The Effect of Severe Femoropopliteal Arterial Calcification on the Treatment Outcome of Femoropopliteal Intervention in Patients with Ischemic Tissue Loss

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INTRODUCTION

Endovascular treatment has the advantage of low peri-procedural risks, short hospital stays, and repeatable interventions. The efficacy of endovascular treatment has been increasing steadily and is now becoming mainstream for femoropopliteal occlusive disease [1,2]. However, as the number of patients with diabetes and renal insufficiency...
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increases, vascular calcification, one of the important barriers in peripheral vascular intervention, is also increasing. Vascular calcification is known to affect the outcome and the technical success rate of the endovascular procedure [3]. Currently, most of the United States Investigational Device Exemption protocols for endovascular devices are not applied for patients with severe calcification [4], as it relates to the occurrence of adverse events, such as dissection, vessel perforation, and atheroembolism.

Many studies reported the risk factors associated with the prognosis of endovascular treatment of femoropopliteal lesions [5-8]. Critical limb-threatening ischemia (CLTI) is known to be associated with a high risk of limb amputation and mortality [9]. CLTI represents the terminal stage of peripheral arterial disease. It occurs when arterial vessels are improperly perfused and unable to maintain tissue viability [10]. However, there are few data on the intermediate or long-term effects of vascular calcification on the endovascular treatment outcome for femoropopliteal lesions in patients with CLTI.

The aim of this study was to investigate the outcomes after endovascular treatment according to the degree of femoropopliteal arterial calcification in patients with ischemic tissue loss.

MATERIALS AND METHODS

A database of patients who underwent endovascular treatment of the femoropopliteal artery for ischemic tissue loss between May 2010 and February 2018 was evaluated. Procedures for chronic femoropopliteal atherosclerotic steno-occlusive disease were included in the study. Interventions in patients with acute limb ischemia, in-stent restenosis, trauma, popliteal aneurysm, re-intervention, and procedures for bypass graft were excluded. The definition of technical success was no residual stenosis (≤50% in angioplasty alone; ≤30% in stent use) and the absence of flow-limiting dissection in treated femoropopliteal artery confirmed by digital subtraction angiography [11]. Major amputation was defined as any procedure that results in an amputation at the level of the ankle or above [11]. A major amputation indication was major tissue loss extending above the metatarsal level (Rutherford category 6). Of 252 limbs that underwent procedures for de novo chronic femoropopliteal lesions in patients with ischemic tissue loss, we excluded interventions for patients with vasculitis (n=2), technical failure (n=7), and major tissue loss, which inevitably necessitates major amputation at presentation, such as involving the metatarsal area (n=8). Additionally, the cases without sufficient data or wound follow-up (n=100) were excluded. Finally, 135 first femoropopliteal endovascular procedures on 135 limbs from 112 patients were included in this study.

The number of technical failures was small (n=7) because it included only cases where guidewire passage was attempted, except for cases without intervention or only diagnostic angiography. For wound healing, it is ideal to make direct in-line flow up to ankle level. However, in this study, technical success focused on the treatment of the femoropopliteal artery. Therefore, if femoropopliteal intervention was successful, even if direct in-line tibial flow up to ankle level was not obtained, it was considered a technical success.

We reviewed demographic data, comorbidities, details of endovascular procedures, and clinical outcomes. Comorbidities included hypertension, diabetes mellitus, ischemic heart disease (history of medical treatment, coronary bypass, or percutaneous coronary interventions), renal insufficiency, renal replacement therapy, and cerebrovascular disease (stroke or transient ischemic attack).

Computed tomography angiography (CTA) has been used limitedly in patients with renal insufficiency. However, CTA was performed without restriction in patients already undergoing renal replacement. Since the degree of calcification was evaluated based on CTA in our study, 11 patients who did not undergo CTA due to renal insufficiency were excluded, and these patients were included in the 100 cases treated with insufficient data. The degree of lesion calcification was analyzed using the Compliance 360° score [11,12]. Compliance 360° score is divided into 5 grades: grade 0, the calcium deposit is absent from the circumference and length; grade 1, the calcium deposit has a circumference less than 180° and less than half of lesion length; grade 2, the calcium deposit has a circumference less than 180° and greater than half of lesion length; grade 3, the calcium deposit has a circumference greater than 180° and less than half of lesion length; and grade 4, the calcium deposit has a circumference greater than 180° and greater than half of lesion length. We divided grade 0 through 3 into the non-severe calcification group and grade 4 into the severe calcification group. Classification of femoropopliteal lesions according to degree of calcification is shown in Fig. 1.

