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Comparison of Clinical Outcome of Infrapopliteal Angioplasty Between Korean Diabetic and Non-Diabetic Patients With Critical Limb Ischemia

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Background: Although infrapopliteal angioplasty may salvage the majority of limbs under threat of amputation, this procedure is still limited in diabetic patients. The purpose of the present study was to compared the outcomes of infrapopliteal angioplasty between Korean diabetic patients and non-diabetic patients with critical lower limb ischemia (CLI).

Methods and Results: Between March 2002 and May 2008, infrapopliteal angioplasty was performed on 108 limbs of 93 patients (71 male; mean age, 68 years, range, 27–91 years) with CLI (Rutherford-Becker category 4, 5 or 6). Freedom from reintervention, limb salvage, and overall survival were analyzed. Median follow-up was 30 months (range, 1–93 months). The number of diabetic patients was 70 (75%). There were no significant differences between the 2 groups in technical success rate (66% vs. 84%, P=0.133) and primary clinical success rate (81% vs. 92%, P=0.234). Kaplan-Meier analysis showed that diabetic patients had a higher frequency of poor primary patency (P=0.012) during 2-year follow-up, but that there were no significant differences between the 2 groups in terms of limb salvage (P=0.930), and survival (P=0.459).

Conclusions: Diabetic patients had an unfavorable 2-year primary patency compared with non-diabetic patients. There were no significant differences, however, between the 2 groups in terms of technical success rate, primary clinical success rate, 2-year limb salvage rate or overall survival. (*Circ J* 2012; **76:** 335–341)

Key Words: Angioplasty; Critical limb ischemia; Diabetes mellitus; Infrapopliteal artery

Although surgical bypass is regarded as the gold standard due to better anatomical and clinical durability relative to the other revascularization methods for critical lower limb ischemia (CLI),[1–3] percutaneous transluminal angioplasty (PTA) in peripheral vascular disease (PVD) is a feasible method of treating CLI, and has similar outcomes to those of bypass surgery.[4,5] PVD in diabetic patients constitutes a major clinical problem and is associated with higher morbidity and mortality.[6] Diabetic patients are 5-fold more likely to develop CLI than non-diabetic patients.[7] One serious complication of PVD is gangrene, which accounts for up to 50% of lower limb amputations in diabetic patients in the Western world.[7]

Although numerous previously published studies involving diabetic patients demonstrated that infrapopliteal intervention in this group may salvage the majority of limbs under threat of amputation, these studies dealt with heterogeneous stages of ischemia such as claudication, resting pain or tissue lesions and, furthermore, the most frequently treated vessels were the distal popliteal artery and the tibioperoneal trunk, whose diameters are more similar to those of above-knee arteries than those of the smaller below-knee arteries.[8–15] A recent study reported that a successful endovascular procedure led to a high percentage of limb salvage at long-term follow-up in the patients with ischemic diabetic foot and isolated below-knee lesions.[16]

In the present study, we compared the outcomes of infrapopliteal angioplasty between Korean diabetic patients and non-diabetic patients with CLI.

Methods

Between April 2002 and May 2008, we retrospectively analyzed 118 limbs in 101 patients with CLI (Rutherford-Becker grades[17] 4, 5, or 6) who had been treated with infrapopliteal angioplasty. Among them, 8 patients with Buerger's disease[18] were excluded from final analysis because Buerger's disease

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Table 1. Demographic Patient Characteristics vs. Diabetes Mellitus

