

Original Article



Medical Resource Consumption and Quality of Life in Peripheral Arterial Disease in Korea: PAD Outcomes (PADO) Research

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Received: Nov 7, 2017

Revised: Mar 28, 2018

Accepted: Apr 10, 2018

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Conflict of Interest

The author has no financial conflicts of interest.

Author Contributions

Conceptualization: Rha SW, Choi SH, Kim DI, Jeon DW, Lee JH, Hong KS, Cha TJ, Cho JH, Lee SK, Park YH, Park WJ, Kim HJ, Kim YJ, Choi D; Formal analysis: Lee J; Writing - original draft: Rha SW, Choi D; Writing - review & editing: Rha SW, Choi SH, Kim DI, Jeon DW, Lee JH, Hong KS, Cha TJ, Cho JH, Lee SK, Park YH, Park WJ, Kim HJ, Kim YJ, Lee J, Choi D.

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ABSTRACT

Background and Objectives: We aimed to investigate the history of medical resource consumption and quality of life (QoL) in peripheral arterial disease (PAD) patients in Korea.

Methods: This was a prospective, multi-center (23 tertiary-hospitals, division of cardiology), non-interventional study. Adult patients (age ≥ 20 years) suffering from PAD for the last 12-month were enrolled in the study if they met with any of following; 1) ankle-brachial index (ABI) ≤ 0.9 , 2) lower-extremity artery stenosis on computed tomography angiography $\geq 50\%$, or 3) peak-systolic-velocity-ratio (PSVR) on ultrasound ≥ 2.0 . Medical chart review was used to assess patient characteristics/treatment patterns while the history of medical resource consumption and QoL data were collected using a patient survey. QoL was measured using EuroQoL-5-dimensions-3-level (EQ-5D-3L) score system, and the factors associated with QoL were analyzed using multiple linear regression analysis.

Results: This study included 1,260 patients (age: 69.8 years, male: 77.0%). The most prevalent comorbidities were hypertension (74.8%), hyperlipidemia (51.0%) and diabetes-mellitus (50.2%). The 94.1% of the patients took pharmacotherapy including aspirin (76.2%), clopidogrel (53.3%), and cilostazol (33.6%). The 12.6% of the patients were receiving smoking cessation education/pharmacotherapy. A considerable number of patients

(500 patients, 40.0%) had visit history to another hospital before diagnosis/treatment at the current hospital, with visits to orthopedic units (50.4%) being the most common. At the time, 29% (or higher) of the patients were already experiencing symptoms of critical limb ischemia. Baseline EQ-5D index and EQ VAS were 0.64 ± 0.24 and 67.49 ± 18.29 . Factors significantly associated with QoL were pharmacotherapy ($B=0.05053$; $p=0.044$) compared to no pharmacotherapy, and Fontaine stage improvement/maintain stage I ($B=0.04448$; $p<0.001$) compared to deterioration/maintain stage II–IV.

Conclusions: Increase in disease awareness for earlier diagnosis and provision of adequate pharmacotherapy is essential to reduce disease burden and improve QoL of Korean PAD patients.

Keywords: Peripheral arterial disease; Disease burden; Quality of life

INTRODUCTION

Peripheral arterial disease (PAD) refers to a set of occlusive vascular diseases that occur in the peripheral arteries, excluding the aorta and coronary arteries.¹ PAD is estimated to affect 3–12% of the total population worldwide,² and known to increase cardiovascular mortality up to 6 times.³

Well-known risk factors for PAD are male gender, age, smoking, diabetes mellitus, hyperlipidemia and hypertension, as similar to that of any other cardiovascular disease.^{4–6}

Pharmacological and behavioral preventive interventions such as smoking cessation therapy, diabetes, lipid control and antihypertensive treatment have proven effective for PAD.² For medical treatment, anti-platelet therapy is especially effective for patients experiencing intermittent claudication (IC) as well as those undergoing bypass surgeries. Among them, aspirin is most widely used since its use has been reported to delay the progression rate of PAD. Clopidogrel is also a commonly used agent, which effectively lowers the risk of cardiovascular-related events in comparison to aspirin (4.9% per year vs. 3.7% per year).⁷ In addition, the use of cilostazol shows improved walking distance and pain-free walking distance in PAD patients.²

PAD is asymptomatic in the early phase,⁸ which makes detection difficult prior to the symptomatic, clinically progressed stages. Symptoms of PAD become aggravated in 10–20% of patients in 5 years and can advance to critical limb ischemia (CLI) in approximately 1–2% of the patients.⁹

