Impact of Longer Hemodialysis Vintage with Higher Serum Phosphorus Level on Clinical Outcomes in Patients with Chronic Limb-Threatening Ischemia Presenting Tissue Loss after Endovascular Therapy

Naoko Higashino¹, Osamu Iida¹, Yosuke Hata¹, Mitsutoshi Asai¹, Masaharu Masuda¹, Shin Okamoto¹, Takayuki Ishihara¹, Kiyonori Nanto¹, Takashi Kanda¹, Takuya Tsujimura¹, Shota Okuno¹, Yasuhiro Matsuda¹, Mitsuyoshi Takahara² and Toshiaki Mano¹

¹Kansai Rosai Hospital Cardiovascular Center, Inabaso, Amagasaki, Hyogo, Japan
²Department of Metabolic Medicine and Department of Diabetes Care Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

Aims: Hemodialysis vintage and serum phosphorus levels adversely affect outcomes in patients on hemodialysis. Whether these factors have a similar prognostic impact on patients who are on hemodialysis and have chronic limb-threatening ischemia (CLTI) has not been systematically studied. We aimed to explore the risk factors, including hemodialysis vintage and serum phosphorus levels, on clinical outcomes after endovascular therapy (EVT) in hemodialysis patients with CLTI.

Methods: The current study retrospectively analyzed 374 hemodialysis patients with CLTI presenting with ischemic tissue loss (age: 72.3 ± 9.0 years, male: 73.3%, diabetes mellitus: 68.2%, Rutherford 5: 75.9%, 6: 24.1%, WIfI stage 4: 50.0%) primarily treated with EVT between April 2007 and December 2016. The primary outcome measure was 1-year amputation-free survival (AFS), while the secondary outcome measure was 1-year wound healing. Predictors for each outcome were evaluated by Cox proportional hazards model.

Results: Multivariate analysis significantly associated longer hemodialysis vintages with higher serum phosphorus levels (hazard ratio [HR], 0.599; 95% confidence interval [CI], 0.394–0.910; p = 0.016) with 1-year AFS. Longer vintages for hemodialysis with higher serum phosphorus levels were marginally, but not significantly, associated with 1-year wound healing. (HR, 0.684; 95% CI, 0.467–1.000; p = 0.050).

Conclusion: Longer hemodialysis vintages with higher serum phosphorus levels adversely affect outcomes after EVT for hemodialysis patients with CLTI presenting with ischemic tissue loss.

Key words: Amputation-free survival (AFS), Chronic limb-threatening ischemia (CLTI), Hemodialysis vintage, Serum phosphorus level, Wound healing

Introduction

The number of patients with chronic kidney disease (CKD), including hemodialysis, has increased over the years, presumably due to the aging society as well as the diabetes mellitus (DM) and hypertension (HTN) pandemics¹. CKD itself is a well-known risk factor in peripheral arterial disease (PAD) etiology since it is a part of cardiovascular disease. A previous study reported that patients with more advanced CKD stages had more severe clinical presentations of PAD at initial diagnosis². The management and prevention of patients with CLTI are pressing issues in terms of both medical costs and public health. They have poor prognoses with high mortality and amputation rates unless they undergo appropriate revascularization³-⁶. Currently, because of recently-developed dedicated devices and accumulated

Address for correspondence: Naoko Higashino, Kansai Rosai Hospital Cardiovascular Center, 3-1-69 Inabaso, Amagasaki, Hyogo 660-8511, Japan
E-mail: naoko.higashino@gmail.com
Received: August 25, 2020      Accepted for publication: December 2, 2020

Copyright © 2021 Japan Atherosclerosis Society
This article is distributed under the terms of the latest version of CC BY-NC-SA defined by the Creative Commons Attribution License.