	All (n=93)	Diabetic patients (n=70)	Non-diabetic patients (n=23)	P value
Age (years)	67.6±12.2	66.0±12.8	72.7±8.5	0.022
Men	71 (76)	52 (74)	19 (83)	0.574
Body mass index	22.9±3.6	23.0±3.7	22.4±3.2	0.558
Comorbid disease				
Hypertension	68 (73)	54 (77)	14 (61)	0.127
Cerebrovascular accident	11 (12)	8 (11)	3 (13)	1.000
Coronary artery disease	53 (57)	41 (59)	12 (52)	0.591
Chronic renal failure*	41 (44)	34 (49)	7 (30)	0.129
Smoker	36 (39)	21 (30)	15 (65)	0.003
Claudication**	27 (25)	16 (19)	11 (44)	0.012
Resting pain**	65 (60)	43 (52)	22 (88)	0.001
Gangrenous change**	53 (49)	49 (59)	4 (16)	<0.001
Clinical category				
Rutherford-Becker 4**[17]	48 (44)	28 (34)	20 (80)	<0.001
Rutherford-Becker 5,6**[17]	60 (56)	55 (66)	5 (20)	<0.001

Data given as mean±SD or n (%).
*Serum creatinine >1.5 mg/dl; **108 limbs (83 diabetic limbs and 25 non-diabetic limbs).

originated from different etiology. Finally 108 limbs in 93 patients were included. The demographic, laboratory, technical, and clinical characteristics were retrospectively collected from their medical records. Blood samples were collected one day before or immediately before the index procedure.

Vascular access for infrapopliteal angioplasty was gained via ipsilateral or contralateral puncture of the common femoral artery. An antegrade approach was preferred when there were no combined lesions requiring proximal iliac or femoral intervention and in patients without obesity, due to better maneuverability of catheters and control of wiring in case of total occlusion. After placement of the 6–7-Fr sheath under local anesthesia, intra-arterial bolus of 5,000 IU heparin was given, and additional heparin was given to maintain an activated clotting time between 250 and 300 s, if procedure time was lengthened. Infrapopliteal lesions were passed with a 0.36–0.89 mm guidewire. If the initial transluminal recanalization failed, total occlusions were recanalized through the subintimal dissection plane with re-entrance into the true lumen using 0.89 mm hydrophilic guidewire (Terumo, Tokyo, Japan). After crossing the lesion, a 4–5-F multipurpose catheter was advanced to the distal patent segment in exchange with 0.36 mm wire. PTA was then performed with adequate sized balloons (2.25–4.0 mm) at 6–10 atm. In case of elastic recoil or a flow-limiting dissection after balloon dilatation, stents were implanted for bailout purpose. When proximal lesions including ipsilateral iliac, femoral or popliteal artery existed, concomitant procedures were performed.

Prior to intervention, patients were premedicated with aspirin (100 mg, daily) and maintained indefinitely after PTA. Follow-up included clinical examination during hospital stay and at 1 month after intervention to document hemodynamic improvement. Subsequent follow-up was considered when there was a question of worsening clinical status. If necessary, repeat peripheral angiography or computed tomography angiogram was scheduled on their visit. The causes and date of death were examined by chart review, telephone contact or checking with national statistical office.

Diabetes mellitus is defined as a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.[19] The criteria for the diagnosis of diabetes were as follows: symptoms of diabetes (eg, polyuria, polydipsia, and unexplained weight loss) plus a casual plasma glucose concentration ≥200 mg/dl or fasting plasma glucose ≥126 mg/dl or 2-h plasma glucose ≥200 mg/dl during an oral glucose tolerance test.[19]

Technical success was defined as PTA resulting in <30% residual stenosis with sufficient antegrade flow; suboptimal result was defined as sluggish flow and/or residual stenosis 30–50% after repeated dilatation. Primary clinical success was defined as an improvement of at least one clinical category of Rutherford-Becker classification.[17] Primary patency was defined as persistent patency without any re-intervention including angioplasty, surgical procedure performed on or at the margins of the treated lesion, or amputation. Limb salvage was defined as prevention of major amputation. Major amputation was defined as limb loss below or above the knee, while minor amputation was defined as transmetatarsal or more distal amputation of the lower extremity. The protocol was reviewed and approved by the institutional review board. Written, informed consent was obtained for all patients enrolled in the study.