Along with clinical prognosis, PAD often leads to impaired patient-perceived outcomes and higher economic burden. Physical functions were the most affected which could significantly affect patients' daily activities and their quality of life (QoL).¹⁰ In one study, the QoL of CLI patients was found to be as low as that of cancer patients.¹¹ Other studies report substantial PAD-related healthcare costs where the average PAD-related expenditures were \$1,653 per patient in 2001.¹² The earlier use of preventive care and outpatient treatments may be more cost-effective by avoiding unnecessary medical resource consumption.¹³

Taking all proven findings into consideration, the treatment for PAD can only be effective if patients are properly diagnosed before marked disease progression.² In other words, it is important to assess attributing factors associated with delayed diagnosis as well as

to understand the current status of treatment and management of PAD. Therefore, this study aimed to examine patient characteristics, treatment patterns including risk factor modifications, patients' medical resource consumption prior to proper diagnosis, as well as QoL and QoL-associated factors in PAD patients in Korea.

METHODS

Study subjects

This was a non-interventional, multi-institutional, prospective, observational study conducted in 23 Cardiology Divisions in nationwide tertiary hospitals in South Korea. The study period was from March 2013 to September 2015. To collect a generalizable data, we estimated the target sample size assuming the standard deviation (SD) of the EQ-5D index in Korean PAD patients to be 0.23.¹⁴⁾ To estimate the EQ-5D index within the confidence interval (CI) of 95%, under maximum error rate of 1.4%, and assuming the follow-up loss rate of 15%, approximately 1,200 patients were needed according to the below equation:

$$n_0 = \frac{Z^2 \sigma^2}{e^2}$$

Z is z-score (1.96, CI of 95%), σ is SD, e is error rate.

Adult patients (age ≥ 20 years) who were diagnosed with PAD within 1 year from the study enrollment were invited to participate and included if they met any of following inclusion criteria at the participating hospitals; 1) ankle-brachial index (ABI) ≤ 0.9 (left and/or right), or 2) lower-extremity artery stenosis on computed tomography angiography $\geq 50\%$, or 3) arterial peak-systolic-velocity-ratio (PSVR) on ultrasound ≥ 2.0 . Patients who were already receiving treatment and those new to treatment were both included in this study. We excluded patients who had serious or unstable medical conditions, or any other patients determined by the treating physicians to be excluded for any other reason. Each participating hospital consecutively enrolled eligible patients during their regular visits to the hospital. Patient enrollment competitively lasted until the complete aggregate of estimated target patients was achieved from all participating hospitals. Patients were informed about the purpose of the study and a written informed consent was obtained prior to study participation. This study was approved by the Institutional Review Board of all participating hospitals.

Data collection

During their regular hospital visit, patients were enrolled if they met all of the inclusion criteria for this study. Data was collected at baseline and at 6-months follow-up within a window period of 4 weeks. If the patient did not visit the hospital for follow-up, the data was collected via a telephonic interview. Patient demographics, clinical characteristics and treatment patterns were collected via medical chart reviews. Clinical characteristics included age, body mass index, gender, left/right ABI, smoking status, comorbidities and treatment history (including diabetes, hyperlipidemia, hypertension, history of percutaneous coronary intervention [PCI], angina pectoris, other vascular comorbidities [carotid, vertebral, subclavian, mesentery, renal, and aorta], and myocardial infarction), HbA1c (%), total cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol and systolic (SBP)/diastolic blood pressure (DBP). The severity of PAD was classified into 4-stages according to

the Fontaine classification; stage I: asymptomatic, stage II: experiencing IC, which was further subdivided into IIa (mild claudication with walking distance greater than 200 m) and IIb (moderate-to-severe claudication with walking distance less than 200 m), stage III: pain at rest, and stage IV: developing ulcerations, ranging from lesions to gangrenes.¹⁵⁾

Treatment pattern data included pharmacotherapy (anti-platelets/others), revascularization, exercise, amputation and risk factor modification (smoking cessation education/ pharmacotherapy, diabetes mellitus pharmacotherapy, lipid-lowering pharmacotherapy, anti-hypertensive pharmacotherapy and diet). QoL and history of medical resource consumption data were collected via a patient survey (retrospective, 1-time survey at baseline). Medical resource consumption data included types of previous healthcare institutions, PAD symptoms at the time of visit, previous diagnoses, previous types of interventions/tests, and previous use of complementary and alternative medicine (CAM).

