type 1 or 2 diabetes diagnosis, presence of hypercholesterolemia, diabetic nephropathy (DN), hypertension, ankle brachial index (ABI) of < 0.9 in either leg at rest, asymptomatic carotid stenosis $\geq 70\%$ or the presence of at least one carotid plaque.⁴⁾

There is a significant overlap between coronary artery disease (CAD) cerebrovascular disease (CBVD) and PAD. Of patients with PAD in the REACH registry, for example, 40% had concomitant CAD, 10% concomitant CBVD and 14% both. Around 65% also had clinical evidence of other vascular disease.

The characteristics of PAD patient populations were defined in a prospective cohort study included 6,880 representative unselected patients ≥ 65 years of age with monitored follow-up over 5 years. Based on physician diagnosis, 5,392 patients had no PAD, 836 had asymptomatic PAD (ABI < 0.9 without symptoms), and



593 had symptomatic PAD (lower-extremity peripheral revascularization, amputation due to PAD, or intermittent claudication symptoms regardless of ABI). The risk of symptomatic compared with asymptomatic PAD was significantly increased for the composite of all-cause death or severe vascular event (i.e., MI, coronary revascularization, stroke, carotid revascularization, or lower-extremity peripheral vascular events). The risk of mortality was found to be similar in symptomatic and asymptomatic patients with PAD and was significantly higher than patients without PAD.⁵⁾

Beraprost sodium was the world's first orally active prostacyclin analogue. It is very stable to gastric pH, has potent antiplatelet and vasodilating properties and improves endothelial function.⁶⁻⁸⁾ Beraprost has several therapeutic properties including vascular endothelial protection, antiplatelet and anti-inflammatory effects, and vasodilatory activity. These properties are demonstrated to improve the pathological process in the lower extremities and reduce the incidence of systemic vascular events. Beraprost contributes to an overall systemic vascular protective action and is expected to have dual effects on improving ischemic symptoms due to PAD and on preventing CV events due to polyvascular disease (PVD; Fig. 1).⁶⁻⁸⁾

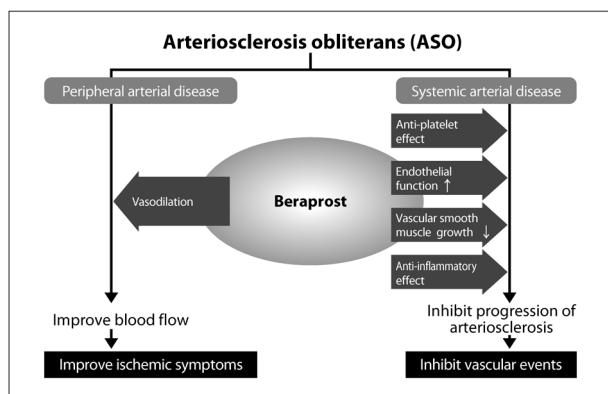


Fig. 1 Proposed dual effects of beraprost to improve PAD ischemic symptoms and prevent CV events.⁷⁻⁹⁾

There are currently two main management strategies for cardiovascular risk reduction and treatment of claudication symptoms in patients with established PAD. For cardiovascular risk reduction in people with established PAD, beraprost or clopidogrel are indicated to reduce the risk of atherothrombotic events (i.e., recent MI, recent ischemic stroke or vascular death). For the pharmacological treatment of claudication symptoms, beraprost is indicated to reduce symptoms of intermittent claudication and can provide HRQoL benefits such as increased walking distance.

The effect of beraprost on systemic vascular events was explored in two meta-analyses. A highly significant reduction in cardio/cerebrovascular events and an improvement of leg symptoms was observed with beraprost demonstrating its efficacy to reduce the risk of vascular events in patients with PAD.⁹⁾

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Management of Diabetic Foot: Clinical Practice Based on the Thai Experience

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DM continues to grow in global prevalence and to consume an increasing amount of health care resources. One of the key areas of associated morbidity is DF,¹⁾ which typically presents as ulceration or ankle destruction. Management of DF usually begins with a comprehensive assessment of the ulcer, the patient's overall medical condition, underlying neuropathy, bony deformity but should explore the presence of PAD. In King Chulalongkorn Memorial Hospital, Thailand during 2016 there were 38 below knee amputations and 28 above knee amputations due to diabetes. There is an urgent ambition to reduce this number.

An important management approach is to consider which risk factors can be modified. These include smoking cessation and controlling blood pressure to <140/90 (DM patient: <130/80); the latter can be achieved with the help of ACE inhibitors and beta blockers. Cholesterol control LDL <100; HDL >35 is important as is diabetes management (HbA1c <6%). The use of vasodilator agents such as beraprost, antiplatelet compounds such as aspirin, clopidogrel and hemorrheologic agents such as cilostazol are all important pharmacotherapies for reducing the risk of DF.²⁾ A graded exercise regimen is another important approach, with at least 30 min of exercise every other day recommended.