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: December 2, 2020   Published online: February 14, 2021
EVT Strategy

Laboratory data and prescribed medications were generally checked upon admission before revascularization. The severity of ischemia in the lower limbs was assessed hemodynamically by the ankle-brachial index (ABI) and skin perfusion pressure (SPP). Lower limb arteries were evaluated routinely by duplex ultrasound, and the morphology of arterial lesions was assessed by diagnostic angiogram before revascularization. EVT was indicated when the lesion showed 75% stenosis or greater of the vessel diameter on diagnostic angiography with hemodynamic significance. EVT was done according to the generally accepted principles. In the aortoiliac lesions, a primary stenting strategy was conducted. In the femoropopliteal lesions, a stent was allowed in angioplasty failure cases, which included severe dissection, residual stenosis, or a significant pressure gradient of 10 mmHg or greater as a provisional stenting strategy. Below-the-knee (BTK) lesions were generally treated with plain angioplasty under a health insurance system. Drug-coated balloon and atherectomy devices were not used because they were not approved in Japan during the study period.

Follow-Up Protocol

The follow-up interval and modality for ischemic changing were basically at the physician’s direction, with the typical practice being every 2–4 weeks until the wound healed and every 3 months after that for as long as possible, using ABI, arterial duplex ultrasound, and SPP, if needed. Re-intervention was generally indicated for limbs with recurrent symptoms or delayed wound healing accompanied by re-occlusion or restenosis with hemodynamic significance measured by ABI, duplex ultrasound, or SPP.
distributed; therefore, the serum phosphorus level’s median value was used for analysis. The median value of the vintage of hemodialysis was used as the cutoff value for analysis.

### Statistical Analysis

Unless mentioned otherwise, data are presented as the median (interquartile range) for continuous variables and as percentages for discrete variables. We performed chi-square test for discrete variables and Mann–Whitney U tests for ordinal variables to assess baseline characteristic differences between groups. Prognostic outcomes were assessed with the Kaplan–Meier method, and the differences between groups were assessed with the log-rank test when necessary. Cox proportional hazards regression analysis was used to determine the association of clinical characteristics with 1-year AFS and wound healing rate.

Multivariate Cox regression analysis determined predictors for 1-year AFS or 1-year wound healing. Clinically specified predictors achieving $p<0.05$ in univariate analysis were entered into the multivariate Cox regression analysis. The hazard ratio (HR) and 95% confidence interval (CI) were reported. A $p$-value $<0.05$ was considered statistically significant. Statistical analyses were performed using SPSS Version 24.0J (SPSS Inc., Chicago, IL, USA).

### Result

Table 1 summarizes the study population's limb
Longer hemodialysis vintages and higher serum phosphorus levels were associated with a significantly lower 1-year AFS and wound healing rate. The subgroup with phosphorus levels >4.5 mg/dl and hemodialysis vintages >6.1 years had a significantly lower 1-year AFS than those with levels ≤4.5 mg/dl and hemodialysis vintages ≤6.1 years. The HR was 0.563 (95% CI, 0.329–0.962; p=0.036), while the subgroup with ≤4.5 mg/dl and with ≤6.1 years and the subgroup with >4.5 mg/dl and >6.1 years had a HR of 0.996 (95% CI, 0.531–1.730; p=0.887) and 0.985 (95% CI, 0.538–1.805; p=0.962), respectively, relative to those with phosphorus levels ≤4.5 mg/dl and hemodialysis vintages ≤6.1 years.

The association of hemodialysis vintage and serum phosphorus level with 1-year AFS is shown in Fig. 4A. The subgroup with phosphorus levels >4.5 mg/dl and hemodialysis vintages >6.1 years did not have a significantly lower 1-year wound healing compared to those with phosphorus levels ≤4.5 mg/dl and hemodialysis vintages ≤6.1 years.

