Asian PAD Workshop is successful series of medical education events sponsored by Astellas Pharma Inc. and Toray Industries, Inc. focused on the importance of early diagnosis and treatment of peripheral artery disease (PAD) in patients with diabetes. PAD has been progressively and sharply increasing in Asian countries. Risk factors for the onset of PAD include aging, dyslipidemia, and smoking but diabetes mellitus is the most critical factor. Unfortunately, the proportion of diabetic patients amongst PAD patients grows annually. This increase of diabetic prevalence clearly contributes to the rise in the incidence of PAD and patients typically have more than 10 years of diabetic history before the onset of PAD. This means, in turn, that timely diagnosis and treatment provision is feasible at an early stage of disease. Moreover, diabetes-induced vascular failures can cause PAD but the disease can also develop vaso-occlusive changes to cerebral vasculature and coronary arteries at high incidence. PAD diagnosis can therefore serve as a crucial “window” for other early stage diagnoses of possible cardiac and cerebral pathogenesis. The faculty of leading experts in the field of diabetes provided in-depth discussions on early-stage diagnostic approaches and primary drug therapies such as beraprost sodium for PAD patients with intercurrent diabetes mellitus. The workshop also featured Professor William Hiatt, one of the foremost experts in PAD diagnosis and treatment and a chief editor of the development of TASC, the world’s most recognized diagnostic guideline on PAD. He reviewed current medical strategies for treating PAD patients. This workshop builds on the success of the previous Asian PAD Workshops (Jeju, 2009; Osaka, 2010; Gyeongju, 2011) in helping to establish the importance of early intervention and individualised therapy to achieve the best patient outcomes possible.

The 5-year survival rate of PAD is poor compared to that in patients with malignant tumors such as breast cancer, colon cancer and malignant lymphoma in Japan. Most reports show a 5-year survival rate of 60-70% in PAD, while breast cancer is 85%, colon cancer 68% and malignant lymphoma 48%.

A recent prospective cohort study assessed the mortality and vascular morbidity risk of elderly individuals with asymptomatic vs symptomatic PAD in the primary care setting in 6,880 representative unselected patients over 65 years of age. According to physicians’ diagnosis, 5,392 patients had no PAD, 836 had asymptomatic PAD and 593 had symptomatic PAD. Compared with patients without PAD, those with asymptomatic PAD or symptomatic PAD had a significantly lower rate of event-free survival, with a significant difference between the two PAD groups (Fig. 1). The risk of symptomatic compared with asymptomatic PAD patients was significantly increased for the composite

### Day 1

Co-chairs:
Dr Bo Yang Suh, Professor, Vascular Surgery, Yeungnam University Hospital, Daegu, Korea
Dr Xiao-Ming Zhang, Professor, Vascular Surgery, Peking University People’s Hospital, Beijing, China

#### Importance of early diagnosis and treatment of PAD in patients with diabetes

Dr Hiroshi Shigematsu
Professor of Vascular Surgery, Director, Sanno Medical Center, International University of Health and Welfare, Tokyo, Japan

The 5-year survival rate of PAD is poor compared to that in patients with malignant tumors such as breast cancer, colon cancer and malignant lymphoma in Japan. Most reports show a 5-year survival rate of 60-70% in PAD, while breast cancer is 85%, colon cancer 68% and malignant lymphoma 48%.

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In this series, no significant differences were observed in all deaths, fatal stroke, CV death, myocardial infarction and stroke for PAD patients over 65 years old. These results therefore show that asymptomatic PAD has the same risk of cardiovascular events as symptomatic PAD (Fig. 2).1,8

Furthermore, the risk of symptomatic compared with asymptomatic PAD patients was significantly increased for the composite
Prevalence and clinical features of PAD in patients with diabetes in Thailand

Dr Swangjit Suraamornkul
Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand

The last two decades has seen a dramatic increase in the number of people with diabetes globally prompting an urgent need for strategies to prevent this emerging global epidemic. According to the International Diabetes Federation, the number of patients of all-cause death or severe vascular event (MI, coronary revascularization, stroke, carotid revascularization, or lower-extremity peripheral vascular events) but not for all-cause death alone, all-cause death/MI/stroke (excluding lower-extremity peripheral vascular events and any revascularizations), cardiovascular events alone, or cerebrovascular events alone.\(^1\)

According to the ACCF/AHA 2011 guidelines for the management of PAD, resting ABI should be used to establish the lower extremity PAD diagnosis in patients with suspected lower extremity PAD, defined as individuals with more than one of the following: exertional leg symptoms, non-healing wounds, age $\geq 65$ years or $\geq 50$ years with a history of smoking or diabetes. ABI results should also be uniformly reported with non-compressible values defined as $>1.40$, normal values $1.00 - 1.40$, borderline $0.91$ to $0.99$ and abnormal $0.90$ or less.\(^2\)