The longer the diabetes history, the greater the likelihood of developing a PAD complication.³⁾ DF ulceration will generally heal if the toe pressure is >55 mmHg.⁴⁾ If toe pressure is <40 mmHg it is considered very unlikely that the wound will heal. The most widely accepted and universally used grading system for lesions of DF is the Wagner–Meggit classification. Grade 3 and beyond suggest the need for surgery or revascularization and surgery is usually indicated only when medical approaches and exercise interventions have failed. Percutaneous transluminal angioplasty (PTA) is preferred where possible in patients ≤50 years as they have a higher risk of graft failure after surgical therapy than older patients.

The current Trans-Atlantic Inter Society Consensus (TASC) for the management of PAD was published in 2007.⁵⁾ Following this, the Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIFI) was published (2014).⁶⁾ This proposed a classification system, based on scoring of wound, ischemia and foot infection, which surgeons can use to predict the risk of amputation at 1 year and estimate the likelihood of benefit of revascularization (assuming infection can be controlled first).⁶⁾

Earlier, the BASIL studies investigated bypass versus angioplasty in severe ischemia of the leg. Among 224 patients assigned to PTA, 217 underwent the procedure, immediate technical failure occurring in 43 (20%). Among 228 assigned to bypass surgery, 196 underwent the procedure.⁷⁾ For patients that have an estimated life expectancy of two years or less, or those who do not have autogenous vein available as a conduit, balloon angioplasty is reasonable as the initial procedure, in selected patients, to improve distal blood flow.⁸⁾

Overall, the available evidence indicates that the treatment of patients with DF should be individualized and multidisciplinary. This should include the expertise of endocrinologist (to control blood sugar), cardiologist (for initial evaluation), nephrologist (to help protect the kidney before and after procedures), orthopedist (what type and how high the amputation and for wound healing strategy), physical medicine and rehabilitation (to cut special shoes for the patient), nutritionist (for lifestyle improvement) and of course the surgeon. The use of hyperbaric chamber can be helpful while stem cell technology shows promise for the future.⁹⁾

Discussion points

- Management of DF is complex and challenging.
- Endocrinologists in Thailand push for as low an HbA1c as possible. It is important to note that testing between different laboratories yields differing HbA1c values.
- Regarding the use of growth factors, while they can be used topically on the wound they are not generally used in practice in Thailand.
- CT angiography is typically used first for most patients with acceptable creatinine clearance and kidney function to evaluate the vessels and to plan a procedure. However, if the patient presents with DF ulcer then feeling the pulse but the creatinine is borderline then angioplasty with an antegrade puncture down the leg is indicated.
- While amputations are not often avoided, they can usually be delayed with appropriate interventions.
- It is useful to try to maintain surgical patients on aspirin and

clopidogrel for as long as possible, ideally at least 6 months.

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Chronic Aortoiliac Occlusion: From Open Surgery to Endovascular Management

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Aortoiliac occlusive disease (AIOD) involves the distal abdominal aorta which may progress proximally to the renal arteries or distally beyond aortic bifurcation into iliac arteries. One-third of lesions in patients with PAD affect the aortoiliac segment. AIOD symptoms range from life-limiting disability to limb-threatening ischemia. The syndrome is classically associated in men with a triad of syndrome comprising intermittent claudication, absent or diminished peripheral pulses and erectile dysfunction. About one-third of AIOD patients have diabetes and multiple level lesions.¹⁾

Although the goal of treatment involves re-establishment of inflow to the lower extremities and pelvis, the therapeutic options are evolving and shifting. AIOD has traditionally been treated with open-surgery²⁾ and aorto-bifemoral/iliac bypass is considered the surgical “gold standard” with a high patency of around 90% at 5 years and 75% at 10 years.³⁾ With the development and improvement of techniques and hardware, endovascular therapy (EVT) has been established as the treatment of a choice for localised AIOD. It is associated with lower peri-operative mortality and morbidity, shorter hospitalisation compared to open surgery

although long-term patency is comparable.⁴⁾

The optimal management of AIOD remains a topic of controversy. According to 2011 guidelines by the European Society of Cardiology, an endovascular-first strategy is recommended in all aortoiliac TASC A–C lesions. A primary endovascular approach may be considered in aortoiliac TASC D lesions in patients with severe comorbidities, if performed by an experienced team.⁵⁾ However, the European Society of Vascular Surgery recommend surgical repair with aortofemoral bypass grafting or aortoiliac endarterectomy, which has proven effective in alleviating ischemic pain and which provides good long-term patency in patients with critical limb ischemia (CLI).⁶⁾

A retrospective study carried out at the author's clinic compared midterm results of aortoiliac stent (AIS) placement with those of surgical treatment in patients with chronic infrarenal aortoiliac occlusion.⁷⁾ Of 68 technically successfully treated patients, 33 had undergone surgical revascularization and 35 had received AIS placement. Surgically treated patients had a longer average postoperative hospital stay ($p=0.001$) and higher rates of postoperative complications, including respiratory failure ($p=0.010$) and transient renal dysfunction ($p=0.002$). Mean ABI increased significantly in both groups ($p<0.001$), but to the same extent. The primary 1-, 3-, and 5-year patency rates were 93.6%, 90.2%, and 90.2% in the surgery group, and 91.4%, 81.8%, and 64.2% in the AIS group ($p=0.054$). No differences were observed in survival rate ($p=0.945$), limb salvage ($p=0.860$), or secondary patency ($p=0.916$).

