Age, Male Gender, and Atrial Fibrillation Predict Lower Extremity Amputation or Revascularization in Patients with Peripheral Artery Diseases: A Population-Based Investigation

Jien-Jiun Chen, M.D.^{1*} Lian-Yu Lin, M.D., Ph.D.^{2*} Chang-Hsing Lee, M.D.^{3,4*}
Chiau-Suong Liao, M.D., Ph.D.⁵

¹ Cardiovascular Center, National Taiwan University Hospital Yun-Lin Branch, Douliou, Taiwan

² Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

³ Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, Taipei, Taiwan

⁴ Department of Occupational Medicine, Ton Yen General Hospital, Hsin-Chu County, Taiwan

⁵ Cardiovascular Center, Buddhist Tzu Chi General Hospital, Taipei Branch, New Taipei, and Department of Internal Medicine, Tzu Chi University, Hualien, Taiwan

Address for correspondence and reprint requests Chiau-Suong Liao, M.D., Ph.D., Cardiovascular Center, Buddhist Tzu Chi General Hospital, Taipei Branch, No. 289, Jianguo Road, Sindian City, Taipei County 231, Taiwan (e-mail: csliao@tzuchi.com.tw).

Int J Angiol 2012;21:35–40.

Abstract

By using the National Health Insurance (NHI) claim data of Taiwan, we sought to determine the predictors for nontraumatic lower extremity amputation (LEA) or peripheral revascularization procedures (PRP) in patients with peripheral artery disease (PAD). From the NHI claim data, we identified 12,206 patients with newly diagnosed PAD between 1998 and 2008, and followed them up to 2008. We explored the age, gender, and whether the patients had concomitant comorbid conditions, such as diabetes mellitus (DM), hypertension (HTN), atrial fibrillation (AF), stroke, hospitalization for coronary artery disease (CAD), myocardial infarction (MI), or heart failure (HF), and whether they were taking cilostazol at the time of recruitment. We searched for clinical parameters that might be important determinants for LEA or PRP in the study population. Of the 12,206 patients, 150 (1.2%) were found to undergo either LEA or PRP or both (LEA 81, PRP 53, both PRP and LEA 16). Old age, male gender, and history of hospitalization for CAD or MI and AF were found to be risk predictors for both procedures. Patients with DM were at lower risk for PRP (odds ratio 0.418, $p = 0.001$). Patients who were taking cilostazol had higher risk for LEA or PRP. HTN was not a risk predictor for LEA or PRP. From this nationwide study, we found that among PAD patients in Taiwan, age, male gender, AF, and hospitalization for CAD or MI are risk predictors for future LEA or PRP. DM is a negative predictor for PRP while both DM and HTN are not risk predictors for LEA.

Keywords

- ▶ peripheral artery disease
- ▶ lower extremity amputation
- ▶ peripheral revascularization procedure
- ▶ atrial fibrillation

*These authors contributed equally to this work.

Peripheral artery disease (PAD) is a part of systemic atherosclerosis process, causing progressive occlusion of peripheral arteries.^{1,2} PAD shares common risk factors with other atherosclerotic diseases, such as coronary artery disease (CAD) and ischemic stroke. Among these risk factors are diabetes mellitus (DM), smoking, hypercholesterolemia, hypertension (HTN), male sex, and old age.³ Severe stenosis or occlusion of lower limb arteries may result in marked ischemia or even gangrenous changes which may be complicated with life-threatening infection, imposing significant morbidity with poor quality of life, and eventually lower extremity amputation (LEA).^{1,2} Peripheral revascularization procedures (PRP), either surgical bypass or transluminal angioplasty, are helpful in relieving symptoms, promoting wound healing, and preventing limb loss.⁴⁻⁶ Other treatment modalities are also important in the management of PAD patients, which include risk-factor modification, exercise training, and cilostazol use.^{2,7}

Previous studies showed that DM increased the risk of LEA in PAD patients.⁸⁻¹⁰ Our previous population-based, cross-sectional investigation (unpublished) found that among PAD patients in Taiwan, those having DM or taking cilostazol had less LEA or PRP, while those having HTN or CAD had more LEA or PRP. However, that study has the limitation of being cross-sectional in nature. The aim of the present investigation is to seek the determinants of LEA and PRP through longitudinal follow-up in PAD patients in Taiwan.

Materials and Methods

A universal National Health Insurance (NHI) program has been implemented in Taiwan since March 1995. About 96% of the total Taiwanese population had been enrolled in the NHI program,¹¹ and by the end of 1996, the Bureau of National Health Insurance (BNHI) had contracted with 97% of hospitals and clinics throughout the nation.¹² BNHI accumulates all administrative and claim data for Taiwan.