Dr Shigematsu and his group measured ABI for elderly people aged over 70 years or diabetic patients aged 50-69 years with or without a history of smoking.\(^3\) This event was conducted on the Memorial Day to respect the elderly people in Japan. Seven hospitals and universities collaborated for the event and ABI of 2,600 people joined in on just one day. Most participants were elderly adults ($\geq 65$ years). And although they were diabetic patients and/or patients with a smoking history, they were in generally good health. Amongst the 2,300 assessed, 2.8% had a low ABI while 6.2% were borderline. Around 9% of those surveyed were found to have a high risk of PAD (Table 1).

In the low ABI group, there were twice as many males to females, with the risk of PAD increasing with increasing age. These findings emphasize the importance of making an early diagnosis of PAD and of initiating early treatment of PAD in patients with diabetes (Table 2).

**REFERENCES**

suffering from diabetes worldwide will increase from 189 million in 2003 to 324 million by 2025 (Fig. 1).1)

In Thailand, the prevalence of diabetes weighted to the national 2004 population was 6.7% (6% of men and 7.4% of women). Diabetes was more common in urban than in rural men but otherwise prevalence was relatively uniform across geographical regions. In more than half of those suffering with diabetes, the disease had not been previously diagnosed.2)

Heart disease and stroke are the leading causes of death in patients with type 2 diabetes mellitus (T2DM). Such patients are also at risk for neuropathy and vascular injuries that occur as part of the diabetic disease process.3) As many as 70% of the world amputations are related to diabetes and more than half of which could have been prevented by earlier diagnosis and intervention. This is important because the mortality rate after lower extremity amputation ranges from 39% to 68%. After an amputation, the chance of another amputation of the same extremity or of the opposite extremity within 5 years is as high as 50%.

PAD is a complication of diabetes that occurs when the blood vessels in the legs become blocked or narrowed due to fat deposits.4) PAD in T2DM patients shows a much higher prevalence compared with those without diabetes.5–8) Of concern, PAD in these patients:

• manifests earlier9)
• has a different localization, mainly affecting the distal arteries10, 11)
• is an accelerated form of the disease12)
• prevalence of PAD in both genders is equally high13)
• is responsible for the vast majority of non-traumatic lower-limb amputations14, 15) - the risk for amputation is 4 times higher in patients with PAD and concomitant T2DM16)

The following studies help to explain and illustrate the problem we face. The prevalence of PAD in a middle-class, urban Thai population was assessed in a cross-sectional study conducted at the Electric Generating Authority of Thailand’s head plant (EGAT), Nonthaburi, in 2002 and 2003. The overall prevalence of PAD was 5.2%; the age-standardized prevalence of PAD was 4% in men and 9% in women. Multiple logistic regression analyses found hypertension, female gender, current smoking, current alcohol drinking, and overweight to be significant predictors of PAD.17)

In the Thailand Diabetes Registry Project (n=9,284), diabetic duration was independently associated with increased risk of having diabetes-related complications. Patients who had diabetes for longer than 15 years (long-DM group) was older than the short-DM group (had diabetes for <15 years), and had higher HbA1c (8.5 vs 8%). The prevalence of diabetic complications in the long-DM group was higher than that in the short-DM group:

• Diabetic neuropathy: 49.4% vs 33.9%;
• Diabetic retinopathy: 54.3% vs 22.8%;
• Myocardial infarction (MI): 9.4% vs 3.5%;
• PAD: 17.3% vs 5.5%;
• Foot ulcer: 13.4% vs 5.3%;
• Stroke: 9.4% vs 7%;
• Amputation: 5.5% vs 2%.

The duration of diabetes significantly affected the risk of diabetic complications after adjustment for age, hypertension, and levels of glycemic control.18)

The international PAD-SEARCH study confirmed PAD as a common complication in Asian T2DM patients. A total of 6,625 T2DM patients aged ≥50 were enrolled from across Korea, China, Taiwan, Hong Kong, Indonesia, Thailand and the Philippines. Patients’ ABI and brachial-ankle pulse wave velocity (baPWV) were determined and 1,172 (17.7%) subjects were diagnosed as PAD by ABI. PAD subjects had a significantly longer duration of diabetes, hypertension, higher HbA1c, and a significantly lower mean body mass index (BMI) than non-PAD subjects. In terms of lipid profiles, triglyceride was the only significant variable. Notably, mean ABI and baPWV in females were significantly poorer than age matched males in subjects with a normal ABI. However, mean ABI and baPWV in males were significantly poorer than in age matched females in subjects with PAD.19)