According to the Chinese Society of Vascular Surgery (2014)⁸⁾ surgical intervention is indicated for intermittent claudication when a patient's HRQoL remains unacceptable after a trial of conservative therapy, and if the patient has a high level of resting pain, if the intervention is feasible, and if the patients' body condition is deemed durable for management.

The most extensive meta-analysis of data regarding morbidity of open aorto-bifemoral bypass revealed that it is reasonable to expect around 4.4% postoperative mortality and 12.2% complication rates.³⁾ Yet endovascular treatments are increasingly finding a place in the treatment of AIOD. In the USA, one study reported an 850% increase in iliac artery angioplasty and stenting, from 0.4 to 3.4 cases per 100,000 adults ($p<0.001$) and a 15% decrease in the rate of AFB declined, from 5.8 to 4.9 cases per 100,000 adults ($p<0.005$).⁹⁾ Although primary patency rates remain inferior, secondary endovascular interventions are often minor procedures resulting in comparable long-term outcomes.¹⁰⁾

Device developments coupled with increasing experience level of interventionists have substantially improved the success rates of recanalization in patients with complex aortoiliac lesions. TASC II have emphasized the role of endovascular intervention.

An antegrade approach via transbrachial access for TASC C–D aortoiliac chronic occlusion improves the technical success rate without the need for re-entry devices.¹¹⁾ Furthermore, covered stents have been increasingly promoted for their long-term durability, particularly in extensive and challenging AIOD lesions.¹²⁾ Covered stents have a demonstrated benefit over bare metal stents, and this benefit is particularly pronounced in patency differences observed in extensive TASC C–D lesions. Balloon expandable covered stents remain the treatment choice for severely, advanced aortoiliac occlusive disease. The COBEST study demonstrated that covered and bare-metal stents produced similar and acceptable results for TASC B lesions. However, covered stents

performed better for TASC C and D lesions than bare stents in longer-term patency and clinical outcome.¹³⁾

Unibody bifurcated endograft have recently been described by Van Haren et al. (2017).¹⁴⁾ These investigators demonstrated that endovascular repair using a unibody bifurcated endograft for TASC D aortoiliac occlusive disease is feasible, effective and has excellent midterm patency. It should therefore be considered an effective treatment option when the disease process involves the aorta, particularly if the patient is surgically unfit for a traditional aortobifemoral bypass.¹⁴⁾ Use of the Endologix AFX unibody stent-graft appears to be a safe and effective endovascular treatment for complex AIOD.¹⁵⁾

EVT for chronic aortoiliac occlusion is associated with a lower perioperative mortality, morbidity and shorter hospital stay. Mid-long term patency results are comparable to surgical treatment. Although the 5-year primary patency is lower than traditional OS, EVT is a safe, minimally invasive and reliable choice. Finally, while OS remains a golden standard treatment for those patients with relatively good condition, EVT is an optimal option for those patients presenting with higher surgical risk.

Discussion points

- Femoral-femoral cross-over bypass is a very important option in the endovascular area. However, aorta to iliac or femoral bypass also achieves high patency rates due to the good blood supply from the aorta.
- AIOD are considered for open surgery if patients have generally good condition to withstand the procedure. Yet many have poor cardiac function and such patients usually receive the relatively simple procedure of endovascular surgery with local anaesthesia.

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The Role of Beraprost in Diabetic Patient with PAD

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PAD is characterized by atherosclerotic occlusive disease of the lower extremities. One-half of patients with diabetes with PAD are asymptomatic or have atypical symptoms. One-third have claudication, and the remainder have more severe forms of the disease.¹⁾ Only 15% have classical claudication, 33% have atypical leg pain with limited functionality with 1–2% of patients having CLI.¹⁾ The Framingham Heart Study noted that 20% of symptomatic patients with PAD had diabetes and 40–70% of DF-related amputation. Early screening and management PAD can decrease the risk of amputation for diabetics by 45–85%. It is therefore the responsibility of healthcare providers to provide early screening and management for PAD in patients with diabetes.¹⁾

Kubota et al. (2011) proposed a mechanism by which vascular impairment occurs in the insulin-resistant state (**Fig. 1**). Insulin signalling in endothelial cells plays a pivotal role in the regulation of glucose uptake by skeletal muscle. The two types of angiopathy, micro and macro, were described. Improving endothelial insulin signalling may serve as a therapeutic strategy for reducing skeletal muscle insulin resistance.²⁾