Statistical Analysis

We analyzed data using SPSS version 15.0 (SPSS, Chicago, IL, USA). Data are presented as mean±SD for continuous variables and as n (%) for categorical variables. Student's t-test was used for comparison of continuous variables and chi-squared analysis was used for comparison of category variables. Event-free survival curves were constructed via the Kaplan-Meier method. All significant univariate predictors of poor primary patency and poor survival were included in multivariate logistic regression analysis. $P<0.05$ was considered significant.

Results

Demographic patient characteristics vs. presence of diabetes mellitus are listed in Table 1. Mean subject age was 67.6±12.2 years, with 71 men (76%) and 22 women (24%). The number of diabetic patients was 70 (75%). Numerous patients had significant comorbidities including hypertension (73%), coro-

Table 2. Patient Laboratory Data vs. Presence of Diabetes Mellitus

	All (n=93)	Diabetic patients (n=70)	Non-diabetic patients (n=23)	P value
White blood cell count (/μl)	8,259±2,868	8,405±2,563	7,735±3,834	0.532
Hemoglobin (g/dl)	11.2±1.8	11.0±1.9	11.7±1.7	0.175
Platelet count (/μl)	272,550±81,731	279,060±78,693	258,330±92,962	0.389
Sodium (mmol/L)	138.3±3.8	138.0±3.9	139.5±3.3	0.168
Potassium (mmol/L)	4.4±0.6	4.4±0.6	4.4±0.4	0.879
Blood urea nitrogen (mg/dl)	26.2±15.7	26.4±16.0	25.5±15.1	0.856
Creatinine (mg/dl)	2.77±2.98	2.96±3.13	2.17±2.46	0.275
eGFR ($ml \cdot min^{-1} \cdot 1.73 m^{-2}$)	50.9±32.0	49.4±33.2	55.4±28.2	0.439

Data given as mean±SD.
eGFR, estimated glomerular filtration rate.

Table 3. Patient Technical Characteristics vs. Presence of Diabetes Mellitus

	All (n=108)	Diabetic limbs (n=83)	Non-diabetic limbs (n=25)	P value
Left limb	57 (53)	41 (49)	16 (64)	0.200
Location				
Anterior tibial artery	80 (74)	61 (74)	19 (76)	0.802
Posterior tibial artery	37 (34)	29 (35)	8 (32)	0.786
Peroneal artery	29 (27)	24 (29)	5 (20)	0.378
Dorsalis pedis artery	3 (3)	2 (2)	1 (4)	0.550
Total occlusion	55 (51)	37 (45)	18 (72)	0.016
Combined procedure	48 (44)	32 (39)	16 (64)	0.025
Iliac artery	7 (7)	3 (4)	4 (16)	0.049
Femoral artery	40 (37)	26 (31)	14 (56)	0.025
Popliteal artery	14 (13)	8 (10)	6 (24)	0.061
Antegrade approach	48 (44)	39 (47)	9 (36)	0.332
Subintimal approach	10 (10)	7 (9)	3 (13)	0.698
Stent implantation	9 (9)	6 (8)	3 (13)	0.440
Technical success	76 (70)	55 (66)	21 (84)	0.133
Suboptimal results	23 (21)	20 (24)	3 (12)	0.269
Complication	23 (21)	20 (24)	3 (12)	0.269
Dissection	23 (21)	20 (24)	3 (12)	0.269
Rupture	6 (6)	6 (7)	0 (0)	0.333
Embolism	1 (1)	0 (0)	1 (4)	0.231

Data given as n (%).

nary artery disease (57%), chronic renal failure (44%), smoking history (39%), and history of cerebrovascular accident (12%). The most frequently observed initial presentation of the limb was resting pain (60%), followed by gangrenous change (49%) and claudication (25%) of the limb with CLI. Sixty patients were identified as fulfilling Rutherford-Becker category 5 and 6 (56%). Although more diabetic patients had gangrenous change (59% vs. 16%, P<0.001), they had a lower mean age (66.0±12.8 years vs. 72.7±8.5 years, P=0.022), and fewer were smokers (30% vs. 65%, P=0.003), had claudication (19% vs. 44%, P=0.012), and resting pain (52% vs. 88%, P=0.001). There were no significant differences, however, between the 2 groups in terms of other demographic characteristics including gender.