Reflecting the need for early diagnosis and intervention, the American Diabetes Association (ADA) recommends screening for PAD patients with diabetes (Table 1).20)

Foot care is also important in diabetic patients as PAD is a major contributor to debilitating diabetic foot problems.21) Common foot problems include loss of feeling, changes in the shape of feet, infection, ulceration, or gangrene that may lead, in severe cases, to

| Table 1 ADA screening recommendations for PAD patients with diabetes²⁰ |
|---------------------------------|---------------------------------|
| **Those >50 years of age**      | **Those <50 years of age who have** |
| • If normal, an exercise test should be carried out | other risk factors associated with PAD: |
| • The ABI test should be repeated every 5 years | • Smoking |
|                                 | • Hypertension |
|                                 | • Hyperlipidemia |
|                                 | • Duration of diabetes >10 years |
amputation of a toe, foot or leg. Prevention of foot problems may be easier than treating them. Overall, these findings illustrate the need for early diagnosis and intervention.

REFERENCES


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**Effects of beraprost sodium in patients with type 2 diabetes complicated by peripheral vascular disease**

Dr Richard Elwyn V. Fernando
St. Luke’s Medical Center QC, Quezon City, Philippines

**Diabetes and PAD in the Philippines**

The Philippines is a country that loves to cook and eat. This trait itself carries a high risk for the development of T2DM. A 9-year cohort study entitled “The Philippine Cardiovascular Outcome Study” showed a diabetes incidence of 16.3%. From a population of nearly 100 million, a prevalence of 28% was computed, with a third of the population being pre-diabetic. In 2009, approximately 4 million Filipinos were diagnosed with diabetes, with 500 cases diagnosed daily. It is thought that by 2025 up to 8 million will be affected. In the Philippines, T2DM is currently the leading cause of adult blindness, kidney failure and non-traumatic limb loss. Furthermore, it is thought that 5% of 9 million Filipinos aged ≥40 have PAD based on ABI; 11% of those aged ≥70 years have PAD by ABI. Of concern, only 0.4% are aware that they have PAD. This likely reflects the fact that while PAD prevalence increases with age, older patients are usually asymptomatic.

**Prostaglandins in diabetes**

Prostaglandins are like hormones in that they act as chemical messengers, but they do not move to other sites, instead working right within the cells where they are synthesized. Prostaglandins exist in almost all organs, tissues, and cells in the body. Prostacyclin (or PGL) is produced in blood vessels, bronchi, kidneys, lungs, etc. The production of PGL is decreased in disease conditions, including diabetes, and exerts a strong inhibitory action on platelet aggregation and gastric secretion. In addition, PGI is a potent vasodilator that may decrease blood pressure. However, while it has a number of beneficial effects, it is chemically unstable, with a very short plasma half-life.
Beraprost in PAD

Beraprost is a stable, orally active PGI₂ analogue with vasodilatory, antiplatelet, antiproliferative and cytoprotective effects. Beraprost acts by binding to prostacyclin membrane receptors, ultimately inhibiting the release of calcium from intracellular storage sites. This relaxes the smooth muscle cells and cause vasodilation. In early clinical studies, beraprost was demonstrated to be generally well tolerated and efficacious in the treatment of patients with PAD. Patients receiving beraprost exhibited reduction of ulcer size, reported improvement of granulation appearance of the tissue and showed improvement of pain at rest and sensation of cold in the extremities.²

Based on the findings of a double-blind, randomised, multicenter controlled trial, Lievre et al. (2000) reported that oral beraprost was effective in the symptomatic treatment of patients (n=549) with intermittent claudication. Pain-free walking distances increased by 81.5% and 52.5%, respectively, in the beraprost and placebo groups and maximum walking distances by 60.1% and 35%, respectively.³

Toyota & Oikawa (2002) documented the effects of beraprost sodium on ankle pressure index (API), subjective symptoms, and intermittent claudication in diabetic patients (n=40) with arteriosclerosis obliterans (ASO). Beraprost sodium was shown to improve API and symptoms in the lower extremities in diabetic patients with ASO. At 3 and 6 months, API had significantly increased and symptoms such as coldness, numbness, and lack of feeling in the lower extremities were significantly improved. Ten evaluable patients increased ambulatory distance by approximately threefold, suggesting an improvement in intermittent claudication.⁴