The treatment of arterial occlusion is determined by the severity of the condition, according to the Fontaine's stages of classification of PAD. Generally, stages I and II can be treated with conservative measures including physical treatment (warming/rest), drug treatment and exercise treatment. Stages III and IV (and sometimes stage II) are treated with circulation-reconstructive surgery plus drug treatment or sympathectomy plus drug treat-

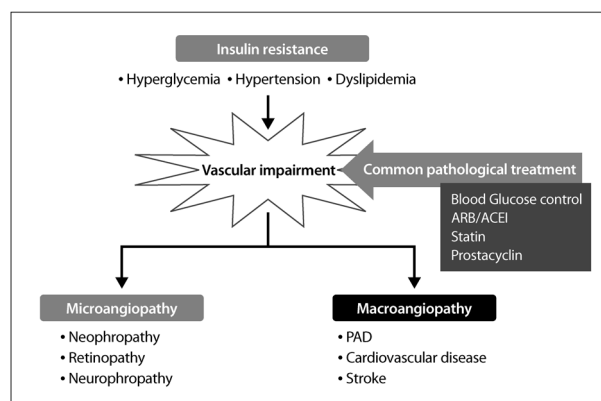


Fig. 1 Vascular impairment in insulin-resistant state.²⁾

ment.³⁾ Medical treatments for PAD in diabetic patients include antiplatelet agents (aspirin, ticlopidine, clopidogrel), anticoagulant agents (heparin, warfarin, low molecular weight heparin), thrombolytic agents, cholesterol lowering agents or prostacyclin analogues.

Prostaglandin analogues play an important role in PAD management. PGI₂ is produced in blood vessels, bronchi, kidneys and lungs. PGI₂ production is decreased in disease conditions and has a strong inhibitory action on platelet aggregation, has potent vasodilative action and inhibitory action on gastric secretion.⁴⁾ The oral prostacyclin analogue beraprost acts by binding to prostacyclin membrane receptors, this inhibits the influx of calcium causing relaxation of the smooth muscle cells and vasodilatation. Specifically, beraprost sodium is a relatively stable orally active prostacyclin (PGI₂).⁴⁾

A detailed review of the case of Mr BY, a 55-year-old and retired labourer who has a history of type 2 diabetes mellitus (T2DM) for the past 8 years, illustrates how beraprost can help treat PAD. Mr BY first controlled his diabetes by means of oral treatment, but after 3 years he was advised to use insulin to control his diabetes. Unfortunately, he refused therapy because of his fear of needles and injections, he was, and continues to be, a chronic smoker. The patient also had a history of hypertension and dyslipidemia and was sporadic at attending for treatment. Two years previously he had undergone photocoagulation for retinopathy. Mr. BY's foot ulcer appeared approximately 1 month before he presented at the Mitra Kemayoran Hospital, Jakarta, Indonesia. He initially assumed he had a blister caused by his shoe, but as time went by it deteriorated and became infected. Consequently, the ulcer became larger and the infection more severe. Mr BY's wound measured 2 cm × 2 cm with an ulcerated area at the base of the first metatarsal involving the interdigital cleft and extending to the forefoot; his blood pressure was 154/98 mmHg and pulse rate was 96 bpm. His dorsalis pedis artery and posterior tibial artery pulses were palpable, and ABI was 0.7. Neurological assessment with 10g monofilament test and vibration perception threshold revealed a loss of sensation in both of Mr BY's feet. On closer examination the ulcer was found to be of full thickness, extending to the underlying bone. Following wound management, the wound area remained the same for the first week, but the exudate decreased considerably. Mr BY's blood glucose was controlled with insulin and he received treatment with beraprost t.i.d. Two weeks after the start of treatment, the wound measured 1.5 cm × 1.5 cm. By week 4, the wound measured 0.5 cm × 0.5 cm. By week 6, the

wound had reduced in size to 0.2 cm × 0.3 cm, the oral antibiotics were stopped and Mr BY had learned how he could take care of his foot, clean his foot and nails, and choose suitable shoes. He was also aware of the level of physical activity he should undertake, his ABI was also better, with ABI 0.9.

The effective management of DF ulceration is based upon the principles of wound debridement; the identification and management of infection and the use of dressings to maintain a moist wound environment whilst offloading to redistribute pressure away from the wound. With combined beraprost and wound management there can be successful management of DF ulceration in many patients.

Finally, Dr Eliana presented some observational data from 10 subjects with diabetes and PAD at the Mitra Kemayoran Hospital, Indonesia collected during October 2016–January 2017. Overall, 16 weeks beraprost treatment showed good improvement in ABI, most notably in patients who were non-smokers.

Discussion points

- Generally, beraprost is prescribed to symptomatic patients; however, if an asymptomatic patient has risk factors such as CHD or stroke then beraprost should be considered.
- How long beraprost treatment should continue for is dependent on the individual patient.