Laboratory patient characteristics vs. presence of diabetes mellitus are listed in **Table 2**. The mean blood urea nitrogen level was 26.2±15.7 mg/dl, and the mean creatinine level was 2.77±2.98 mg/dl. The mean estimated glomerular filtration rate was 50.9±32.0 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$, but there were no significant differences between the 2 groups in terms of laboratory characteristics.

Technical patient characteristics vs. presence of diabetes mellitus are listed in **Table 3**. A total of 149 lesions were treated in 108 limbs of 93 patients with CLI. Anterior tibial artery the most common treated location (54%), and totally occluded arteries were observed in 55 limbs (51%). Concomitant procedures in the proximal lesion, involving the ipsilateral iliac or femoral artery, were performed in 48 limbs (44%). Among them, femoral artery procedure was most commonly performed (37%). Antegrade access was used in 48 limbs (44%), and subintimal angioplasty was done in 10 limbs (10%). Initial technical success was achieved in 76 limbs (70%). On final angiography, suboptimal result was obtained in 23 limbs (21%), which showed diffuse and heavily calcified lesion at initial presentation. There were 9 technical failures due to 7 unsuccessful attempts to insert the guidewire, 1 heavy calcified lesion, and 1 arterial rupture. No major complication requiring surgical intervention occurred after PTA. Minor procedural complications such as flow-limiting dissection, rupture, and embolization occurred in 23 limbs (21%),

Table 4. Clinical Patient Characteristics vs. Presence of Diabetes Mellitus

	All (n=108)	Diabetic limbs (n=83)	Non-diabetic limbs (n=25)	P value
Primary clinical success	90 (83)	67 (81)	23 (92)	0.234
Re-PTA	5 (5)	5 (6)	0 (0)	0.588
Surgery	39 (36)	37 (45)	2 (8)	0.001
Major amputation	5 (5)	4 (5)	1 (4)	1.000
Minor amputation	36 (33)	35 (42)	1 (4)	<0.001
One-year primary patency*	56 (74)	37 (67)	19 (91)	0.046
Two-year primary patency*	56 (74)	37 (67)	19 (91)	0.046
One-year limb salvage*	74 (97)	54 (98)	20 (95)	0.479
Two-year limb salvage*	74 (97)	54 (98)	20 (95)	0.479
One-year survival**	79 (85)	58 (83)	21 (91)	0.505
Two-year survival**	68 (73)	50 (71)	18 (78)	0.521

Data given as n (%).
*Seventy-six limbs (55 diabetic limbs and 21 non-diabetic limbs) with initial technical success; **93 patients (70 diabetic patients and 23 non-diabetic patients).
PTA, percutaneous transluminal angioplasty.