Table 2. Baseline lower limb and lesion characteristics

| Number of patients | 374 |
|--------------------|-----|
| Rutherford classification |     |
| 5, n (%) | 284 (75.9) |
| 6, n (%) | 90 (24.1) |
| CRP, mg/dl | 1.30 ± 5.64 |
| WIfI classification |     |
| 1 (Very low risk) | 27 (7.2) |
| 2 (Low risk) | 64 (17.1) |
| 3 (Moderate risk) | 96 (25.7) |
| 4 (High risk) | 187 (50.0) |
| Ankle-brachial index on admission | 0.65 ± 0.20 |
| Skin perfusion pressure at dorsalis pedis side | 29.8 ± 18.2 |
| plantar side, mmHg | 28.0 (17.0–40.5) |
| 32.3 ± 18.1 |
| 31.0 (20.0–43.0) |
| Aorto-iliac lesion, n (%) | 46 (12.3) |
| Femoro-popliteal lesion, n (%) | 190 (50.8) |
| BTK lesion, n (%) | 333 (89.0) |
| Isolated BTK lesion, n (%) | 171 (45.7) |

Data are shown as mean ± standard deviation or median with the first and third quartile as continuous data as appropriate. Categorical data are expressed as number with percentages.

CRP, C-reactive protein; WIfI, Wound, Ischemia, and foot Infection classification system; BTK, Below-the-knee

As shown in Fig. 2, the 1-year AFS and 1-year wound healing rates were 70.5% ± 2.5% and 57.1% ± 3.0%, respectively. The study population was categorized into four subgroups according to serum phosphorus levels (>4.5 mg/dl or ≤4.5 mg/dl) and hemodialysis vintages (>6.1 years or ≤6.1 years). The 1-year AFS was significantly lower in the group with longer hemodialysis vintages and higher serum phosphorus levels than in the group with others (p=0.009) (Fig. 3A). The 1-year wound healing rate was significantly lower in the group with longer hemodialysis vintages and higher serum phosphorus levels (p=0.019) (Fig. 3B). The subgroup with phosphorus levels >4.5 mg/dl and hemodialysis vintages >6.1 years had a significantly lower 1-year AFS than those with levels ≤4.5 mg/dl and hemodialysis vintages ≤6.1 years. The HR was 0.563 (95% CI, 0.329–0.962; p=0.036), while the subgroup with >4.5 mg/dl and with ≤6.1 years and the subgroup with ≤4.5 mg/dl and with >6.1 years had an HR of 0.996 (95% CI, 0.531–1.730; p=0.887) and 0.985 (95% CI, 0.538–1.805; p=0.962), respectively, relative to those with phosphorus levels ≤4.5 mg/dl and hemodialysis vintages ≤6.1 years. The association of hemodialysis vintage and serum phosphorus level with 1-year AFS is shown in Fig. 4A. The subgroup with phosphorus levels >4.5 mg/dl and hemodialysis vintages >6.1 years did not have a significantly lower 1-year wound healing compared to those with phosphorus levels <4.5 mg/dl and hemodialysis vintages <6.1 years.
A 1-year AFS (2-A) and wound healing (2-B) rate were 70.5±2.5% and 57.1±3.0, respectively.

Fig. 2. Kaplan-Meier analysis for amputation-free survival (AFS) and wound healing

Table 3 shows predictors of 1-year AFS after EVT. After multivariate analysis, body mass index (HR, 1.090; 95% CI, 1.020–1.164; \( p = 0.012 \)), non-ambulatory status (HR, 0.530; 95% CI, 0.343–0.818; \( p = 0.004 \)), low serum albumin level (HR, 1.692; 95% CI, 1.184–2.415; \( p = 0.004 \)), WIfI stage 4 (HR, 0.561; 95% CI, 0.364–0.865; \( p = 0.009 \)) and longer vintages for hemodialysis with higher serum phosphorus levels (HR, 0.599; 95% CI, 0.394–0.910; \( p = 0.016 \)) were significantly associated with 1-year AFS.