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Role of Prostacyclin Analogue, Beraprost Sodium, in Diabetes and its Complications

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Approximately 4.8 million Koreans aged 30 years or older have diabetes (2014 data), equating to 1 in 7 Koreans. In addition, nearly a quarter of Korean adults have prediabetes (i.e., impaired fasting glucose). Of these, 3 of 10 with diabetes are not aware of their condition. Nearly half of people with diabetes are obese or hypertensive and one-third have hypercholesterolemia. Nearly one-third of people with diabetes have albuminuria or decreased renal function.¹⁾ Diabetic peripheral neuropathy is a common complication of diabetes. A cross-sectional study in almost 4,000

patients demonstrated a high prevalence of peripheral neuropathy in patients with T2DM in Korea; such patients were far more likely to have complications or co-morbidities.²⁾

Won et al. (2012) reported that 3.4% of Korean diabetic patients were reported to have a history of PAD, and 37.7% of this population experienced muscle cramps in their legs and/or feet suggestive of PAD.²⁾ Unpublished data show that 61.8% of patients that presented with PAD suffered from carotid artery occlusive disease. This not only supports the need for PAD screening but also the need to screen for coronary arterial diseases, especially in patients with PAD and diabetes.

T2DM is linked to central obesity and associated with increased risk of CVD. In diabetes, hyperglycemia in combination with dyslipidaemia and hypertension impair endothelial function in both macro- and microvascular beds in animal studies and in human subjects.³⁾ Prolonged exposure to hyperglycemia is the major trigger in the pathogenesis of diabetic complications.³⁾

Prostaglandin belongs to a class of autacoids involved in multiple aspects related to DM and PAD pathogenesis, notably the primary endothelial dysfunction. The anti-thrombotic effects of prostacyclin are mediated by stimulation of cAMP production in endothelial and smooth muscle cells leading to vasodilatation and anti-proliferative effects.⁴⁾ **Table 1** outlines the diverse cellular functions of prostacyclins.⁵⁻⁸⁾

Table 1 Prostacyclins have diverse cellular functions⁵⁻⁸⁾

Prostacyclin effect	Cellular response	Mechanism
Classical functions		
Vessel tone	↑ Vasodilation	↑ cAMP, ↑ K ⁺ , ↓ Ca ²⁺
Anti-proliferative	↓ SMC proliferation ↓ Fibroblast growth ↑ Apoptosis	↑ cAMP, ↑ K ⁺ , ↓ ET-1 ↑ PPARγ (α?)
Anti-thrombotic	↓ Platelet aggregation ↓ Platelet adherence to vessel wall	↓ Thromboxane A ₂ ↓ PDGF, ↓ AMs
Novel functions		
Anti-inflammatory	↓ Pro-inflammatory cytokines ↑ Anti-inflammatory cytokines	↓ IL-1, IL-6 ↑ IL-10
Anti-mitogenic	↓ ECM remodelling ↓ Fibrosis	↓ MMP 2 & 9 ↓ TGF-β, ↓ CTGF
Anti-tumorigenic	↓ Tumour formation and metastasis	↑ PPARγ

As a prostacyclin analogue, beraprost consequently has multiple mechanisms of action (**Fig. 1**). Beraprost also inhibits vascular smooth muscle cell migration via activation of the cAMP effector Epac. This indicates that beraprost may be beneficial following angioplasty to prevent neointimal hyperplasia.¹¹⁾ Beraprost also acts on regression of atherosclerosis process by inhibiting the expression of vascular cell adhesion molecule-1 (VCAM-1). The inhibitory effect of beraprost on VCAM-1 expression in vascular endothelial cells is suggested to be a cause for the prevention of atherosclerosis progression in diabetic patients.¹²⁾

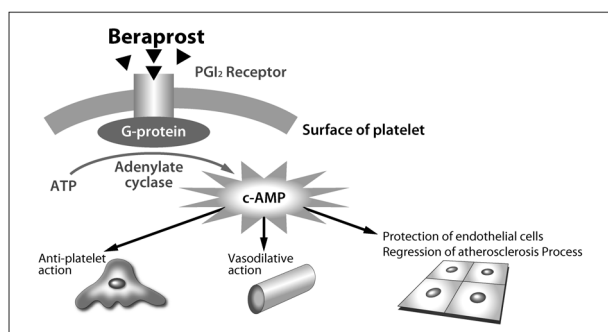


Fig. 1 Mechanism of action of beraprost.⁹⁻¹¹⁾

In a phase III clinical trial of beraprost, patients ($n = 549$) with intermittent claudication and with a pain-free walking distance of between 50 and 300 m were entered into a 4-week single-blind placebo run-in phase. Patients whose pain-free walking distance had changed by $< 25\%$ were then randomised to receive either beraprost or placebo in a double-blind manner for 6 months. Success was observed more frequently with beraprost (43.5%) than with placebo (33.3%; $p = 0.036$). Pain-free walking distances increased by 81.5% with beraprost vs 52.5% with placebo ($p = 0.001$) and maximum walking distances by 60.1% and 35.0% ($p = 0.004$). These results show that beraprost is an effective symptomatic treatment of patients with intermittent claudication.¹³⁾