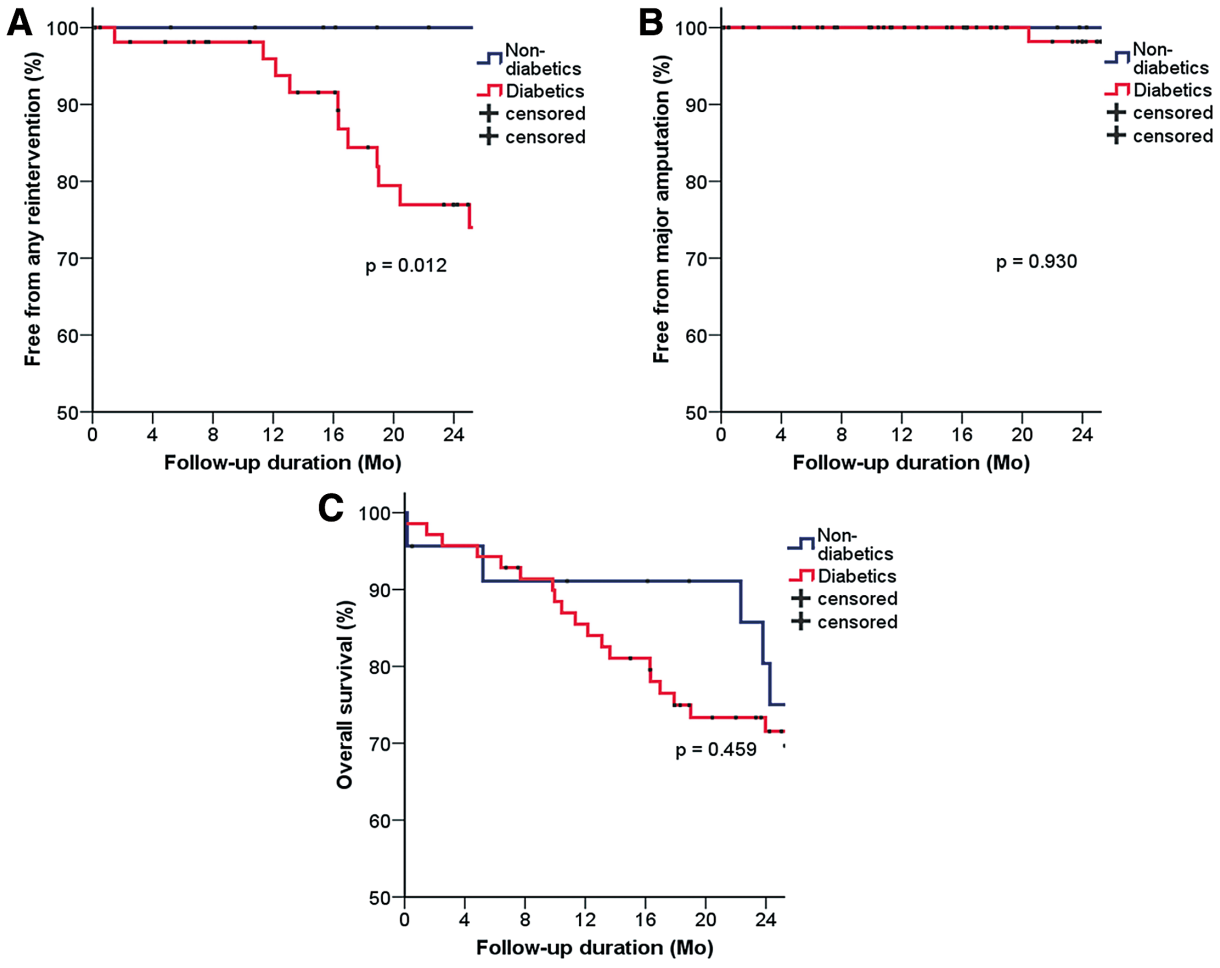

Figure. Kaplan-Meier analysis of (**A**) primary patency, (**B**) limb salvage rate and (**C**) overall survival between diabetic patients and non-diabetic patients during 2-year follow-up. (**A**) Diabetic patients had a higher frequency of poor primary patency compared with non-diabetic patients (P=0.012) during 2-year follow-up, but there were no significant differences between the 2 groups in terms of (**B**) limb salvage (P=0.930) and (**C**) survival (P=0.459) during 2-year follow-up.

which were treated conservatively or with stent implantation. In 9 cases of elastic recoil or flow-limiting dissection, stents were implanted for bailout purpose. All types of stents were bare-metal coronary stents. Moreover, balloon-expandable or self-expandable stents were implanted in the ipsilateral iliac and superficial femoral artery. Diabetic patients had a lower frequency of total occluded arteries (45% vs. 72%, P=0.016). Concomitant procedures in the proximal lesion involving the ipsilateral iliac or femoral artery were less frequently performed in diabetic patients (39% vs. 64%, P=0.025), but there were no significant differences between the 2 groups in terms of other technical characteristics including technical success rate (66% vs. 84%, P=0.133).