Quality of life (QoL)

QoL was assessed via the EuroQoL-5 dimensions-3-level (EQ-5D-3L) survey-Korean version. The survey consists of a descriptive system and visual analogue scale (VAS), with higher scores indicating higher QoL. The descriptive system comprises of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems and extreme problems. The scores from the descriptive system can be converted into a single EQ-5D index value by using existing value sets, with a score range of -0.229 – 1.0 .¹⁶⁾ The EQ VAS records the respondent's self-rated health on a vertical scale where the endpoints are labelled 'Best imaginable health state' (score 100) and 'Worst imaginable health state' (score 0).¹⁵⁾

Statistical analysis

Patients' demographic/clinical characteristics, treatment patterns, history of medical resource consumption and QoL were summarized as frequency (n) and percentage (%) for categorical variables and as mean with SD for continuous variables. Change in Fontaine stage and EQ-5D index after 6 months from baseline were assessed using McNemar-Bowker's test and paired t-test, respectively. To examine an association between the aforementioned variables and QoL change, measured by EQ-5D index score, univariable analysis was conducted using Student's t-test, analysis of variance, Pearson's correlation analysis and Kruskal-Wallis test, as appropriate, according to variable characteristics. To identify independent factors associated with QoL change, patients' EQ-5D index and multiple linear regression model was used. In this model, age, gender, comorbidities, and other variables with p value <0.1 from the univariable analysis were included. However, if the variables (PAD risk factor modification, Δ HbA1c, Δ Total cholesterol, Δ LDL cholesterol, Δ Triglyceride, Δ HDL cholesterol, Δ SBP, Δ DBP) had considerable missing values that could affect the generalizability of the study results, they were excluded. All p values obtained from statistical analyses resulted from 2-sided tests, in which the statistical significance level was set at $p < 0.05$. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline patient characteristics

A total of 1,260 patients (mean age: 69.8 years, male: 77.0%) were enrolled in this study. Patients' mean left and right ABIs (mean \pm SD) were 0.85 ± 0.22 and 0.86 ± 0.21 , respectively.

Table 1. Baseline patient characteristics

Variable	Value (n=1,260)
Age (years)	69.76±9.94
BMI (kg/m ²)	23.58±3.34
Sex, male	970 (77.0)
Left ABI (n=697)	0.85±0.22
Right ABI (n=700)	0.86±0.21
HbA1c (n=550)	7.48±1.51
Total cholesterol (n=423)	148.67±38.60
LDL cholesterol (n=388)	80.72±28.75
Triglyceride (n=390)	142.78±94.38
HDL cholesterol (n=389)	43.24±14.65
SBP (mmHg) (n=916)	127.91±16.95
DBP (mmHg) (n=916)	73.45±11.42
Current smoker	312 (24.8)
Comorbidities and treatment history ^{*,†}	1,206 (95.7)
Hypertension	942 (74.8)
Hyperlipidemia	643 (51.0)
Diabetes mellitus	632 (50.2)
History of PCI	541 (42.9)
Angina pectoris	429 (34.1)
Other vascular comorbidities [‡]	271 (21.5)
Myocardial infarction	207 (16.4)
Stroke	175 (13.9)
Heart failure	130 (10.3)
Coronary artery calcification	92 (7.3)
History of CABG	52 (4.1)
Fontaine stage (n=1,208)	
I (asymptomatic)	524 (43.4)
IIa (mild claudication, ≥200 m)	533 (44.1)
IIb (moderate-to-severe claudication, <200 m)	106 (8.8)
III (ischemic rest pain)	23 (1.9)
IV (ulceration or gangrene)	22 (1.8)

Values are presented as mean ± standard deviation or number (%). Current smoker: smoking history within recent 6 months.

ABI = ankle-brachial index; BMI = body mass index; CABG = coronary artery by-pass graft; DBP = diastolic blood pressure; HbA1c = glycated hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PCI = percutaneous coronary intervention; SBP = systolic blood pressure.

*Multiple response item; †Incidence of 3% or less is not shown; ‡Carotid, vertebral, subclavian, mesentery, renal, and aorta (stenosis in aorta, n=117).

Of the total patients, 24.8% were currently smoking. The most prevalent comorbidity was hypertension (74.8%), followed by hyperlipidemia (51.0%) and diabetes mellitus (50.2%). The 42.9% of patients had history of PCI. The baseline Fontaine stages recorded were; 43.4% in stage I (asymptomatic), 44.1% in stage IIa (mild claudication), 8.8% in stage IIb (moderate-severe claudication), 1.9% in stage III (ischemic rest pain), and 1.8% in stage IV (ulceration or gangrene) (**Table 1, Supplementary Table 1**).