Cold intolerance frequently occurs after successful digital revascularization and replantation. A series of 11 patients with cold intolerance 6 to 24 months after digital revascularization/replantation were treated daily for 2 weeks with beraprost. Pain was reduced in 9 of 11 cases after treatment and digital thermography showed significantly increased surface temperature after the 2-week course of beraprost. These findings support the use of beraprost to relieve symptoms of cold intolerance after digital revascularization.¹⁴⁾

Yoon et al. (2013) evaluated the effects of beraprost on subjective leg symptoms in patients with PAD caused by T2DM. There was significant improvement in all estimated subjective in the lower extremities at 12 weeks ($p < 0.001$). Beraprost improved various subjective symptoms in the lower extremities such as burning, coldness, edema, exertional pain, stabbing and paresthesias.¹⁵⁾ A meta-analysis of the effect of beraprost on incidence of vascular events in patients with PAD using two studies (BERCI-2 and US trial) demonstrated significant reduction in lower limb vascular disease and all vascular events but not for cardio/cerebrovascular events.¹⁶⁾

Endothelial dysfunction is considered a main pathobiology of atherosclerosis especially in T2DM. It has previously been reported that a decrease in hepatocyte growth factor (HGF), which has many protective functions against endothelial damage by high d-glucose, might be a trigger of endothelial injury. Some studies suggest that HGF has a protective function against high-glucose induced endothelial damage and increased local vascular HGF production by a PGI₂ analogue may prevent endothelial injury, potentially resulting in the improvement of endothelial dysfunction. This is supported by results of an in vivo study showing that 4 weeks of beraprost treatment in diabetic rats increased expression of HGF mRNA in the blood vessels as well as aorta of diabetic rats.¹⁷⁾

Metabolic syndrome is a clinical phenotype of insulin resistance and endothelial dysfunction and is associated with an

increased risk of CVD.²⁾ Beraprost dose-dependently suppressed serum glucose, insulin, A1C, and TG levels in obese animals, and also suppressed the post-glucose loading elevation of serum glucose. Beraprost also inhibited the progression of hepatic steatosis, pancreatic fibrosis, hypertrophy of adipose tissue and glomerular and tubular abnormalities.¹⁸⁾

These findings suggest that beraprost has a role in controlling hyperglycaemia in patients with T2DM. Chen et al. (2013) showed that the addition of beraprost in patients with T2DM taking pioglitazone had a significant synergistic effect in reducing the HbA1C levels compared to treatment with pioglitazone alone.¹⁹⁾

DN is a leading cause of end-stage renal failure. Microalbuminuria is a risk factor associated with increased risk for CVDs. Albuminuria develops in early stage hyperglycemia.²⁰⁾ A study found that 8-week treatment with beraprost improved lipid profiles, blood glucose levels and inflammation.²¹⁾

Diabetic cardiomyopathy (DCMP) is one of the major cardiac complications in patients with diabetes. The incidence of DCMP is very high, and the disease is highly dangerous, directly causing mortality due to cardiovascular events in DM patients. Studies have suggested that p38 MAPK signalling pathway plays an important role in the pathogenesis of DCMP. The circulating levels of BNP and ANP increased in patients with heart failure and reflects the early stage of cardiac dysfunction. Li et al. (2014) found that the expression of BNP and ANP proteins in the beraprost treatment group were significantly decreased compared with DM group.²²⁾ Treatment with beraprost reduced the expression of inflammatory factors such as TNF- α , HIF-1 α , and MMP-9 inhibited myocardial cell apoptosis and decreased the expression of BNP and ANP, delaying the progression of DCMP.²²⁾

There are many vascular benefits of beraprost treatment for patients with T2DM. Beraprost inhibits platelet aggregation, inhibits proliferation of human artery smooth muscle cells in vitro, induces direct vasodilation of the systemic arterial vascular beds and has vasodilatory effects to reduce right and left ventricular afterload and increase cardiac output and stroke volume. Beyond its vascular benefits, beraprost significantly prevents pathological changes in diabetic animal models: nephropathy, cardiomyopathy, endothelial dysfunction, and pathologic changes in liver, pancreatic and adipose tissue. Results from clinical trials indicate that concomitant administration of pioglitazone and beraprost may be useful in the treatment of T2DM. Beraprost has extensive functions in the prevention and treatment of microvascular complications and hyperglycaemia in patients with T2DM. These effects appear to be mediated by the improvement of glucose and lipid metabolism and a reduction of oxidative stress.

Discussion points

- Beraprost added to pioglitazone significantly reduces HbA1c levels in patients with DM and beraprost is thought to improve insulin resistance in mediating this effect, although the precise mechanism remains unknown. However, studies suggest that prostacyclin levels are lower in patients with T2DM. Beraprost has diverse pleiotropic effects in patients and its action differs depending on tissue type but may act to correct this reduction.
- The side effects of beraprost in patients with PAD are generally minor and uncommon, with typically less than 5% experiencing treatment-related headaches. Most patients continue with treatment even with subsequent dose escalation.