The National Health Research Institute (NHRI) of Taiwan has cooperated with BNHI to establish NHI research databases. NHRI safeguarded the privacy and confidentiality of all beneficiaries and transferred the health insurance data to health researchers upon request, after ethical approval had been obtained. To ensure the accuracy of the claim files, BNHI quarterly performed expert reviews on random samples of every 50 to 100 ambulatory and inpatient claims, and faults found in the claim cases, including the diagnosis, resulted in severe penalty from the BNHI.^{13,14} For this study, we used system sampling database from 1997 to 2008 with a total of 1,000,000 subjects.

Using the ambulatory and inpatient claim datasets, we identified 12,206 patients who were above 30 years of age and who had newly diagnosed PAD after 1998. The diagnosis of PAD was based on International Classification of Disease, Ninth Revision (ICD-9). Diagnosis codes of 250.6, 443, 443.81, 443.9, 44.2, and 785.4 were regarded as presence of PAD. Patients with PAD diagnosis in the claim data after 1998, but not in 1997, were defined as patients with newly diagnosed PAD and were recruited in our study. For outcome data, we

linked to inpatients' claim data to find PAD patients who had procedure codes of nontraumatic LEA (ICD-9 codes of 84.1 and 84.10-84.18) and nontraumatic PRP (ICD-9 codes of 35.25, 35.29, and 35.59). The patients were followed up for 10 years (1998 to 2008). For other comorbid conditions, we searched whether the patients had DM (ICD-9 codes of 250.0-250.7, 250.9), HTN (ICD-9 codes of 401.0, 401.1, 401.9), AF (ICD-9 code of 427.31), transient ischemic attack (TIA; ICD-9 codes of 435.8, 435.9), cerebral vascular accident (CVA; ICD-9 codes of 434.91, 434.11, 434.01, 434.01, 430, 431, 432.0-432.9), or if they had ever been hospitalized with principal diagnoses of CAD (ICD-9 codes of 414.0, 414.2, 414.00, 414.01), myocardial infarction (MI; ICD-9 codes of 410.0-410.9), or heart failure (HF; ICD-9 codes of 428.0, 428.1, 428.9). For medication, we searched if the patients were taking cilostazol.

Statistics

We used SPSS 15 for Windows XP (Chicago, IL) for statistical analysis. Continuous variables were expressed as mean $\pm$ standard deviation while categorical variables were expressed as percentage. The continuous variables were compared between LEA/PRP and control group by Student *t* test while the category parameters were compared by Mann-Whitney U-test. The strength of associations between the comorbidities and LEA or PRP was examined by Cox regression model.

Results

The study population included 12,206 patients with newly diagnosed PAD from 1998 to 2008. The basic demographic profiles of the patients are summarized in ►Table 1. At the time of diagnosis, 81.6% of them had concomitant DM, 35.8% had HTN, 0.5% had TIA, and 1.1% had stroke. Of the 12,206 patients, some had ever been hospitalized for CAD (0.9%, mainly for coronary revascularization procedures), MI (0.2%), or HF (0.2%). AF was present in 0.4% of the patients. Cilostazol was given to 2.5% of the patients.

Of the 12,206 patients, 150 (1.2%) underwent LEA or PRP at a mean follow-up period of 676 ± 570 days. The remaining patients were followed up for 2778 ± 684 days. Among the 150 patients, 97 had LEA (trauma-related operations were excluded) and 69 had PRP, either angioplasty or surgical bypass. Comparing with the patients who did not receive LEA or PRP, those who had ever received the procedures were older at the time of diagnosis of PAD. A larger proportion of them had AF or TIA/CVA, had ever been admitted for CAD/MI or HF, and used cilostazol (►Table 2).