It has also been reported that PGI₂ has pleiotropic effects that are anti-inflammatory and anti-atherogenic. With this in mind, Moriya et al. (2010) studied the effect of beraprost in haemodialysis patients with the aim of investigating the relationship between PGI₂ and renal anemia. The findings of this study may have a bearing on clinical management as many diabetic patients with PAD also have renal anaemia.⁵

The mechanism behind the beneficial effects of beraprost has partially been elucidated by in a series of preclinical studies. For example, Niwano et al. (2003) reported that treatment of mouse aorta and cultured human and bovine aortic endothelial cells with beraprost sodium increased endothelial nitric oxide synthase (eNOS) expression and nitric oxide production. Beraprost increases the stability of eNOS mRNA and increased the promoter activity of the human eNOS gene, possibly leading to improved vasodilation.⁶ Meanwhile, Li et al. (2001) found that beraprost inhibits neointimal formation after balloon injury in the canine coronary artery through its inhibitory effect on smooth muscle cell proliferation by preventing p27kip1 down-regulation.⁷ Beraprost inhibited p27kip1 down-regulation through cAMP signalling.

Finally, the following before and after treatment images are based on the clinical work of Dr Roman Oabel, who has used beraprost sodium in the majority of his patients at 120 µg in three divided daily dose (Fig. 1). These images provide compelling visual evidence of the clinical benefits of beraprost sodium treatment in patients with PAD and intercurrent T2DM.

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The effect of oral beraprost sodium on microvascular dysfunction in high-risk diabetic patients

Dr Donghoon Choi
Professor, Division of Cardiology, Yonsei Cardiovascular Center, Yonsei University College of Medicine, Seoul, Korea

Consider the following typical case of a diabetic patient with PAD. A male patient, aged 51 years, was admitted with substantial ulceration and resting pain of the left foot (Fig. 1). The patients had a long history of diabetes, and was currently being treated with insulin. He also had a history of coronary artery disease (CAD class IVD) and had an ST-segment elevation myocardial infarction 7 years ago. He also had end-stage renal disease due to diabetes-related nephropathy and had been on hemodialysis. So this patient had multiple risk factors for atherosclerosis and diabetes.

If this was your patient, which of the following tests does he need?

1. Pseudoexfoliation
2. ABI
3. CT angiography
4. MR angiography
5. Angiography

An ABI was taken first but the patient had heavily calcified peripheral arteries and so the ABI did not indicate the severity of his disease. The results of the pulse volume recording (PVR) and CT lower extremities angiography show the extent of arterial calcification (Fig. 2), however CT angiography did not show any meaningful results.

In your opinion, which treatment does this patient need? Should we consult orthopedics for amputation? Perhaps use antibiotics and more adequately control his blood sugar level? Or maybe do the peripheral angioplasty and wait for the wound to heal while the patient receives antiplatelet treatment? We decided to go ahead with peripheral angioplasty as this gave the best chance for long-term success in this case. The images in Fig. 3 show the progressive improvement in the condition of the patient’s foot following the successful balloon angioplasty procedure of the totally occluded anterior tibial artery.

But the important question was then, what should we do after successful angioplasty? The primary goals of PAD management are to reduce ischemic pain and disability, to prevent progression of local disease, and to reduce the risk of ischemic events in other vascular beds that may lead to MI, stroke, or vascular death (Table 1). To reduce the ischemic events, such patients should receive counseling and treatment for the control of all cardiovascular risk factors (e.g., diabetes, hyperlipidemia, and hypertension). Regarding the symptomatic treatment of PAD, a number of studies have shown that exercise improves pain-free walking distance in patients with intermittent claudication. Possible explanations for the benefits of exercise include increased blood fluidity and enhanced oxidative capacity of muscle cells, thereby increasing the efficiency of oxygen metabolism. The benefits of exercise are sustained only for the duration of the exercise regimen. Continued cigarette smoking is associated with worsened cardiovascular outcome, thus all patients with intermittent claudication should be urged to quit smoking. Antiplatelet therapy has been shown to reduce the risk of vascular ischemic events (MI, stroke and vascular death) in this population and the risk of death and disability from stroke and MI merits the use of these agents. Several trials suggest it may improve walking distance in PAD patients; however, six trials could not demonstrate consistent benefit. Surgical revascularization or angioplasty procedures may be indicated for patients with limb threatening ischemia or those who are disabled due to functional ischemia.