History of medical resource consumption

A considerable number of study patients (500 patients, 39.7%) had previously visited another healthcare institution before diagnosis/treatment at the current hospital. Of those, visits to orthopedic divisions in general hospitals (50.4%) were most common, followed by oriental medical clinics (26.8%), and general internal medicine clinics (15.6%). The mean number of types of institutions used were 2, ranging from 1 to 7 per patient (**Figure 1A**).

The most prevalent PAD symptom at the time of these visits was claudication when walking (74.4%), followed by claudication when resting (29.2%), cold hands and feet (13.8%), foot

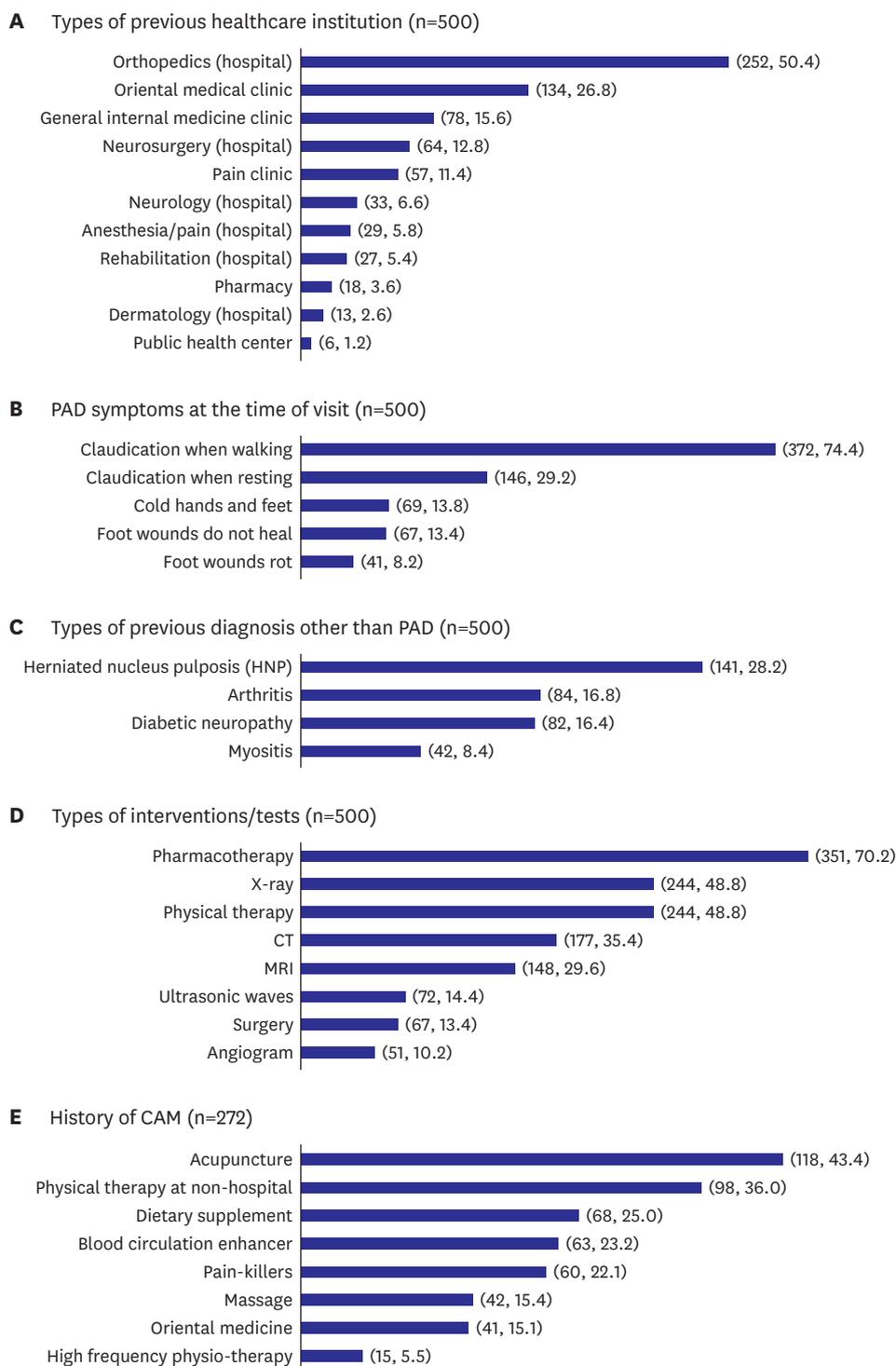


Figure 1. (A) Average number of institutions visited, mean (min, max): 1.52/patient (1, 7). (B) Average number of type of symptoms experienced, mean (min, max): 1.47/patient (1, 5). (C) Average number of diagnosis, mean (min, max): 1.14/patient (1, 3). (D) Average number of interventions/tests, mean (min, max): 2.88/patient (1, 8). (E) Average number of CAMs used, mean (min, max): 1.90/patient (1, 8). Data are presented as number and percentage (%). CAM = complementary and alternative medicine; CT = computerized tomography; MRI = magnetic resonance imaging; PAD = peripheral-arterial disease.

Table 2. Treatment patterns

Variable	Value (n=1,260)
Pharmacotherapy (anti-platelet/others)*,†	1,186 (94.1)
Aspirin	904 (76.2)
Clopidogrel	632 (53.3)
Cilostazol	399 (33.6)
Warfarin	47 (4.0)
Trimetazidine	45 (3.8)
Revascularization	530 (42.1)
Exercise	300 (23.8)
Amputation	49 (3.9)
PAD risk factor modifications*	
Lipid-lowering pharmacotherapy (n=643)	638 (99.2)
Anti-hypertensive pharmacotherapy (n=942)	908 (96.4)
Diabetes mellitus pharmacotherapy (n=632)	606 (95.9)
Diet	256 (20.3)
Smoking cessation education	157 (12.5)
Smoking cessation pharmacotherapy (n=312)	2 (0.6)

Values are presented as number (%).

PAD = peripheral-arterial disease.

*Multiple response item; †Incidence of 3% or less is not shown.

wounds that do not heal (13.4%) and foot wounds that rot (8.2%) (**Figure 1B**). The most prevalent type of diagnosis at these visits was herniated nucleus pulposus (HNP) (28.2%), followed by arthritis (16.8%) and diabetic neuropathy (16.4%) (**Figure 1C**).