Hazard ratios (HR) of the determinants for LEA or PRP in PAD patients are summarized in ►Table 3. The older the patients having PAD the higher the risk for LEA, but not for PRP (for LEA or PRP, HR 1.021 for each year increase in age, $p = 0.003$; for LEA, HR 1.025, $p = 0.006$; and for PRP, HR 1.016, $p = 0.125$). Males were at higher risk for both LEA and PRP than females (for LEA or PRP, HR 2.147, $p < 0.001$; for LEA, HR 2.266, $p = 0.006$; and for PRP, HR 1.916, $p = 0.010$). HTN did not impose significant risk for either LEA or PRP. Patients with

Table 1 Basic Demographic Profiles of the Study Subjects

<i>n</i> = 12,206	Number	%
Mean age, years (SD)	61.9 (12.39)	
Male	5,816	47.6
DM	9,956	81.6
HTN	4,368	35.8
CAD	111	0.9
MI	27	0.2
HF	19	0.2
TIA	62	0.5
CVA	133	1.1
AF	43	0.4
Cilostazoluse	307	2.5
LEA or PRP	150	1.2
LEA	97	0.8
PRP	69	0.6

SD, standard deviation; DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; MI, myocardial infarction; HF, heart failure; TIA, transient ischemic attack; CVA, cerebral vascular accident; AF, atrial fibrillation; LEA, lower extremity amputation; PRP, peripheral revascularization procedure.

DM had less PRP (odds ratio [OR] 0.418, $p = 0.001$), but the association with LEA was not significant. Patients who had ever been hospitalized due to CAD or MI had higher risk for LEA or PRP (for LEA or PRP, HR 6.366; for LEA, HR 7.264; and for PRP, HR 6.710, all $p < 0.001$), while hospitalization for HF or TIA/CVA did not predict future LEA and/or PRP. Patients with AF were at a significantly high risk for future LEA (OR 8.218, $p < 0.001$). For the PAD patients taking cilostazol, the risk for LEA or PRP was higher (for LEA or PRP, HR 2.542, $p = 0.001$; for LEA, HR 2.180, $p = 0.055$; and for PRP HR 2.379, $p = 0.052$).

Discussion

In this population-based, nationwide, longitudinal study, we found that among PAD patients in Taiwan, risk factors including age, male gender, presence of AF, and hospitalization due to CAD/MI predicted future LEA or PRP. DM and HTN were found not to increase the risk of LEA and patients taking cilostazol were shown to have higher LEA and PRP during follow-up period.

PAD is a consequence of atherosclerotic process.¹ Aging, HTN, hyperlipidemia, smoking, and DM are common risk factors for CAD and PAD.³ This study shows that patients having concomitant PAD and CAD have higher risk for LEA and PRP. This study also demonstrates that older patients have higher rates of LEA and PRP. Previous observations have indicated that older people tend to have more severe PAD¹⁵ and more artery calcification. The severity of tibial artery calcification has been shown to identify PAD patients who are at high risk for amputation.¹⁶ The present study shows that AF is a significant risk factor for LEA. Patients with AF have higher risks for embolic stroke, especially when they have other comorbid conditions such as DM, HTN, congestive heart failure, or when they are above 75 years of age.¹⁷ Whether this is a consequence of embolic occlusion or systemic inflammation requires further investigation.

In this study, 81.6% of PAD patients had DM at the time of diagnosis. PAD patients with DM did not have higher LEA rate and actually they had lower PRP performed. Furthermore, the incidence of LEA was lower as compared with Western population.^{4,8} This is inconsistent with certain previous observations which showed that PAD patients with diabetes have a higher rate of LEA than nondiabetic patients.^{8–10} Taiwan's NHI system has implemented a pay-for-performance program for diabetes since 2001.¹⁸ This program for diabetes care provides financial incentives for health care providers to increase comprehensive follow-up visits

Table 2 Comparison of Demographic Profiles of Patients with and without LEA/PRP

Variable	With LEA or RPR (<i>n</i> = 150)		Without LEA and PRP (<i>n</i> = 12,056)		<i>p</i> Value
	<i>n</i>	%	<i>n</i>	%	
Age, years (SD), in 1998	65.8 ± 11.2		61.9 ± 12.4		
Male	98	65.3	5718	47.4	<0.001
DM	117	78.0	9825	81.5	0.357
HTN	62	41.3	4249	35.2	0.077
CAD or MI	14	9.3	117	1.0	<0.001
HF	3	2	16	0.1	<0.001
TIA or CVA	6	4	187	1.6	0.017
AF	4	2.7	39	0.3	<0.001
Cilostazoluse	13	8.7	294	2.4	<0.001

LEA, lower extremity amputation; PRP, peripheral revascularization procedure; SD, standard deviation; DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; MI, myocardial infarction; HF, heart failure; TIA, transient ischemic attack; CVA, cerebral vascular accident; AF, atrial fibrillation.