Table 4 shows the predictors of 1-year wound healing after EVT. After multivariate analysis, WIfI stage 4 (HR, 0.713; 95% CI, 0.519–0.979; \( p = 0.037 \)) was significantly associated with 1-year wound healing. Longer vintages for hemodialysis with higher

hemodialysis vintages <6.1 years (Fig. 4B). The HR was 0.680 (95% CI, 0.437–1.057; \( p = 0.087 \)), while the subgroup with >4.5 mg/dl and with ≤ 6.1 years and the subgroup with ≤ 4.5 mg/dl and with >6.1 years had an HR of 1.040 (95% CI, 0.695–1.556; \( p = 0.849 \)) and 1.204 (95% CI, 0.806–1.798; \( p = 0.364 \)), respectively.

Table 3. Kaplan-Meier analysis for amputation-free survival (AFS) and wound healing by serum phosphorus level and vintages of hemodialysis

A: 1-year AFS was significantly lower in the group with longer hemodialysis vintages and higher serum phosphorus levels than in the group with others (\( p = 0.009 \)).
B: 1-year wound healing was significantly lower in the group with longer hemodialysis vintages and higher serum phosphorus levels than in the group with others (\( p = 0.019 \)).
hemodialysis vintage and serum phosphorus levels on clinical outcomes. The results revealed longer hemodialysis vintages and higher serum phosphorus levels, poorer comorbidities, and severe wound status were significantly associated with 1-year AFS. On the other hand, WIfI stage 4 was the sole risk factor for 1-year wound healing, while longer hemodialysis vintages with higher serum phosphorus levels were marginally but not significantly associated with 1-year wound healing.

**Table 3.** Cox-regression analysis for 1-year amputation-free survival (AFS)

|                      | Univariate analysis |           | Multivariate analysis |           |
|----------------------|---------------------|-----------|-----------------------|-----------|
|                      | Hazard ratio (95%CI) | P value   | Hazard ratio (95%CI)  | P value   |
| Male gender          | 1.506 (0.607-2.188) | P=0.868   | 1.090 (1.020-1.164)   | P=0.012   |
| Body mass index      | 1.145 (1.071-1.225) | P<0.001   | 0.530 (0.343-0.818)   | P=0.004   |
| Non-ambulatory status| 0.373 (0.246-0.564) | P<0.001   | 0.599 (0.394-0.910)   | P=0.016   |
| Hypertension         | 0.775 (0.519-1.154) | P=0.210   | 0.561 (0.364-0.865)   | P=0.009   |
| Diabetes mellitus    | 0.697 (0.464-1.049) | P=0.084   | 0.599 (0.394-0.910)   | P=0.016   |
| Coronary artery disease | 0.880 (0.591-1.307) | P=1.137   | 0.599 (0.394-0.910)   | P=0.016   |
| Cerebrovascular disease | 0.909 (0.497-1.664) | P=0.757   | 0.599 (0.394-0.910)   | P=0.016   |
| Serum calcium level  | 1.110 (0.862-1.429) | P=0.419   | 0.599 (0.394-0.910)   | P=0.016   |
| Serum phosphorus level | 0.909 (0.810-1.020) | P=0.106   | 0.599 (0.394-0.910)   | P=0.016   |
| Serum albumin level  | 2.232 (1.631-3.049) | P<0.001   | 1.692 (1.184-2.415)   | P=0.004   |
| WIfI stage 4         | 0.438 (0.289-0.664) | P<0.001   | 0.561 (0.364-0.865)   | P=0.009   |
| HD>6.1 years and P>4.5 mg/dl | 0.577 (0.380-0.874) | P=0.009   | 0.599 (0.394-0.910)   | P=0.016   |

The model included HD >6.1 years and P>4.5 mg/dl, body mass index, non-ambulatory status, serum albumin level, WIfI stage 4. WIfI, Wound, Ischemia, and foot Infection classification system; HD, hemodialysis; P, phosphorus.