Intervention/tests taken during these visits included pharmacotherapy (70.2%), X-ray (48.8%) and physical therapy (48.8%) (**Figure 1D**). Mean number of interventions/tests used were 3, ranging from 1 to 8 per patient.

Of the total patients, 21.6% reported that they had previously received CAM. Types of CAMs included acupuncture (43.4%), physical therapy at non-hospitals (36.0%), use of dietary supplements (25.0%), blood circulation enhancers (23.2%) and over-the-counter pain-killers (22.1%). The mean number of CAMs used were 2, ranging from 1 to 8 per patient (**Figure 1E**).

The 1,186 patients (94.1%) were receiving pharmacotherapy (anti-platelet/others) for PAD. Other types of treatment included revascularization (42.1%), exercise (23.8%) and amputation (3.9%). The most commonly prescribed medication was aspirin (76.2%), followed by clopidogrel (53.3%) and cilostazol (33.6%). The proportion of patients receiving risk factor modification treatment was highest for those who had hyperlipidemia (lipid-lowering pharmacotherapy, 99.2%), followed by hypertension (anti-hypertensive pharmacotherapy, 96.4%), diabetes mellitus (diabetes mellitus pharmacotherapy, 95.9%). Those practicing diet control were 20.3%, while 12.6% received smoking cessation education/pharmacotherapy (**Table 2**).

Changes in Fontaine stage and peripheral-arterial disease (PAD) risk factors after 6 months from baseline

After 6 months, 58.9% of patients had improved Fontaine stage or maintained stage I compared to baseline. The smoking status of the patients were mostly continuous non-smoking (73.8%), followed by continuous smoking (22.1%) (**Table 3**).

Table 3. Changes in Fontaine stage and PAD risk factors

Variable	Value (n=1,208)
Fontaine stage*	
Improved/maintained stage I	742 (58.9)
Deteriorated/maintained stage II–IV	518 (41.1)
Smoking status†	
Continuous non-smoking	891 (73.8)
Continuous smoking	267 (22.1)
Smoking cessation	28 (2.3)
Start smoking	22 (1.8)
ΔHbA1c‡ (%) (n=440)	-0.19±1.30
ΔTotal cholesterol‡ (mg/dL; n=278)	-9.61±37.57
ΔLDL cholesterol‡ (mg/dL; n=238)	-8.13±30.64
ΔTriglyceride‡ (mg/dL; n=236)	-5.26±77.59
ΔHDL cholesterol‡ (mg/dL; n=235)	0.13±13.24
ΔSBP‡ (mmHg; n=823)	1.00±20.21
ΔDBP‡ (mmHg; n=823)	-0.74±12.23

Values are presented as mean ± standard deviation or number (%).