Table 3 HR of Variable Risk Factors for LEA and PRP

Variable	LEA or PRP		LEA		PRP	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Patient number	150		97		69	
Age	1.021 (1.007–1.035)	0.003	1.025 (1.007–1.043)	0.006	1.016 (0.996–1.036)	0.125
Gender	2.147 (1.530–3.013)	<0.001	2.266 (1.483–3.463)	<0.001	1.916 (1.170–3.136)	0.010
DM	0.837 (0.557–1.258)	0.393	1.550 (0.849–2.831)	0.153	0.418 (0.247–0.707)	0.001
HTN	1.193 (0.847–1.679)	0.313	1.107 (0.726–1.687)	0.638	1.388 (0.835–2.307)	0.206
CAD/MI	6.366 (3.437–11.792)	<0.001	7.264 (3.501–15.070)	<0.001	6.710 (2.696–16.699)	<0.001
HF	1.764 (0.493–6.316)	0.383	1.373 (0.288–6.559)	0.691	1.901 (0.225–16.079)	0.556
TIA/CVA	1.769 (0.765–4.089)	0.182	1.758 (0.631–4.903)	0.281	1.350 (0.321–5.682)	0.682
AF ^a	4.802 (1.792–13.341)	0.003	8.218 (2.901–23.276)	<0.001	NA	NA
Cilostazoluse	2.542 (1.406–4.596)	0.002	2.180 (0.984–4.827)	0.055	2.379 (0.992–5.703)	0.052

^aAF in PRP was not entered due to small population.

HR, hazard ratio; LEA, lower extremity amputation; PRP, peripheral revascularization procedure; CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; MI, myocardial infarction; HF, heart failure; TIA, transient ischemic attack; CVA, cerebral vascular accident; AF, atrial fibrillation.

including enhanced self-care education and annual diabetes-specific physical examinations such as foot inspection and laboratory tests.¹⁸ Both diabetologists and certified diabetes educators were responsible for the care of these patients. With better sugar control, antiplatelet medication use, and foot care, the complications of PAD needing LEA, such as gangrene change and poor wound healing may be prevented. Other studies had shown that, imposing diabetic foot clinic program could bring about reduction in the incidence of amputation, while with an increase in revascularization procedures.^{19,20}

Our analysis showed that patients taking cilostazol tend to have more LEA or PRP procedures in the follow-up years. Cilostazol acts by inhibiting phosphodiesterase type 3, thus increasing intracellular concentration of cyclic adenosine monophosphate. Cilostazol inhibits platelet aggregation, prevents formation of arterial thrombi and proliferation of vascular smooth muscles, and also causes vasodilatation.^{2,19–21} Cilostazol had been proved in randomized control trials to increase walking distance of PAD patients,²² and in some trials, increase the quality of life.²³ Cilostazol had been shown to decrease the restenosis rate after percutaneous transluminal angioplasty for CAD^{24,25} and PAD.²⁶ In Taiwan, cilostazol is usually prescribed when a patient had intermittent claudication due to PAD. For patients who had symptoms requiring cilostazol, their PAD might be more severe, and the risk for future LEA or PRP might be higher, mainly due to the disease per se rather than the effects of drug.

Our study has several limitations. First, we rely on claim data exclusively, which may carry a potential disease misclassification bias, as the type of reimbursement system could influence the assignment of hospital discharge codes to increase hospital reimbursements.^{14,27} Second, the data we used for patient recruitment and data analysis

started from 1997 to 1998, 2 to 3 years after the start of our health insurance program. The case number of each disease might not be accurate because it was at the point when patients started to get medical help more liberally. Third, the prescription of medication was not based on strict principles but on each primary physician's propensity. The prescription of cilostazol did not necessarily reflect the severity of disease. Fourth, we investigated the risk factors of nontraumatic LEA. Yet, the causes of nontraumatic LEA are not necessarily PAD. DM foot with life-threatening infection may need LEA. However, in these patients, PAD may impair wound healing and contribute to disease progression.

Conclusions

From this population-based, longitudinal study using Taiwan's NHI claim data, we found that the risk factors of future LEA or PRP in PAD patients include male gender, old age, AF, and history of hospitalization for CAD/MI. DM or HTN did not increase the risk of LEA. A meticulous DM caring program can potentially decrease the risks for future LEA or PRP in PAD patients.