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Day 2: Special Morning Lecture

Chairpersons:

Dr. Hiroshi Shigematsu

Executive Director of Vascular Surgery, Sanno Medical Center, Professor of Clinical Research Center for Medicine, International University of Health and Welfare, Tokyo, Japan

Dr. In Sung Moon

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Perspectives on Recent Treatment Strategies for PAD: Where to Go as a Vascular Surgeon

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Although intermittent claudication (IC) is the initial symptom of PAD along with lumbar spinal canal stenosis (LSCS), in the real world it is approximately 25% of patients have combined LSCS and PAD.¹⁾ Consequently, clinicians must be cautious before treating PAD in an invasive way. CLI due to PAD leads to leg pain and infection. For the appropriate treatment of CLI, early detection and accurate diagnosis are essential. Without this the patient's HRQoL may be significantly impaired. The mission of a vascular surgeon in the treatment of PAD is to achieve early diagnosis and proper risk modification, screening of PVD and thorough intervention for limb salvage. This involves consideration of

various factors at different stages, as follows.

Early diagnosis

Some patients with CLI lack symptoms of IC before the onset of CLI. Shirasu et al. (2015) found that patients without IC before CLI onset have several unique features, and non-IC is an independent risk factor for poor outcome.²⁾ In diabetic patients who lost their leg, more than 50% of patients were found to be asymptomatic 6 months before amputation.³⁾ In diabetic patients, symptoms cannot always be an alert to disease progress because many factors disrupt early detection. This presents a challenge to clinicians who are seeking early detection of CLI. In response to this, "TAKII* footscan," an institutional screening system of leg disease was developed. This is a system of early detection of foot lesion by the attending nurse in all hospitalised patients (**Fig. 1**). To date, 125 patients had been reported in this system during 22 months; 32% were newly discovered and in 8% the lesions were known but not yet be appropriately assessed. Overall, 40% of patients benefit from this system.

*TAKII: The hospital location.

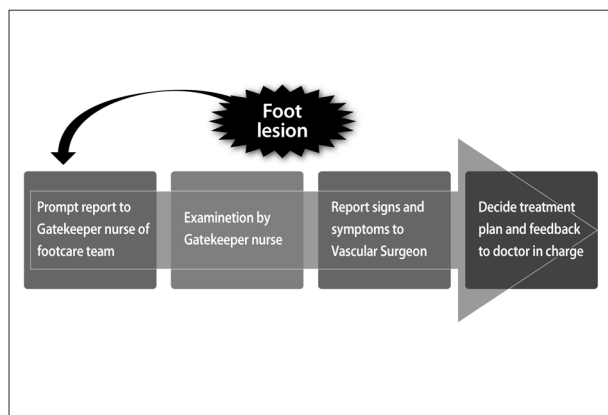


Fig. 1 The TAKII footscan – a system of early detection of foot lesion by attending nurse in all hospitalized patients.

The need for a similar early detection system in the community led to the "KITAKAWACHI** footscan," a community based footcare consulting system. Community clinics and hospitals can easily gain access to the footcare team via e-mail at nurse level. At this point the patient can be referred for consultation with a specialist. This community-based early detection and treatment system for leg lesions is currently working well.

**KITAKAWACHI: The region where the hospital is located.

Screening of PVD

The risk of mortality is similar in symptomatic and asymptomatic patients with PAD but is significantly higher than those without PAD.⁴⁾ ABI is a simple and useful marker of PAD and thought to be a good tool of early detection. When ABI and 1-year cardiovascular event rates are compared, the lower the ABI the more cardiovascular events occur. It is interesting to note that while patients with ABI from 0.91 to 1.00 are thought to be normal, the hazard ratio is already raised to nearly 1.8 compared to the reference range of 1.11 to 1.20.⁵⁾ The recently revised ACCF/AHA

guidelines state that an ABI of ≤ 0.9 is abnormal and borderline abnormal is now 0.9 to 0.99.⁶⁾

Cardiovascular event rate increases markedly with the occurrence of PAD in both CAD and cerebrovascular disease.⁴⁾ This is because atherosclerosis is a whole-body disease. The REACH registry revealed a PVD rate of around 20% in patients with CAD or cerebrovascular disease; the rate of PVD in PAD patients was 43%, suggesting that PAD is the most severe atherosclerotic disease.⁷⁾ A new early detection programme was trialled in an out-patient clinic based on the Japanese guidelines for prevention of atherosclerotic cardiovascular diseases (**Table 1**). If a patient has ≥ 3 or more risk factors for atherosclerosis this programme can be applied if the patient consents.