The patients who had a successful endoluminal intervention received dual anti-platelets. Patients underwent routine clinical ankle–brachial index (ABI) measurements 1, 3, and 6 months after the procedure and every 6 months thereafter. During follow-up, a duplex scan or CTA was performed if patients were symptomatic or if noninvasive tests suggested the presence of restenosis or an occlusion.

Hypertension was defined as using antihypertensive medication for high blood pressure or having a systolic blood pressure ≥140 mm Hg and/or diastolic blood pres-
sure ≥90 mm Hg. Diabetes mellitus was defined as using blood glucose-lowering medication and/or having a fasting glucose level of ≥126 mg/dL. Dyslipidemia was defined as using lipid-lowering medication and/or having a cholesterol level >200 mg/dL and/or low-density lipoprotein cholesterol level >130 mg/dL. Renal insufficiency was defined as having a serum creatinine level >1.5 mg/dL or being on renal replacement therapy.

Clinical outcome variables included limb salvage, patient survival, and amputation-free survival. Limb salvage was defined as not receiving any major amputations. Amputation-free survival was defined as not receiving above-ankle amputation of the index limb or dying. Primary patency was defined as treated vessel without a significant stenosis (a peak systolic velocity ratio >2.4 on duplex scan and >50% stenosis on angiography). Secondary patency was defined patency of the target lesion after treatment of a re-occlusion of the index lesion.

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp, Armonk, NY, USA). The Kaplan–Meier method with the log-rank test was used to calculate primary patency, secondary patency, limb salvage, patient survival, and amputation-free survival. Chi-squared and Fisher exact tests were used to compare the degree of calcification and various patient characteristics between the groups. Multivariate analysis of prognostic relevance was evaluated by multivariate Cox regression analysis. A value of P<0.05 was considered statistically significant in all analyses.

The study protocol was developed in accordance with...
the Declaration of Helsinki, and approved by the Dongsan Medical Center Institutional Review Board (DSMC no. 2019-07-008). The requirement for informed consent was waived due to the retrospective nature of study.

RESULTS

1) Patient population

A comparison of demographics and cardiovascular comorbidities are shown in Table 1. The distribution rates of non-severe (n=100) and severe (n=35) calcification groups were 74.1% (77.0% male; age 71.5±8.3 years) and 25.9% (62.9% male; age 68.6±9.7 years), respectively. There was no difference in the prevalence of diabetes, hypertension, and smoking. However, the prevalence of ischemic heart disease (P<0.001), renal insufficiency (P<0.001), and renal replacement therapy (P<0.001) were significantly higher in the severe calcification group.

2) Lesion characteristics and procedural details

The lesion characteristics and procedural details are shown in Table 1. In the comparison of the Trans-Atlantic

Table 1. Patient, lesion and procedure characteristics

| Characteristic                  | Non-severe calcification group (n=100) | Severe calcification group (n=35) | P-value |
|--------------------------------|---------------------------------------|----------------------------------|---------|
| Age (y)                        | 71.5±8.3                              | 68.6±9.7                        | 0.09    |
| Male                           | 77 (77.0)                             | 22 (62.9)                       | 0.122   |
| Comorbidities                  |                                       |                                  |         |
| Diabetes mellitus              | 67 (67.0)                             | 27 (77.1)                       | 0.293   |
| Hypertension                   | 75 (75.0)                             | 31 (88.6)                       | 0.101   |
| Current or ex-smoker           | 68 (68.0)                             | 22 (62.9)                       | 0.678   |
| Ischemic heart disease         | 22 (22.0)                             | 18 (51.4)                       | <0.001  |
| Medical treatment              | 10 (10.0)                             | 3 (8.6)                         |         |
| PCI                            | 11 (11.0)                             | 10 (28.6)                       |         |
| Coronary bypass                | 1 (1.0)                               | 4 (11.4)                        |         |
| Stroke                         | 21 (21.0)                             | 14 (40.0)                       | 0.042   |
| Renal insufficiency            | 36 (36.0)                             | 25 (71.4)                       | <0.001  |
| TASC classification            |                                       |                                  | 0.028   |
| A/B                            | 21 (21.0)/39 (39.0)                   | 4 (11.4)/10 (28.6)              |         |
| C/D                            | 22 (22.0)/18 (18.0)                   | 17 (48.6)/4 (11.4)              |         |
| Lesion length(cm)              | 15.3±11.1                             | 24.1±4.9                        | <0.001  |
| Runoff (n)                     |                                       |                                  | 0.160   |
| >1                             | 44 (44.0)                             | 10 (28.6)                       |         |
| ≤1                             | 56 (56.0)                             | 25 (71.4)                       |         |
| Concomitant procedure          |                                       |                                  |         |
| Iliac angioplasty              | 28 (28.0)                             | 7 (20.0)                        | 0.502   |
| BTK angioplasty                | 64 (64.0)                             | 25 (71.4)                       | 0.535   |
| Type of F-P procedures         |                                       |                                  |         |
| POBA                           | 39 (39.0)                             | 17 (48.6)                       |         |
| DCB                            | 28 (28.0)                             | 6 (17.1)                        |         |
| POBA+BMS                       | 27 (27.0)                             | 7 (20.0)                        |         |
| DCB+BMS                        | 3 (3.0)                               | 1 (2.9)                         |         |
| POBA+DES                       | 2 (2.0)                               | 1 (2.9)                         |         |
| Supera stent                   | 1 (1.0)                               | 2 (5.7)                         |         |
| Atherectomy                    | 0 (0.0)                               | 1 (2.9)                         |         |