DBP = diastolic blood pressure; FU = follow-up; HbA1c = glycated hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PAD = peripheral-arterial disease; SBP = systolic blood pressure.

*Improved: at least 1 stage lower from baseline to 6-month FU, Deteriorated: at least 1 stage higher from baseline to 6-month FU; †Smoking history for the past 6 months; ‡Δ: parameter difference (6-month FU – baseline) among those who have the risk factor(s).

Quality of life (QoL)

EQ-5D Index at baseline and at 6-month follow-up were 0.64 ± 0.24 and 0.68 ± 0.20 , respectively ($\Delta\text{QoL} = 0.04 \pm 0.20$, $p < 0.001$, **Figure 2A**). EQ VAS scores at baseline and at 6-month follow-up were 67.49 ± 18.29 and 71.56 ± 16.33 , respectively ($\Delta\text{QoL} = 3.67 \pm 17.16$, $p < 0.001$, **Figure 2B**).

At baseline/follow-up, patients who answered some or severe problems on each dimension were as follows; mobility (68.0%/56.4%), pain/discomfort (65.3%/56.8%), usual activity (45.7%/37.6%), anxiety/depression (35.6%/33.9%) and self-care (25.7%/24.5%) (**Supplementary Figure 1**).

Factors associated with change in Quality of life (QoL)

Pharmacotherapy ($B = 0.05053$; $p = 0.044$) compared to no pharmacotherapy, and Fontaine stage improvement or maintaining Fontaine stage I ($B = 0.04448$; $p < 0.001$) compared to deterioration or maintaining Fontaine stage II–IV, were associated with increase in QoL (**Table 4**).

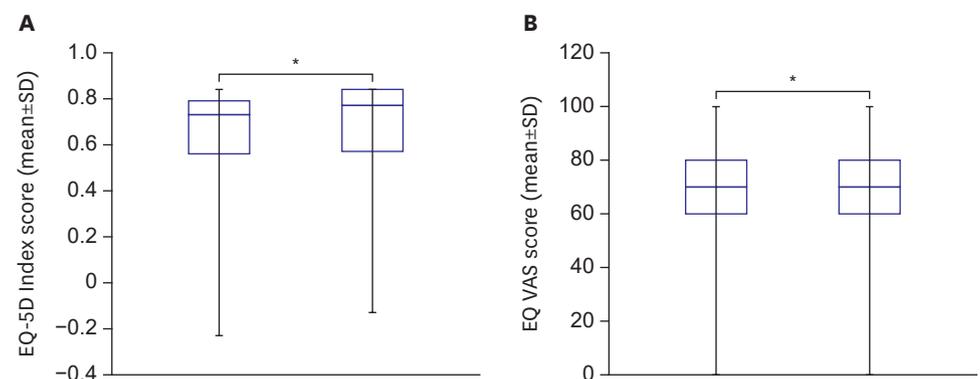


Figure 2. (A) Left: baseline, 0.64 ± 0.24 ; Right: follow-up, 0.68 ± 0.20 ; $\Delta\text{QoL} = 0.04 \pm 0.20$, * $p < 0.001$ by t-test. (B) Left: baseline, 67.49 ± 18.29 ; Right: follow-up, 71.56 ± 16.33 ; $\Delta\text{QoL} = 3.67 \pm 17.16$; SD = standard deviation; QoL = quality of life. * $p < 0.001$ by t-test.

Table 4. Factors associated with change in QoL (n=1,165)

Variable	Univariable		Multivariable	
	Mean±SD	p*	B	p†
Age (years)	-0.0152 [§]	0.598	-0.00011	0.856
BMI (kg/m ²)	-0.0116 [§]	0.691		
Sex		0.367	-0.01695	0.221
Female (Ref.)	0.03±0.19			
Male	0.05±0.23			
Left ABI	-0.0610 [§]	0.115		
Right ABI	-0.0478 [§]	0.215		
Current smoker		0.115		
No (Ref.)	0.03±0.20			
Yes	0.05±0.19			
Comorbidities/treatment history		0.515	-0.00869	0.756
No (Ref.)	0.05±0.16			
Yes	0.04±0.20			
Pharmacotherapy		0.006	0.05053	0.044
No (Ref.)	-0.01±0.14			
Yes	0.04±0.20			
Revascularization		0.095	0.01962	0.098
No (Ref.)	0.03±0.19			
Yes	0.05±0.21			
Exercise		0.143		
No (Ref.)	0.04±0.20			
Yes	0.02±0.19			
Amputation		0.240		
No (Ref.)	0.04±0.19			
Yes	0.09±0.32			
Fontaine stage [‡]		<0.001	0.04448	<0.001
Deteriorated/maintained stage II-III (Ref.)	0.01±0.21			
Improved/maintained stage I	0.06±0.19			
Smoking		0.100		
Smoking cessation/continue non-smoking (Ref.)	0.03±0.21			
Start smoking/continue smoking	0.05±0.18			

Reference variable for multivariable analysis (Ref.).