However, all patients with PAD should undergo risk-factor modification to achieve the desired levels of cholesterol, blood pressure, and plasma glucose control. Smoking cessation has been shown to slow the progression of PAD to critical limb ischemia (CLI) and reduce the risk of MI and death from vascular causes. Lowering cholesterol levels in patients with CAD may also produce benefits in patients with PAD. Intensive control of blood glucose levels prevents the microvascular complications of diabetes and should be adhered to by patients with PAD. Blood pressure reduction is also very important in this high-risk group of patients and aggressive treatment of hypertension is warranted. In addition to lowering blood pressure, angiotensin converting enzyme inhibitors

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Table 1: The effect of oral beraprost sodium on the condition of diabetic patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>Result</th>
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<tbody>
<tr>
<td>Severe ulceration</td>
<td>Improved</td>
</tr>
<tr>
<td>Pain-free walking distance</td>
<td>Increased</td>
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<tr>
<td>Pain perception</td>
<td>Reduced</td>
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Fig. 1 Severe ulceration of the patient’s left foot
may confer additional protection against cardiovascular events independent of blood pressure lowering and can reduce renal complications in patients with T2DM. In the general population, blood pressure of 120/80 mmHg is optimal; this is, however, almost unachievable by antihypertensive treatment in regular clinical practice. Antiplatelet therapy has been shown to reduce the risk of vascular ischemic events in this population.4)

Beraprost plays an important role in the symptomatic treatment of PAD and endothelial dysfunction. Beraprost can improve both functioning and reduce pain. In a large pivotal trial study in patients (n=549) with intermittent claudication, pain-free walking distances increased by 81.5% with beraprost and 52.5% in the placebo group (p=0.001) and maximum walking distances by 60.1% and 35.0%, respectively (p=0.004).5)

A placebo-controlled, double-blind, randomized trial was designed with the overall aim of assessing the efficacy of beraprost in painful diabetic neuropathy (DPN) in patients with T2DM.6) A total of 99 T2DM patients (41% male, age 60 ± 6 years) with DPN were randomized to receive either beraprost sodium (40 µg, t.i.d.) or placebo for 8 weeks. The intensity and frequency of symptoms were recorded as a subjective index at the beginning and end of the study. The primary endpoint was the improvement of the total pain score above baseline. Result will be reported at a future meeting.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The two complementary objectives for PAD management</th>
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<tbody>
<tr>
<td>Risk reduction of ischemic events</td>
<td>Symptomatic treatment</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Exercise&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Smoking cessation&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Pharmacologic therapy</td>
</tr>
<tr>
<td>Antiplatelet therapy&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Selective use of interventional therapy&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
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</table>
It is also increasingly apparent that the approaches to target the molecules expressed in vascular are important for preventing the atherosclerosis in T2DM. It is therefore useful to note that beraprost sodium lowered circulating vascular cell adhesion molecule-1 (VCAM-1) concentration and prevented the progression of carotid atherosclerosis in T2DM patients. This was probably through inhibiting VCAM-1 expression in vascular endothelium.\(^7\)

To conclude, beraprost sodium is a valuable option to improve symptoms by controlling pain and improving blood flow. Beraprost has important antiplatelet, antithrombotic, vasodilating and cytoprotective effects that can help improve a variety of debilitating symptoms.

**REFERENCES**


**Importance of early diagnosis and treatment for PAD in patients with diabetes**

Dr Toyoshi Inoguchi  
Professor, Innovation Center for Medical Redox Navigation, Kyushu University, Fukuoka, Japan

The prevalence of PAD was examined in Japanese diabetic patients using ABI.\(^1\) Outpatients with diabetes (n=4,249) who were regularly visiting Kyushu University Hospital, and its 17 related hospitals, Ryukyu University Hospital and its 6 related hospitals were enrolled in the Kyushu Prevention Study for Atherosclerosis from 2001 to 2003. Valid information was available for 3,906 diabetic patients (mean age: 60.8 years) including 1,612 elderly patients (>65 years). Patient characteristics are shown in Table 1.

Patients with a low ABI (<0.9) on either side or on both sides were considered to have PAD. The prevalence of PAD patients with ABI <0.9 was 7.6% in all diabetic subjects (Fig. 1).

It is useful to note that elderly patients (>65 years) had a higher prevalence of PAD (12.7%, Fig. 2) compared with younger patients (<65 years) (4.0%).

In addition, the rate of patients who had been diagnosed accurately as having PAD before enrollment was low (24.4%) (Fig. 3). Treatment with any anticoagulant or platelet inhibitor because of any atherosclerotic diseases including PAD, CAD and cerebrovascular accident (CVA; a stroke) were also low (45.1%) in low ABI subjects. The prevalence of PAD was high in Japanese patients with diabetes, especially in elderly patients, in contrast to the observed low rates of accurate diagnosis.\(^1\)

During the follow-up period, 54 patients (15.8%) with low ABI had died and ABIs of 8.6% of 151 survivors had deteriorated. However, in ABI >0.9 subjects, 211 (5.8%) patients had died and...
ABIs of 11% of 1,786 survivors had deteriorated (Fig. 4).