Values are presented as mean±standard deviation or number (%).
PCI, percutaneous coronary intervention; TASC, Trans-Atlantic Inter Society Consensus; BTK, below-the-knee; POBA, plain old balloon angioplasty; DCB, drug-coated balloon; BMS, bare metal stent; DES, drug-eluting stent.

*Student t-test. Chi-square test. Fisher’s exact test.
Inter Society Consensus (TASC) classification of the femoropopliteal artery, there was a significant difference between the non-severe and severe calcification group (P=0.028). However, there was no difference in the patent tibial runoff evaluated by intraoperative angiography (P=0.160). In the non-severe calcification group, angioplasties of the iliac and below-the-knee (BTK) arteries were performed simultaneously in 28.0% and 64.0% of limbs, respectively. With regards to the balloon angioplasty, a plain balloon was used in 68.0% of limbs, and a drug-coated balloon (DCB) was used in 32.0%. A bare-metal stent (BMS) after plain balloon angioplasty was used in 27.0% of limbs for residual stenosis or flow-limiting dissection. In the severe calcification group, angioplasties of the iliac and BTK arteries were performed simultaneously in 20.0% and 71.4% of limbs, respectively. For the balloon angioplasty, plain balloons and DCBs were used in 71.5% and 28.5% of limbs, respectively. A BMS after plain balloon angioplasty was used in 20.0% of limbs for residual stenosis or flow-limiting dissection. A BMS after angioplasty using a DCB was used in 2.9% of limbs.

3) Early clinical outcome

Early clinical outcomes within 30 days after the procedure are shown in Table 2. Puncture site hematoma occurred immediately after procedures in 5.0% (n=5) of cases in the non-severe calcification group and 5.7% (n=2) in the severe calcification group. Distal embolization occurred in 2.0% (n=2) of cases in the non-severe calcification group and 2.9% (n=1) in the severe calcification group. Major amputation immediately after the procedure occurred in

| Table 2. Immediate safety outcome (<30 days) | Non-severe calcification (n=100) | Severe calcification (n=35) |
|--------------------------------------------|---------------------------------|-----------------------------|
| Procedural complications                   |                                 |                             |
| Puncture site hematoma                     | 5 (5.0)                         | 2 (5.7)                     |
| Puncture site pseudoaneurysm               | 0 (0.0)                         | 1 (2.9)                     |
| Distal embolism                            | 2 (2.0)                         | 1 (2.9)                     |
| MALE                                        |                                 |                             |
| Major amputation                           | 12 (12.0)                       | 4 (11.4)                    |
| Major reintervention                       | 3 (3.0)                         | 2 (5.7)                     |
| MACE                                        |                                 |                             |
| Myocardial infarction                      | 3 (3.0)                         | 2 (5.7)                     |
| Stroke                                     | 0 (0.0)                         | 0 (0.0)                     |
| Death from any cause                       | 4 (4.0)                         | 2 (5.7)                     |

Values are presented as number (%).

MALE, major adverse limb events; MACE, major adverse cardiovascular events.