ABI = ankle-brachial index; BMI = body mass index; FU = follow-up; SD = standard deviation; QoL = quality of life.

*p value by Student's t-test unless otherwise indicated; †p value by multiple linear regression model, with age, gender and other variables with p<0.1 from univariable analysis were included; however, variables with significant missing values (PAD risk factor modifications, clinical characteristics after 6 months) were not included; ‡Change of Fontaine stage from baseline to 6-month follow-up; Improved: at least 1 stage lower from baseline to 6-month FU or constant stage at stage I, Deteriorated: at least 1 stage higher after 6 months from baseline or constant stage at stage IIa, IIb, III, IV; §Pearson's correlation coefficient; ||Pearson's correlation analysis.

DISCUSSION

In all fields of medicine, burden of disease assessments are needed to guide treatment decision making processes, and to decide whether the treatment allows actual improvements in health outcomes and QoL for the patient.¹⁶⁾ Therefore, in our study we elaborately assessed history of medical resource consumption and factors associated with QoL in Korean PAD patients. Since this study was conducted in a real-world treatment setting in the general population, the results from this study will provide valuable insights in reducing disease burden and ameliorating QoL of PAD patients.

Our study comprehensively assessed the history of patients' medical resource consumption before their treatment at current tertiary hospitals. We assumed that this history can provide a rough estimate of the patients' use of unnecessary medical resources due to delayed diagnosis and treatment. Among patients who visited a different medical institution prior to the current hospital, more than half of these visits were to the orthopedic units (50.4%),

followed by oriental medical clinics (26.8%). This suggests poor awareness of PAD among at-risk Korean patients. Furthermore, the proportion of visits to pain clinic (11.4%), anesthesia/pain division in general hospital (5.8%), and dermatology (2.6%) further implies severe disease symptoms at the time of these visits. In effect, more than 20% of the patients had already developed gangrene/ischemic foot injury at the time. Low disease awareness amongst the treating physicians is also implied by the finding that the most common initial diagnosis was HNP, which may relate to the fact that most visits were to medical institutions unrelated to cardiovascular complications. Furthermore, we found that patients had taken an average of 3 tests or interventions, mostly pharmacotherapy (70.2%), along with X-ray (48.8%) or physical therapy (48.8%), and computerized tomography (CT) (35.4%) at the time of these visits, all of which would have resulted in additional medical expenses. This data indicates substantial medical cost at initial disease diagnosis. Improving disease awareness in patients and other healthcare providers appears to be an exigent issue in the Korean context.

Our study is unique since we also assessed out-of-pocket expenditures that could have been avoided by earlier diagnosis of the disease. CAM refers to “a broad domain of healing resources that encompasses all health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health system of a particular society or culture in a given historical period.”¹⁷⁾ Common examples of CAM include acupuncture, aromatherapy and herbal medicines. Costs from these treatments are categorized as non-payment items, and therefore, they are not covered by the national insurance in Korea. Consequently, costs from CAM make up a considerable portion in out-of-pocket healthcare expenditures. In the United States, it was reported that CAMs consist of 11.2% of the total out-of-pocket expenditure on health care.¹⁸⁾ In this study, 22% of patients had history of CAM use for PAD. The most used CAM was acupuncture (43.4%), followed by physical therapy (36.0%) and dietary supplements (25.0%). This is similar to other countries; in an earlier systematic review, the most widely used CAMs in PAD included acupuncture and the dietary supplements such as *Allium sativum*, *Ginkgo biloba*, and omega-3 fatty acids.¹⁹⁾ The study concluded that other than some dietary supplements (e.g., *Ginkgo biloba*), there is no evidence beyond reasonable doubt to suggest effectiveness of the other remaining CAMs. Therefore, patients must be guided by their healthcare providers that appropriate mainstream therapies should also supplement PAD treatment and management.