**Discussion**

**Summary of the Current Study**

The current study analyzed the impact of serum phosphorus levels (HR, 0.684; 95% CI, 0.467–1.000; p=0.050) were marginally but not significantly associated with 1-year wound healing.
of our knowledge, the current study was the first to examine the relationship between longer hemodialysis vintages, higher serum phosphorus levels, and AFS. Another highlight of the current study was to assess the impact of hemodialysis vintage and serum phosphorus level on 1-year wound healing rate. The 1-year wound healing of 57.1% in the current study was consistent with previous studies\(^{12}\). A multivariate analysis demonstrated that WIfI stage 4 was significantly associated with 1-year wound healing, while longer vintages for hemodialysis with higher serum phosphorus levels were marginally but not significantly associated. Major tissue loss and severe wound infection are both well-known risk factors for delayed wound healing that generally require absolute blood flow\(^{17}\). Previous literature had reported that WIfI stage 4 was a strong prognostic factor reflecting wound healing\(^{13, 18}\). When the study population was limited to hemodialysis patients with CLTI presenting with ischemic tissue loss, a consistent result was found. Additionally, the current study did not identify the Rutherford classification as an interacting factor like the WIfI classification, presumably because it was not accurate to classify wound severity. At least in performing revascularization in this population, the WIfI classification would be more informative than the Rutherford classification for predicting wound healing. In terms of longer vintages for hemodialysis with higher serum phosphorus levels, we speculated that these would accelerate vessel calcification, leading to the results of suboptimal angioplasties and consequently delayed wound healing. Clinically, serum phosphorus levels, as well as longer vintages for

| Table 4. Cox-regression analysis for 1-year wound healing |
|---|---|---|
| Univariate analysis | Multivariate analysis |
| Hazard ratio (95%CI) | P value | Hazard ratio (95%CI) | P value |
| Male gender | 0.757 (0.555-1.034) | P=0.080 | 0.792 (0.572-1.099) | P=0.163 |
| Body mass index | 1.009 (0.971-1.050) | P=0.639 |  |
| Non-ambulatory status | 0.677 (0.496-0.923) | P=0.014 |  |
| Hypertension | 0.891 (0.654-1.215) | P=0.467 |  |
| Diabetes mellitus | 1.038 (0.753-1.431) | P=0.891 |  |
| Coronary artery disease | 1.135 (0.842-1.528) | P=0.406 |  |
| Cerebrovascular disease | 0.890 (0.583-1.360) | P=0.591 |  |
| Serum calcium level | 1.153 (0.961-1.382) | P=0.125 |  |
| Serum phosphorus level | 0.903 (0.815-1.000) | P=0.051 |  |
| Serum albumin level | 1.451 (1.118-1.884) | P=0.005 | 1.249 (0.943-1.654) | P=0.121 |
| WIfI stage 4 | 0.616 (0.455-0.835) | P=0.002 | 0.713 (0.519-0.979) | P=0.037 |
| HD > 6.1 years and P > 4.5 mg/dl | 0.638 (0.437-0.932) | P=0.020 | 0.684 (0.467-1.000) | P=0.050 |

The model included HD > 6.1 years and P > 4.5 mg/dl, non-ambulatory status, serum albumin level, WIfI stage 4. WIfI, Wound, Ischemia, and foot Infection classification system; HD, hemodialysis; P, phosphorus