Fig. 2. Kaplan–Meier (KM) curves of primary and secondary patency rates comparing non-severe and severe calcification groups. Patencies were significantly worse in severe calcification group.
12.0% (n=12) of cases in the non-severe calcification group and 11.4% (n=4) in the severe calcification group. Reintervention in each group was 3.0% (n=3) and 5.7% (n=2), respectively. Death immediately after the procedure occurred in 4.0% (n=4) of cases in the non-severe calcification group and 5.7% (n=2) in the severe calcification group.

4) Midterm outcome

Fig. 2 shows the primary patency and secondary patency according to the degree of calcification. The primary patency was significantly different between the two groups (non-severe calcification group vs severe calcification group at 1-year, 2-years, and 3-years: 88.7%, 77.2%, and 60.6% vs. 64.1%, 49.3%, and 44.4%, respectively, P=0.009).

Fig. 3. Kaplan-Meier (KM) curves of limb salvage rate (A), overall survival rate (B), and amputation-free survival rate (C) in patients with Trans-Atlantic Inter Society Consensus (TASC) C/D lesions. Overall survival rate was significantly worse in severe calcification group.
Also, the secondary patency was significantly different between the two groups (non-severe calcification group vs. severe calcification group at 1-year, 2-years, and 3-years: 93.8%, 92.6%, and 76.8% vs. 79.1%, 75.3%, and 75.3%, respectively, P=0.034).

Among 74 limbs with TASC A or B lesions, there were 60 limbs (81.1%) with non-severe calcification lesions and 14 limbs (18.9%) with severe calcification lesions. For TASC A or B groups, there were no statistically significant differences in limb salvage (P=0.51), survival (P=0.13), and amputation-free survival (P=0.22), according to the degree of calcification. Among 61 limbs with TASC C or D lesions, there were 40 limbs (65.6%) with non-severe calcification lesions and 21 limbs (34.4%) with severe calcification lesions. There was no statistically significant difference in limb salvage between the non-severe calcification and severe calcification groups in patients with TASC C or D lesions (P=0.75). However, the survival rate was significantly different between the two groups (non-severe calcification group vs severe calcification group at 1-year, 2-years, and 3-years: 88.6%, 79.7%, and 61.0% vs. 70.0%, 56.0%, and 28.0%, respectively, P=0.01). In comparing amputation-free survival rates, there was not a significant difference between the two groups in patients with TASC C or D lesions (P=0.11) (Fig. 3). In multivariate analysis of influencing factors for poor survival in TASC A or B using the Cox proportional hazards model, ischemic heart disease (hazard ratio [HR], 1.064; 95% confidence interval [CI], 0.390-2.904; P=0.904), renal insufficiency (HR, 1.627; 95% CI, 0.642-4.127; P=0.305), severe calcification (HR, 1.590; 95% CI, 0.569-4.442; P=0.376) showed no statistical significance. In multivariate analysis of influencing factors for poor survival in TASC C or D using the Cox proportional hazards model, ischemic heart disease (HR, 1.177; 95% CI, 0.470-2.947; P=0.727), renal insufficiency (HR, 1.276; 95% CI, 0.566-2.878; P=0.557) showed no statistical significance. However, severe calcification (HR, 2.362; 95% CI, 1.035-5.391; P=0.041) was statistically significant risk factor (Table 3, Supplementary Table 1).

**DISCUSSION**

Endovascular therapy has been extensively used in the revascularization of peripheral arterial disease with low mortality and less invasive procedures compared to bypass surgery [13,14]. In previous treatment guidelines, endovascular therapy was recommended only for single, short, and focal lesions, but recommendations have changed to advocate endovascular therapy, rather than open surgery, for most lesions due to advances in technologies and techniques [15]. However, the presence of vascular calcification, particularly in the infragingual vasculature, represents a significant challenge to current endovascular device strategies [4]. Severe calcification may be associated with increased dissection, perforation, and atheroembolism. It is also known that balloon angioplasty for severely calcified lesions is limited by early elastic recoil and poor early and long-term outcomes [5]. Although several studies have investigated the effect of significant calcification on restenosis after endovascular treatment, we focused on clinical characteristics, such as limb salvage and survival according to degree of vascular calcification, because clinical outcomes, such as wound healing, limb salvage, and survival, are more ultimate endpoints of treatment than technical or anatomical endpoints [16].