Clinical characteristics of the patients vs. presence of diabetes mellitus are given in **Table 4**. Primary clinical success was obtained in 90 limbs (83%), 17 limbs had persistent gangrene and 1 other limb had persistent pain. The mean follow-up was 33 months (range, 1–94 months). Re-PTA was performed in 5 limbs (5%), surgery in 39 limbs (36%), major amputation in 5 limbs (5%), and minor amputation in 36 (33%) during follow-up. Diabetic patients had a higher frequency of surgery (45% vs. 8%, P=0.001), especially minor amputation (42% vs. 4 %, P<0.001), but there were no significant differences between the 2 groups in terms of major amputation (5% vs. 4%, P=1.000) and primary clinical success rate (81% vs. 92%, P=0.234).

Among 76 patients who had initial technical success, freedom from any reintervention was 74% at 1 year and at 2 years, and the limb salvage rate was 97% at 1 year and at 2 years (**Table 4**). Overall survival was 85% at 1 year and 73% at 2 years. Kaplan-Meier analysis demonstrated that diabetic patients had a higher frequency of poor primary patency compared with non-diabetic patients (P=0.012; **Figure A**) during 2-year follow-up. There were no significant differences, however, between the 2 groups in terms of limb salvage (P=0.930; **Figure B**) and survival (P=0.459; **Figure C**) during 2-year follow-up.

Discussion

To the best of our knowledge, the present study is the first to compare the outcomes of infrapopliteal angioplasty between Korean diabetic patients and non-diabetic patients with CLI. In this study, 2-year primary patency was unfavorable in diabetic patients compared with non-diabetic patients, but there were no significant differences between the 2 groups in terms of other outcomes including limb salvage and overall survival.

Although bypass surgery using outflow vessels below the ankle should be considered the standard treatment in patients with CLI due to infrapopliteal arterial disease,[20] this requires a good vein conduit and at least one open foot artery and is associated with considerable perioperative mortality, postoperative complications, myocardial infarction, and early re-operation for graft thrombosis.[21] In addition, as previously mentioned, diabetic patients are more likely to develop CLI and its serious complications including gangrene, and to have higher morbidity and mortality;[6,7] also, diabetes mellitus is the possible determinant factor of graft failure in patients with CLI.[22] For these reasons, infrapopliteal angioplasty is currently proposed as the primary treatment for CLI in diabetic patients.[5,8,12–14] Infrapopliteal angioplasty, however, has been criticized because of the small diameter and length of the treated vessel, both of which have a tendency towards a high restenosis rate; furthermore, it is not clear whether the clinical success of infrapopliteal angioplasty is due solely to technical success.[23–26]

A previous study evaluated the effectiveness of PTA as the first-choice revascularization procedure in diabetic patients with CLI.[5] It was reported that 1.7% of patients experienced major amputations; that 5-year primary patency was 88%; and that 5-year survival was 74%. That study, however, dealt with heterogeneous treated vessels including iliac arteries and superficial femoral arteries despite being a prospective study. A recent retrospective study investigated the long-term outcomes after infrapopliteal angioplasty in diabetic patients with CLI.[16] In that study the limb salvage rate was 93%, minor amputation rate was 64%, and mortality rate was 9% after a mean follow-up of 1,048 days.

The present study has noted a higher primary patency compared with a recent study.[16] Another previous study, however, found a higher primary patency compared with the present study.[5] In other words, there are differences in primary patency between studies. This may be due to the heterogeneity of the patient groups or to the easy access of orthopedic surgery rather than to the differences in angioplasty technique.

The present study has found a similar limb salvage rate compared with previous studies.[5,16] A recent study noted a relatively higher restenosis rate despite a suitable limb salvage rate.[16] In that study this discrepancy was explained as probably reflecting the fact that long-term complete patency of the treated vessel is less important in such patients than in those with coronary, carotid or renal arterial disease.[16] Recanalization temporarily increases blood flow to the foot and has a positive effect in eradicating infection and healing ulcers and surgical wounds. Because foot tissue healing reduces oxygen demand, less blood flow is generally required to maintain tissue integrity and keep the limb asymptomatic.[9,27] This is clearly demonstrated by the fact that most of the limbs (95%) were free from major amputation during the follow-up period. Because color duplex ultrasound or peripheral angiography were not performed in all patients during follow-up period in the present study, we could not identify a discrepancy between limb salvage rate and restenosis.