Summary of Previously Reported Studies

CKD, including hemodialysis, is a well-known prognostic factor of mortality and major amputation in CLTI patients after endovascular or surgical revascularization\(^{10-12}\). In the population limited to CKD patients with CLTI, several comorbidities were prognostic factors after revascularization. The current study’s result supported findings from prior investigations that body mass index, non-ambulatory status, low serum albumin level, and WIfI stage 4 affected 1-year AFS in hemodialysis patients with CLTI presenting with tissue loss\(^{13}\). Although these studies analyzed CLTI patients with Rutherford 4 to 6, the current study was limited to CLTI patients with ischemic tissue, leading to a somewhat different result. Another study reported that serum phosphorus level was a predictor of AFS prognosis in CLTI patients\(^{14}\). In the current study, the serum phosphorus level was not significantly associated with 1-year AFS among a cohort of hemodialysis patients with ischemic tissue loss, which was different from previous reports\(^{15}\). One major possibility for this difference might be the historical background of each study. The previous study enrolled CLTI patients but included Rutherford 4 and non-dialysis CLTI patients. Guidelines for renal replacement therapy have reported that hemodialysis’s vintages are one of the risk factors for vascular calcification and that dialysis vintage significantly increased the risk of cardiac death\(^{16}\). Taken together, longer vintages for hemodialysis with higher serum phosphorus levels adversely impact AFS. To the best of our knowledge, the current study was the first to examine the relationship between longer hemodialysis vintages, higher serum phosphorus levels, and AFS.

Another highlight of the current study was to assess the impact of hemodialysis vintage and serum phosphorus level on 1-year wound healing rate. The 1-year wound healing of 57.1% in the current study was consistent with previous studies\(^{12}\). A multivariate analysis demonstrated that WIfI stage 4 was significantly associated with 1-year wound healing, while longer vintages for hemodialysis with higher serum phosphorus levels were marginally but not significantly associated. Major tissue loss and severe wound infection are both well-known risk factors for delayed wound healing that generally require absolute blood flow\(^{17}\). Previous literature had reported that WIfI stage 4 was a strong prognostic factor reflecting wound healing\(^{13, 18}\). When the study population was limited to hemodialysis patients with CLTI presenting with ischemic tissue loss, a consistent result was found. Additionally, the current study did not identify the Rutherford classification as an interacting factor like the WIfI classification, presumably because it was not accurate to classify wound severity. At least in performing revascularization in this population, the WIfI classification would be more informative than the Rutherford classification for predicting wound healing. In terms of longer vintages for hemodialysis with higher serum phosphorus levels, we speculated that these would accelerate vessel calcification, leading to the results of suboptimal angioplasties and consequently delayed wound healing. Clinically, serum phosphorus levels, as well as longer vintages for...
dialysis, have been associated with the presence and extent of arterial calcification among patients on dialysis\(^\text{19, 20}\). The description regarding the relation between endothelial function, vessel calcification, and serum phosphorus levels has been accordingly added as follows; increasing evidence supports a role for phosphate in the pathogenesis of medial and intimal calcification. Vascular smooth muscle cells respond to increased phosphate levels by undergoing osteochondrogenic differentiation with subsequent mineralization of the extracellular matrix\(^\text{21, 22}\). When an endovascular approach is clinically applied to hemodialysis patients with CLI, the presence of calcified arterial lesions is generally opposed to the achievement of technical success, mainly due to the following two clinical issues: 1) difficulty of acquiring acute gain by balloon dilatation, and 2) difficulty of maintaining vessel patency because of early recoil due to calcified arterial walls. Our findings indicate that vessel calcification caused by longer vintages for hemodialysis with higher serum phosphorus levels might reflect such technical difficulties during procedures, and early recoil or restenosis in un-dilatable calcified lesions would result in a lower wound healing rate after endovascular therapy.

**Study Limitations**

There were several limitations in the current study. First, this investigation consisted of a retrospective, single-center study and only enrolled patients undergoing EVT and not surgical bypass therapy. Further studies in other groups are required to confirm these results. Second, detailed data on the continuation of medical intervention was not collected. Some literature has reported that these procedures, and early recoil or restenosis in un-dilatable calcified lesions would result in a lower wound healing rate after endovascular therapy.

Although efforts were made to obtain consistent and accurate wound evaluations, some amount of error was inevitable. Fourth, we could not collect the baseline characteristics for a substantial amount of the population, leading to unfortunate exclusion. This may impact the study’s outcomes.