Smoking increases the risk for PAD by damaging arteries, by inducing endothelial dysfunction and disrupting lipoprotein metabolism, coagulation, and platelet function.²⁰⁾²¹⁾ It follows that smoking cessation in PAD patients is strongly recommended according to the 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease.²²⁾ In a study conducted in Korean male patients with PAD, the risk of PAD was numerically elevated with the increase in yearly use of cigarettes compared to never-smokers, but it reduced as the smoking cessation duration was increased among ever-smokers.²³⁾ In our study, approximately a quarter of the patients (312 patients) were current smokers. Despite its seriousness, only 159 patients were receiving smoking cessation education or pharmacotherapy at the time of enrollment. After 6 months, 267 patients were still smoking, and an additional 22 patients were new smokers. More strategic smoking control measures should be implemented in PAD patients. A combination of pharmacological interventions, including nicotine replacement therapy, bupropion and varenicline, and behavioral support can be effective.²⁴⁾²⁵⁾

PAD is known to considerably impair patients' QoL and imposes significant barriers to walking, functional status and the ability to complete daily activities.¹⁶⁾ Baseline EQ-5D

index score (0.64 ± 0.24) from our study was lower than that of renal failure ($0.6637-0.7739$) and arthritis ($0.7621-0.8644$) from a different study conducted in Korea,²⁶⁾ with mobility dimension (78.0%) most affected by the disease. This further implies significant disease progression in these patients.

Although aspirin is the most frequently used agent as the 1st line of anti-platelet therapy, its efficacy in PAD treatment still remains controversial. The CAPRIE trial showed that clopidogrel-treated patients had a significantly lower rate of ischemic events by 24% (hazard ratio [HR], 0.76; 95% CI, 0.64–0.90; $p=0.001$) than aspirin-treated patients.²⁷⁾ In addition, vasodilators (e.g., cilostazol) should be considered for PAD management, especially for claudication as cilostazol is highly recommended as per the 2016 AHA/ACC guideline.²²⁾ While some may argue against the essence of its use, a recent meta-analysis revealed improvement in pain-free walking distance and QoL in cilostazol users.²⁸⁾ Although the selection of specific drugs for pharmacotherapy is dependent on their clinical profile and efficacy, there is no doubt that pharmacotherapy can have a beneficial clinical effect on PAD management in patients.

As the prominent effect of pharmacotherapy on clinical outcomes was demonstrated in previous studies, our study shows the association of pharmacotherapy with patient-reported outcomes in the multivariable analysis results, which in turn pinpoints factors significantly associated with QoL increase. Pharmacotherapy and Fontaine stage improvement/maintaining asymptomatic Fontaine stage I ($B=0.04448$; $p<0.001$) were found to be independent factors contributing to QoL of PAD patients. In a previous study from Netherlands, PAD patients who had lower QoL (HR, 5.4; 95% CI, 2.3–12.5) had worse survival rates, after adjusting for established prognostic factors.¹⁴⁾ Therefore, managing QoL should be considered critical since it can also predict long-term survival of patients and provide a prognostic value above other established risk factors.¹⁴⁾

There are some limitations to this study. First, even though this was a prospective study, the follow up period was limited to 6 months. A longer observation period could have allowed further assessment on the causal relationship between the variables and QoL. Second, patients who participated in the surveys were those receiving treatment in tertiary hospitals, which may limit the generalizability of these results since these patients may have advanced disease compared to general PAD population. Third, due to missing data, we could not include variables of risk factor modification in the multivariable analysis. Despite these limitations, our findings aptly pinpoint the significant disease burden and factors associated with QoL in Korean PAD patients.

Findings from this study highlight substantial medical resource consumption as well as significant debilitation in patients' QoL. Previous studies have proven the importance of QoL in patients' long-term survival. Therefore, provision of adequate pharmacotherapy and raising disease awareness to reduce patients' disease burden and preventing disease progression is pivotal in the treatment of Korean PAD patients.

ACKNOWLEDGEMENTS

This research was sponsored by Pfizer Pharmaceuticals Korea Ltd.

We appreciate PADO research investigators; Professor Yu Jeong Choi, June Namgung, Han Cheol Lee, Joon-Han Shin, Young Joon Hong, Jae Kean Ryu, Yoonhaeng Cho, Ji Hun Ahn, Jae Woong Choi, Jung-Hee Lee, and Kyoo-Rok Han, for their support.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Fontaine stage at baseline and 6 months FU (n=1,208)

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Supplementary Figure 1

Proportion of patients in each level of QoL dimension.

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