It is important to note that the definitions of normal and abnormal ABI values have been modified based on the publication of results of the ABI Collaboration. This includes a normal ABI range of 1.00 to 1.40, and abnormal values continue to be defined as those ≤0.90. ABI values of 0.91 to 0.99 are considered “borderline” and values >1.40 indicate non-compressible arteries.2)

The cause of death amongst patients with PAD and T2DM has also been investigated and the distribution of cause of death was quite similar to that of general population in Japan. Low ABI was found to be a strong mortality risk. Interestingly, the rate of infectious disease was increased in low ABI group. In contrast, the rate of cardiovascular deaths was remarkably increased in high PWV group.

The beneficial effects of beraprost on PAD symptoms (coldness of limbs and numbness) were demonstrated in a Japanese Beraprost Sodium Study Group trial.3) The study included 40 PAD patients with concurrent diabetes mellitus (25 males and 15 females with a mean age of 63.9 years; according to the Fontaine classification, n=30 were in stage I, 7 in stage II, 1 in stage III and 2 in stage IV). Patients received beraprost 120μg/day consecutively for six months. The subjective symptoms were classified into stages on questionnaire basis. At 3 and 6 months, significant improvements were seen in coldness of limbs after one month and numbness after three months, demonstrating the enhanced improvement in the severity over time (Fig. 5). In addition, 10 evaluable patients increased ambulatory distance by approximately three-fold, suggesting an improvement in intermittent claudication.

An interesting meta-analysis of two placebo-controlled randomized trials (a US trial and the Beraprost et Claudication Intermittente [BERCI] Research Group study) evaluated the effect of beraprost sodium on the vascular events occurring in PAD patients. Each study was a comparative trial of beraprost (40 μg t.i.d.) and placebo (t.i.d.), with a six-month follow-up period. The combined analysis included 594 patients in the beraprost group and 590 in the placebo group. Data also demonstrated a 39% reduction for exacerbation of leg symptoms and cardio/cerebrovascular events with beraprost vs placebo(Fig. 6).4) A similar result was also obtained for cardio/cerebrovascular events.
A recent animal study demonstrated that insulin signaling in vascular endothelium greatly contributes to insulin sensitivity in peripheral skeletal muscles, and therefore to the pathogenesis of microangiopathy and macroangiopathy. Kubota et al. (2011) reported that reduced function of vascular endothelium results in reduced insulin sensitivity. Impaired insulin signaling in endothelial cells, due to reduced insulin receptor substrate 2 expression and insulin-induced phosphorylation of endothelial nitric oxide synthase, caused attenuation of insulin-induced capillary recruitment and insulin delivery, which in turn reduced glucose uptake by skeletal muscle (Fig. 7). The restoration of insulin-induced phosphorylation of endothelial nitric oxide synthase in endothelial cells also completely reversed the reduction in capillary recruitment and insulin delivery. Beraprost ameliorated the permeability of skeletal capillaries and improved insulin transfer into skeletal muscles. These studies showed that beraprost not only improves ischemic extremities through its vasodilatory properties, but also reduces insulin resistance which affects vascular endothelium. The findings suggest that beraprost may contribute to an overall systemic vascular protective action.

In summary, Japanese patients with diabetes had a higher prevalence of PAD, especially in elderly patients. The rates of accurate diagnosis for PAD before the enrollment in this study was only 24.4%, demonstrating the problem of under-diagnosis of PAD in Japanese diabetic patients. PAD patients with diabetes have a high mortality and borderline PAD has a higher mortality. The evidence suggests that treatment with platelet inhibitors or anti-thrombotic agents may be effective for preventing the deterioration of PAD. In diabetic patients, screening by ABI measurement is therefore needed for early diagnosis for PAD and then early and intensive treatments may improve quality of life and the life prognosis. Based on the insights from Kubota et al. (2011), it is anticipated that, by improving insulin resistance via increased insulin delivery, beraprost sodium may prove to be a valuable therapeutic option in the overall management of PAD with T2DM.