**Conclusion**

Longer hemodialysis vintages with higher serum phosphorus levels adversely impact on outcomes after EVT for hemodialysis patients with CLI presenting with ischemic tissue loss.

**Conflicts of Interest**

None.

**Financial Disclosure**

None.

**References**

1) US Renal Data System 2014 Annual Data Report: Epidemiology of Kidney Disease in the United States. Chapter 10 International comparison. Am J Kidney Dis, 2015; 63: 187-210

2) Ann O, Daniel B, Anton S, Michael S, Saunak S, Mary-Margaret C. Renal Insufficiency and Use of Revascularization among a National Cohort of Men with Advanced Lower Extremity Peripheral Arterial Disease. Clin J Am Soc Nephrol, 2006; 1: 297-304

3) Shikhar A, Karan S, Shishehbor H. Nationwide Trends of Hospital Admission and Outcomes Among Critical Limb Ischemia Patients From 2003–2011. J Am Coll Cardiol, 2016; 67: 1901-1913

4) Louis N, Gregory M, Michael C, Dennis B, Alexander C, Lynn S, PREVENT III Investigators. Prospective multicenter study of quality of life before and after lower extremity vein bypass in 1404 patients with critical limb ischemia. J Vasc Surg, 2006; 44: 977-983; discussion: 983-984

5) Ann O, Daniel B, Anton S, Michael S, Saunak S, Mary-Margaret C. Renal Insufficiency and Use of Revascularization among a National Cohort of Men with Advanced Lower Extremity Peripheral Arterial Disease. Clin J Am Soc Nephrol, 2006; 1: 297-304

6) Alap S, Andrew K, Andrew S, John M, Stephen A, Mark N, William H, Ivan C. Clinical outcomes using aggressive approach to anatomic screening and endovascular revascularization in a Veterans Affairs population with critical limb ischemia. Catheter Cardiovasc Interv, 2009; 74: 11-19

7) Jana O, Brigitta G, Nicolas D, Tobias T, Iris B. Survival benefits of revascularization in patients with critical limb ischemia and renal insufficiency. J Vasc Surg, 2012; 56: 737-745

8) Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, FowkesFG, Kevin B, Joseph C, Isabelle D, Komori K, Lammer J, Liapis C, NovoS, Razavi M, Robbs J, Schaper N, Shigematsu H, Sapoval M, White C, White J, Clement D, Creager M, Jaff M, Mohler E, Rutherford RB, Sheehan P, Sillesen H, Rosenfield K. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg, 2007; 33 Suppl 1: S1-75

9) Haneda M, Noda M, Origasa H, Noto H, Yabe D, Fujita Y, Goto At, Kondo T, Araki E. Japanese Clinical Practice Guideline for Diabetes 2016. J Diabetes Investig, 2018; 9: 657-697