Table 1 Early detection programme for detection of PVD

Physical examination	Physiological function test
Leg pulsation	ECG
Carotid bruit	ABI
Blood pressure	Echocardiogram (on demand)
Extended test	Radiological test (on demand)
Urine albumin	Head and neck MRA
LDL cholesterol	Thoracoabdominal CT
Triglyceride	
Blood sugar	

The early detection programme reveals a new lesion in 55% of patients. These patients were all referred to the hospital from their family doctors for assessment of PAD, so they have already been checked and screened, suggesting the programme works well for patients.

Unfortunately, preventive therapies for PAD patients are still neglected; 61% of patients with PAD and an ABI < 0.9 do not take anti-platelet drugs. In patients with ABI < 0.9 without heart disease, this rises to 73%.⁸⁾ Treatment with multiple therapies is associated with reduced all-cause mortality, and yet many patients do not receive this intervention.

Thorough intervention for limb salvage

Advances in endovascular interventions have expanded the options available for the invasive treatment of lower extremity PAD. Endovascular interventions are now performed much more commonly than bypass surgery in the treatment of lower extremity PAD. This has resulted in $> 25\%$ reduction in major lower extremity amputation rates.⁹⁾ Patients with asymptomatic PAD appear to have the same increased risk of cardiovascular events and death found in claudicants.¹⁰⁾ The prognosis of asymptomatic PAD patients who have been diagnosed arterial stenosis in leg angiogram was evaluated. Asymptomatic peripheral angiographic stenosis and occlusions were found to become symptomatic in one-third of patients, necessitating treatment in 13.9%. With appropriate treatment, only 2.5% of patients lost their leg, but 16.4% died. These data suggest that asymptomatic patients should probably receive prevention for PVD rather than invasive therapy for stenosis.¹¹⁾

In 2013 the Japanese Society for Vascular Surgery (JSVS) performed a national survey of "inappropriate treatment for PAD" and revealed 12 amputations in claudicants, 5 amputations in asymptomatic patients and one death due to complications after

inappropriately indicated angioplasty.¹²⁾ Although these numbers are very small among the many angioplasty patients, we must strive for zero adverse outcomes.

Japanese surgeons perform bypass and angioplasty and both procedures are increasingly used in parallel with increasing rates of reconstruction of crural and foot arteries. As a part of the national clinical database (NCD), the Japan critical limb ischemia database (JCLIMB) has been operational since 2013. CLI patients are registered and followed for 5 years at 107 participating institutes. Data show that 1,213 limbs were treated by surgeons in 2013, including 219 below the knee endovascular treatment and 384 distal bypass procedures. The early mortality and morbidity data are both acceptable in both procedures and mid- and long term results are awaited.

CLI patients are very frail and sick and so angioplasty tends to be performed as a first-line treatment, with re-stenosis occurring in about 70% of below-knee lesions in 3 months. Therefore, endovascular therapy for below-knee lesion might be limited in CLI. Regarding distal bypass, it is possible to place a vein graft to paramalleolar or inframalleolar tibial arteries. The procedure is more invasive but durability and healing time of the tissue loss is reported to be advantageous.

Results of paramalleolar distal bypass for CLI in patients with PAD were reviewed to determine factors affecting the long-term patency of this procedure in Japanese subjects. A total of 65 legs from 60 consecutive patients with CLI who underwent distal bypass to the ankle were retrospectively reviewed. The accumulated primary and secondary patency rates were both 81.0% at 1 year and 78.7% at 3 and 5 years. The amputation-free rates and survival rates at 1 year, and 3 and 5 years were 94.5% and 82.6%, 82.6% and 88.1%, 76.7% and 69.7%. These findings illustrate that distal bypass to the paramalleolar tibial artery is an effective strategy for PAD with reasonable long-term reliability. Diabetes and old age were found to be the possible determinant factors of graft failure in Japanese patients.¹³⁾

Several options are available in the treatment of PAD. Conservative therapy, endovascular therapy and surgical bypass. However, to use only one therapy, or to use a favorite therapy, is the wrong approach. It is essential to treat with patient-orientated way with an individualized approach with the goal to save legs with ulcer or necrosis and to save lives by salvaging CLI legs or by appropriate medical therapy to the claudicants. Finally, it is critical to improve patients' HRQoL by increasing their walking distance and improving their exercise tolerance. Achieving these goals involves accurate knowledge or evidence of PAD and enthusiasm for salvaging legs by all means necessary. Together with patients, the vascular surgeon should continue treatment even if amputation is ultimately required.

Discussion points

- Total Footcare is an increasingly important approach to ensure optimal outcomes for patients. This approach is exemplified by the "Green Ivy" program in Japan. An ivy leaf looks like heart. A vine of the ivy looks like artery. The green color signifies youthfulness and hope. An endocrinologist-led foot care program is also available in hospitals in Thailand.
- For patients who cannot be revascularized, we will try a different approach instead, most likely involving hyperbaric therapy or pharmacotherapy.

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Closing remarks

Dr. In Sung Moon closed the 8th PAD Workshop by summarising the key points of each international expert and thanking the organisers and participants. Delegates attended from across Asia, notably from China, Indonesia, Korea, Thailand and Japan.