The present study has reported a higher mortality rate compared with a recent study.[16] This may be due to diverse causes including heterogeneous demographic characteristics, strictness or looseness of clinical follow-up, and presence of simultaneous above-the-knee involvement. Nevertheless, the present study produced similar results to a previous study.[5]

As previously mentioned, the present study found that 2-year primary patency was unfavorable in diabetic patients compared with non-diabetic patients, but that there were no significant differences between the 2 groups in terms of other outcomes including limb salvage and overall survival. In diabetic patients, occlusive PVD is characterized by distal, long, multiple, and calcified obstructions with a higher percentage of occlusions with respect to stenosis.[28,29] The main obstacle to recanalization is the complete calcified occlusion of the arteries, which does not permit balloon catheter passage.[5] Although the present study found that diabetic patients had a lower frequency of total occluded arteries, in contrast to previous studies, there were no significant differences in clinical outcomes. This may be explained by the significance of distal, long, multiple, and calcified stenosis than that of occlusion in diabetic patients. Further prospective studies are needed.

The present study found a tendency towards lower initial technical success and lower primary patency in diabetic patients during 2-year follow-up. This may be explained by complexity of the lesions and failure of blood flow mainte-

nance despite recanalization, previously mentioned. Although there was a tendency towards lower initial technical success in diabetic patients, the difference did not reach statistical significance. Therefore, the occurrence of restenosis or multiple calcified lesions may explain the fact that diabetic patients had a lower primary patency during 2-year follow-up despite the lack of significant difference in initial technical success. Further prospective studies are needed. Moreover, there were no significant differences between the 2 groups in terms of primary clinical success, 2-year limb salvage, and 2-year overall survival. Thus, we may apply the same treatment strategy to infrapopliteal angioplasty irrespective of presence of diabetes mellitus.

Furthermore, the outcome of diabetic patients with PVD could be improved by using cilostazol to decrease levels of high sensitivity C-reactive protein and of the soluble form of the CD40 ligand and to increase adiponectin level, thereby delaying the progression of atherogenesis and chronic inflammation.[30] Moreover, a recent study suggested that prostaglandin E1 in lipid microspheres improved walking ability and the quality of life as self-evaluated by patients with PVD.[31] In addition, supervised exercise training improved cardiovascular mortality and morbidity in patients with PVD, which suggests that exercise training should be considered as a secondary prevention strategy for these patients.[32] The authors, however, did not analyze the differences of technical and/or clinical outcomes vs. presence of medication and/or rehabilitation program.

Several limitations of the present study need to be considered. First, this was a retrospective study from a single institution, which can create referral bias. Also, extrapolation of the present results to most patients with CLI has limited validity due to the small size of the subject group. Second, we did not perform follow-up angiography or use other imaging modalities for long-term patency in asymptomatic patients. In addition, ankle-brachial index was applied in only a small number of patients. Therefore, regular follow-up based on ankle-brachial index or duplex scan is needed to obtain better patency results in future prospective studies. Third, the efficacy of proximal PTA in cases of combined proximal and distal angioplasty could not be distinguished from that in distal angioplasty alone. Finally, non-diabetic patients had more inflow lesions and underwent more procedures compared with diabetic patients, but the different distribution of diseased arteries in the 2 groups meant that only a simple comparison of clinical outcome could be made.

Conclusion

Diabetic patients had an unfavorable 2-year primary patency compared with non-diabetic patients, but there were no significant differences between the 2 groups in terms of technical success rate, primary clinical success rate, 2-year limb salvage rate or overall survival. Infrapopliteal angioplasty therefore has acceptable clinical outcome and is feasible as the primary choice of treatment in Korean diabetic patients with CLI.

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Disclosures

The authors have no commercial, proprietary, or financial interest in any products or companies described in this article.

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