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These rates reflected a statistically significant relative-risk reduction of 8.7% in favor of clopidogrel. Corresponding on-treatment analysis yielded a relative-risk reduction of 9.4%.13) Current guidelines recommend antiplatelet therapy in patients with PAD. Given that the majority of patients with PAD also have concomitant symptomatic CAD or cerebrovascular disease, aspirin is an acceptable antiplatelet in this setting. Clopidogrel monotherapy is also a reasonable alternative treatment strategy.11)

Therapies for symptomatic improvement

Exercise therapy has also been shown to be effective for the treatment of claudication. Patients who underwent 3-5 supervised sessions per week for 35-50 minutes of exercise per session for up to 6 months resulted in 100%-150% improvement in maximal walking distance and improved quality of life.14) In the CLaudication: Exercise Versus Endoluminal Revascularization (CLEVER) study, 111 patients with aortoiliac PAD were randomly assigned to receive 1 of 3 treatments: optimal medical care (OMC), OMC plus supervised exercise (SE), or OMC plus stent revascularization (ST). All participants received cilostazol 100 mg b.i.d. (a phosphodiesterase type 3 inhibitor). At the 6-month follow-up, the change in peak walking time (the primary end point) was greatest for SE, intermediate for ST, and least with OMC (Fig. 2). Although disease-specific quality of life as assessed by the Walking Impairment Questionnaire and Peripheral Artery Questionnaire also improved with both SE and ST compared with OMC, for most scales, the extent of improvement was greater with ST than SE. Free-living step activity increased more with ST than with either SE or OMC alone, but these differences were not statistically significant.15)

Cilostazol has been licensed for the treatment of intermittent claudication in the United States since 1999. Meta-analysis results of data pooled from nine randomized, controlled trials are shown in Fig. 3 and reveal that treatment with cilostazol achieved benefits in walking distance that are sustained at 24 weeks and observed...
irrespective of patients’ baseline clinical characteristics.\textsuperscript{16})

It is essential to note that many of the drugs we may consider for our patients have insufficient evidence of clinical utility in treating claudication. These include:\textsuperscript{9)}

- Pentoxifylline
- Antiplatelet drugs (aspirin, clopidogrel)
- Vasodilators
- L-Arginine
- ACAT (acyl coenzyme A-cholesterol acyltransferase) inhibitors
- 5-HT antagonists (ketanserine, AT-1015, sarpgorelrate)
- Prostaglandins: iloprost, beraprost
- Buflomedil, defibrotide
- Others (e.g., chelation, omega-3 fatty acids, ginkgo biloba)

Beraprost is a PGI\textsubscript{2} analogue with some unique pharmacological properties that is widely used in Asian countries including Japan, Korea and China for the treatment of PAD. Beraprost has demonstrated positive results in clinical trials conducted in Europe and China for the endpoint of claudication, although not in the US trial (Table 1). Suggestive evidence exists for beraprost to reduce cardiovascular events risk in the PAD population based on trials conducted in Europe and the US (Table 1). In two studies, these events were prospective adjudicated. It is worth considering that the beraprost meta-analysis demonstrated a 39\% reduction in adverse vascular events compared with placebo. This was a combined analysis of two trials and included 594 patients treated with beraprost compared with 590 in the placebo group. The risk ratio for all vascular events was 0.608 (95\% CI: 0.41 to 0.90, p=0.012), demonstrating the efficacy of beraprost.\textsuperscript{17)}

Given that PAD is a manifestation of atherosclerosis, antiplatelet therapy should be a critical component of any PAD treatment plan. It should also be noted that while there is suggestive evidence for beraprost to reduce risk in the PAD population, no formal cardiovascular outcome trials with beraprost have been performed in PAD.

To summarize, while the medical options for claudication are effective, clinical benefits (e.g., effect on maximum walking distance and quality of life) have not been extensively studied or demonstrated. While exercise training in a supervised setting is effective in well selected populations and single-site studies, the overall population benefit and efficacy are not known. The CLEVER comparative effectiveness trial demonstrated exercise better than revascularization. The PDE-3 inhibitor cilostazol is effective.

Eicosanoids with vasodilating and angiogenic properties have been postulated to be effective therapies for critical leg ischemia (CLI) secondary to atherosclerotic PAD.\textsuperscript{18)}

No drug has shown consistent benefit on the primary endpoint of Amputation Free Survival (AFS). While prostaglandins may reduce ischemic pain and heal ischemic ulcers they do not impact

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**Fig. 2** Change in peak walking time in PAD patients

**Fig. 3** Results of the meta analysis of cilostazol studies\textsuperscript{11)}

**Table 1** Randomised controlled trials of beraprost for PAD\textsuperscript{18)}
Agents (e.g., propionyl-L-carnitine) may, however, be beneficial. As a clinical event (heart attack or stroke), aspirin clearly works. Drugs have proven clinical benefit. And regarding surgery, while exercise works in highly selected single-site studies, the long-term compliance and effectiveness of this intervention remain un-known. As a result, we are also going to start a mechanistic study in humans with PAD using muscle biopsy techniques at the site of injection of cells (that are selected for antiangiogenic and anti-inflammatory properties) in patients with less severe disease to see if we can identify which pathways are active. These are exciting and early endeavors but there is a lot yet to be learned about this approach.