Determining the relevant score components by selecting the appropriate calcification grading system is an important factor in correlating the outcome in this analysis [17]. The existing scoring system, the peripheral arterial calcium scoring system (PACSS), highlights the pathologic location of calcification (intima, media, or combined) along with the length of the segment affected [4]. However, the lack of a validated, quantitative calcium scoring system makes it difficult to evaluate the outcomes of endovascular therapies in patients with calcified peripheral arteries. A calcification scoring system based on angiography is a useful tool for selecting treatment modality and device during the procedure [17]. However, objective scoring of vascular calcification by conventional angiography was impossible in this retrospective study. According to the protocol of our institution, pre-procedural CTA were obtained in all cases; therefore, we evaluated the degree of vascular calcification based on CTA according to the score using the 360° trial [11,12].

Severe calcification is known to reduce the durability of endovascular therapy of femoropopliteal lesions. In our

**Table 3.** Risk factors for poor survival in TASC A/B and TASC C/D

| Variable          | P     | HR (95% CI)       |
|-------------------|-------|-------------------|
| **TASC A/B**      |       |                   |
| Ischemic heart disease | 0.904 | 1.064 (0.390-2.904) |
| Renal insufficiency    | 0.305 | 1.627 (0.642-4.127) |
| Severe calcification      | 0.376 | 1.590 (0.569-4.442) |
| **TASC C/D**       |       |                   |
| Ischemic heart disease | 0.727 | 1.177 (0.470-2.947) |
| Renal insufficiency    | 0.557 | 1.276 (0.566-2.878) |
| Severe calcification      | 0.041 | 2.362 (1.035-5.391) |

By Cox’s proportional hazard model.

TASC, Trans-Atlantic Inter Society Consensus; HR, hazard ratio; CI, confidence interval.
study, there was also statistically significant differences in primary patency and secondary patency according to the degree of calcification. de Athayde Soares et al. [15] reported that severe calcification were related to loss of primary patency. In their study, one tibial vessel or isolated popliteal artery runoff, high calcification grade, small vessel diameter (<4 mm), or primary angioplasty without stenting were associated with loss of primary patency. Okuno et al. [18] reported that PACSS grade 4 was significantly associated with both major adverse life events and mortality.

In the present study, in patients with TASC C or D lesions, limb salvage and amputation-free survivals were not affected by the degree of calcification, but the survival rate was. Clinical implications of the presence of calcification in the coronary artery leading to an increased cardiovascular risk have been well demonstrated [19]. However, little is known about the association between lower extremity arterial calcification and clinical outcomes [20]. Only a few studies reported that the calcium score in the iliac or tibial artery was associated with amputation and mortality in patients who had symptomatic peripheral arterial disease [20,21]. In the present study, there were significantly more patients with comorbidities of ischemic heart disease, stroke, renal insufficiency, and renal replacement in the severe calcification group than in the non-severe calcification group. However, in the multivariate analysis of the TASC C/D lesions, severe calcification was found to be a significant factor related with poor survival, independent of ischemic heart disease and renal insufficiency.

This study has some limitations. First, initial wound data and follow-up data were not available in many cases due to the retrospective design, and, thus, these cases were excluded. Also, because it was a retrospective study, WIFI classification was difficult to confirm, and all cases were classified as Rutherford category 5 as minor tissue loss. Secondly, we did not distinguish whether the calcification was intimal or medial. Since this study did not distinguish between intimal and medical calcification, many of the cases classified as severe calcification were medial calcification cases. In the case of medial calcification, lesions seen in DSA are often less severe than those seen in CT. In addition, since with medial calcification lesions it is easy to guide wire passage and dissection does not occur easily, it seems that the severe calcification group required less bailout stenting than expected. In this study, bailout stenting in the non-severe calcification group was 42.6% in plain old balloon angioplasty (POBA) and 9.7% in DCB, and severe calcification was 32.0% in POBA and 14.3% in DCB. Also, in our center's strategy, preballooning was performed using a plain balloon with a 1 mm-smaller diameter than DCB, which resulted in a protective effect against dissection. For this reason, less bailout stenting were used when using DCB.

**CONCLUSION**

In conclusion, severe calcification of the femoropopliteal artery with TASC A or B lesions did not affect the clinical outcomes in patients with ischemic tissue loss. In TASC C or D lesions, severe calcification of femoropopliteal artery did not affect limb salvage in patients with ischemic tissue loss. However, femoropopliteal arterial calcification was significantly associated with poor survival in TASC C or D lesions.

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**SUPPLEMENTARY MATERIALS**

Supplementary data can be found via https://doi.org/10.5758/vsi.200005.

**CONFLICTS OF INTEREST**

The authors have nothing to disclose.

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