10) Theodosios B, Giovanni T, Konstantinos S. The CRITISCH Registry Investigators provide an overview of registry data examining various treatment options for
patients with CLI. ENDOVASCULAR TODAY MAY 2019 VOL. 18, NO. 5
11) Michael SC, Andrew B, Philippe K, John VW, Florian D, Robert F, Joseph LM, Jean-Baptiste R, Kalkunte RS, Murad MH, GVG Writing Group. Global vascular guidelines on the management of chronic limb-threatening ischemia. J Vasc Surg, 2019; 69: 3S-125S
12) Iida O, Nakamura M, Yamauchi Y, Fukunaga M, Yokoi Y, Yokoi H, Soga Y, Kan Zen, Suematsu N, Inoue N, Suzuki K, Hirano K, Shintani Y, Miyashita Y,urasawa K, Kitano I, Tsuchiya T, Kawamoto K, Yamaoka T, Uesugi M, Shinke T, Oba Y, Ohura N, Uematsu M, Takahara M, Hamasaki T, Nanto S. A Prospective, Multi-Center, Three-Year Follow-Up Study on Endovascular Treatment for Infra-Ingual Vessel in Patients With Critical Limb Ischemia OLIVE 3-Year Follow-Up Study. JACC Intv, 2015; 8: 1493-1502
13) Joseph L, Michael S, David G, Frank B, Andres S, George A. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIfI). J Vasc Surg, 2014; 59: 220-234
14) Sara LZ, Peter AS, Klaas HJU, Crystal S, Jinhee O, Kevin M, Marc LS, Raul JG. Elevated serum phosphate levels are associated with decreased amputation-free survival after interventions for critical limb ischemia. J Vasc Surg, 2017; 65: 431-437
15) Hioki H, Miyashita Y, Shiraki T, Iida O, Uematsu M, Miura T, Ebisawa S, Ikeda U. Impact of deteriorated calcium-phosphate homeostasis on amputation-free survival after endovascular revascularization in patients with critical limb ischemia on hemodialysis. Vascular Medicine, 2016; 21: 137-143
16) Lijie M, Sumei Z. Risk factors for mortality in patients undergoing hemodialysis- A systematic review and meta-analysis. International Journal of Cardiology, 2017; 238: 151-158
17) Shiraki T, Iida O, Takahara M, Soga Y, Yamauchi Y, Hirano K, Kawasaki D, Fujihara M, Utsunomiya M, Tazaki J, Yamaoka T, Shintani Y, Suematsu N, Suzuki K, Miyashita Y, Tsuchiya T, Uematsu M. Predictors of delayed wound healing after endovascular therapy of isolated infrapopliteal lesions underlying critical limb ischemia in patients with high prevalence of diabetes mellitus and hemodialysis. Eur J Vasc Endovasc Surg, 2015; 49: 565-573
18) Jeremy DD, John CM, Peter AS, Yifan M, Mark CW, Allen DH, Hence JF, Marc LS. Predictive ability of the Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIfI) classification system following infrapopliteal endovascular interventions for critical limb ischemia. J Vasc Surg, 2016; 64: 616-622
19) Bryan K, Joshua NS, Kyle DR, Donald JP, Stephen LS, Bessie Y, Donald JS, Dennis LA. Serum Phosphate Levels and Mortality Risk among People with Chronic Kidney Disease. J Am Soc Nephrol, 2005; 16: 520-528
20) Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, Elashoff RM, Salusky IB. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med, 2000; 342: 1478-1483
21) Cecilia MG. The emerging role of phosphate in vascular calcification. Kidney Int, 2009 May; 75: 890-897
22) Ketteler M, Bongartz P, Westenfeld R, Wildberger JE, Mahnken AH, Bohm R, Metzger T, Wanner C, Jahn-Dechent W, Floege J. Association of low fetuin-A (AHSG) concentrations in serum with cardiovascular mortality in patients on dialysis: a cross-sectional study. Lancet, 2003; 361: 827-833
23) Matsukura M, Hoshina K, Shigematsu K, Miyata T, Watanabe T. Paramalleolar Arterial Bollinger Score in the Era of Diabetes and End-Stage Renal Disease - Usefulness for Predicting Operative Outcome of Critical Limb Ischemia. Circ J, 2016; 80: 235-242
24) Nakama T, Watanabe N, Haraguchi T, Sakamoto H, Kamoi D, Tsukubimoto Y, Ogata K, Satoh K, Urasawa K, Andoh H, Fujita H, Shibata Y. Clinical Outcomes of Pedal Artery Angioplasty for Patients with Ischemic Wounds: Results From the Multicenter RENDEZVOUS Registry. JACC Cardiovasc Interv, 2017; 10: 79-90
25) Sushant KD, Yi FY, Mao QL. Predictors of delayed wound healing after successful isolated below-the-knee endovascular intervention in patients with ischemic foot ulcers. J Vasc Surg, 2018; 67: 1181-1190