The ACC/AHA 2011 Guideline Update has down-graded aspirin from 1A to 1B based on recent trials and meta-analysis. However, cilostazol, remains in a class of 1A recommendation. The forthcoming TASC III will be the most comprehensive guideline for PAD. Endpoints will be re-defined to support a more patient-focused approach, offering consistency across therapeutic strategies. TASC III will be appropriate for regulatory approval, reimbursement and recognized by patients as clinically important. Comparative effectiveness trials are needed to understand overall risks, benefits, costs and long-outcomes.

Which antiplatelet drug should be used in patients with PAD who have diabetes? Regardless of whether the patient has PAD or T2DM, if their primary presentation is coronary disease, manifest as a clinical event (heart attack or stroke), aspirin clearly works. But if we take a step back and ask does aspirin work in everybody, or does it work in patients with just T2DM without any cardiac event, then we can consider three trials that have looked at primary prevention. If we pool all the primary prevention literature, the hazard ratio is around 0.88, which does not give us statistical significance. So the story with aspirin is quite clear, if the patient has heart disease, then from an evidence-based perspective, the patient should take aspirin. But if the patient is high risk for heart disease (PAD, diabetes, etc.), then aspirin alone will not help. In fact, the risk of bleeding with aspirin offsets any potential benefit. So, new trials into more potent anti-platelet therapies may help us to answer the question of how best to approach primary prevention.

Finally, it is useful to briefly consider the current challenges in Claudication therapies. It is important that we appreciate the difference between efficacy and effectiveness. For example, while exercise works in highly selected single-site studies, the long-term compliance and effectiveness of this intervention remain unknown. Furthermore, it is clear that only a limited number of drugs have proven clinical benefit. And regarding surgery, while revascularization works it may lose benefit over time and the actual clinical benefit is not well established. We need to address the lack of comparative effectiveness studies that can adequately guide our decision making to optimize patient outcomes. Recent Claudication drug trials have been disappointing, with lipid modification (modulation of LDL and HDL cholesterol), antibiotic therapy, and also gene therapy shown to be ineffective. Metabolic agents (e.g., propionyl-L-carnitine) may, however, be beneficial.

REFERENCES


DISCUSSION

The discussion that followed the presentations covered several important issues. The prevalence and risk factors for PAD appear to differ slightly in Thailand relative to other countries, with a higher prevalence observed in females. However, no good explanation for this was found in observational studies. The presence of insulin secretory dysfunction in the pathogenesis of diabetes may suggest the potential for additional devastating effects in PAD in patients with diabetes. Possible differences between Western and Asian populations may exist in this regard and such differences may also indicate differences in treatment approaches. Given the various complications of diabetes, it is important to clinically differentiate between atherosclerosis (focus on vascular lumen) and diabetic neuropathy (look for loss of sensation in hands and feet). Also discussed was the need for national registries to monitor the rate of amputations amongst patients with PAD. The relative efficacy of antiplatelet agents and PGI2 analogues in PAD with diabetes is a delicate issue and no head-to-head studies exist. It seems likely, however, that their efficacy is similar and, in some countries such as the Philippines, it is feasible to combine the two classes of agent. It is possible that such combinations are more effective than monotherapies but, again, we do not have the studies to prove this. Following coronary stent in patients with CAD, we should treat with dual antiplatelet therapy, usually aspirin and clopidogrel for one year followed by monotherapy. Dual antiplatelet treatment may continue, for example, if the patient has T2DM or has had multiple stents. Again, data are limited on the optimal regimens for these situations, particularly where patients have intercurrent T2DM and PAD. Options, such as beraprost, that help to reduce pain are also valuable in this setting, as they will help to improve patient functioning. Furthermore, the multiple pharmacodynamic actions of beraprost (i.e., vasodilatory, antiplatelet, antiproliferative and cytoprotective actions) can offer significant advantages over other options, particularly with regard to symptom improvement in patients with PAD and T2DM. Finally, the recent insights into the improvement of insulin resistance via increased insulin delivery, suggests that beraprost sodium may prove to be a valuable therapeutic option in the overall management of PAD with T2DM.

The Chairman closed this highly successful 4th Asian PAD workshop, thanking the expert faculty for providing a highly stimulating and educational program. Thanks were also extended to the many delegates who had travelled from across Asia to gain invaluable insights into the early diagnosis and intervention of PAD, including the multiple benefits of treatment with beraprost.