References

- 1 Ross R. The pathogenesis of atherosclerosis—an update. *N Engl J Med* 1986;314(8):488–500
- 2 Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med* 2001;344(21):1608–1621
- 3 Fowkes FG, Housley E, Riemersma RA, et al. Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. *Am J Epidemiol* 1992;135(4):331–340

- 4 American Diabetes Association. Peripheral arterial disease in people with diabetes. *Diabetes Care* 2003;26(12):3333–3341
- 5 Kudo T, Chandra FA, Ahn SS. The effectiveness of percutaneous transluminal angioplasty for the treatment of critical limb ischemia: a 10-year experience. *J Vasc Surg* 2005;41(3):423–435, discussion 435
- 6 Marso SP, Hiatt WR. Peripheral arterial disease in patients with diabetes. *J Am Coll Cardiol* 2006;47(5):921–929
- 7 Hankey GJ, Norman PE, Eikelboom JW. Medical treatment of peripheral arterial disease. *JAMA* 2006;295(5):547–553
- 8 Jude EB, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. *Diabetes Care* 2001;24(8):1433–1437
- 9 Calle-Pascual AL, Redondo MJ, Ballesteros M, et al. Nontraumatic lower extremity amputations in diabetic and non-diabetic subjects in Madrid, Spain. *Diabetes Metab* 1997;23(6):519–523
- 10 Trautner C, Haastert B, Giani G, Berger M. Amputations and diabetes: a case-control study. *Diabet Med* 2002;19(1):35–40
- 11 Lu JF, Hsiao WC. Does universal health insurance make health care unaffordable? Lessons from Taiwan. *Health Aff (Millwood)* 2003;22(3):77–88
- 12 Chiang TL. Taiwan's 1995 health care reform. *Health Policy* 1997;39(3):225–239
- 13 Tseng CH. Mortality and causes of death in a national sample of diabetic patients in Taiwan. *Diabetes Care* 2004;27(7):1605–1609
- 14 Chen HF, Ho CA, Li CY. Age and sex may significantly interact with diabetes on the risks of lower-extremity amputation and peripheral revascularization procedures: evidence from a cohort of a half-million diabetic patients. *Diabetes Care* 2006;29(11):2409–2414
- 15 Garcia LA. Epidemiology and pathophysiology of lower extremity peripheral arterial disease. *J Endovasc Ther* 2006;13(Suppl 2):II3–II9
- 16 Guzman RJ, Brinkley DM, Schumacher PM, Donahue RM, Beavers H, Qin X. Tibial artery calcification as a marker of amputation risk in patients with peripheral arterial disease. *J Am Coll Cardiol* 2008;51(20):1967–1974
- 17 Ryder KM, Benjamin EJ. Epidemiology and significance of atrial fibrillation. *Am J Cardiol* 1999;84(9A):131R–138R
- 18 Lee TT, Cheng SH, Chen CC, Lai MS. A pay-for-performance program for diabetes care in Taiwan: a preliminary assessment. *Am J Manag Care* 2010;16(1):65–69
- 19 Creager MA. Medical management of peripheral arterial disease. *Cardiol Rev* 2001;9(4):238–245
- 20 Igawa T, Tani T, Chijiwa T, et al. Potentiation of anti-platelet aggregating activity of cilostazol with vascular endothelial cells. *Thromb Res* 1990;57(4):617–623
- 21 Kohda N, Tani T, Nakayama S, et al. Effect of cilostazol, a phosphodiesterase III inhibitor, on experimental thrombosis in the porcine carotid artery. *Thromb Res* 1999;96(4):261–268
- 22 Robless P, Mikhailidis DP, Stansby GP. Cilostazol for peripheral arterial disease. *Cochrane Database Syst Rev* 2008(1):CD003748
- 23 Regensteiner JG, Ware JE Jr, McCarthy WJ, et al. Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with intermittent claudication due to peripheral arterial disease: meta-analysis of six randomized controlled trials. *J Am Geriatr Soc* 2002;50(12):1939–1946
- 24 Tsuchikane E, Fukuhara A, Kobayashi T, et al. Impact of cilostazol on restenosis after percutaneous coronary balloon angioplasty. *Circulation* 1999;100(1):21–26
- 25 Douglas JS Jr, Holmes DR Jr, Kereiakes DJ, et al; Cilostazol for Restenosis Trial (CREST) Investigators. Coronary stent restenosis in patients treated with cilostazol. *Circulation* 2005;112(18):2826–2832
- 26 Iida O, Nanto S, Uematsu M, et al. Cilostazol reduces target lesion revascularization after percutaneous transluminal angioplasty in the femoropopliteal artery. *Circ J* 2005;69(10):1256–1259
- 27 Assaf AR, Lapane KL, McKenney JL, Carleton RA. Possible influence of the prospective payment system on the assignment of discharge diagnoses for coronary heart disease. *N Engl J Med* 1993;329(13):931–935