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Research article

Arterial calcification and long-term outcome in chronic limb-threatening ischemia patients

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ABSTRACT

Purpose: Within five years after presentation 50–60% of patients with chronic limb-threatening ischemia (CLI) have died or had an amputation. We assessed the predictive value of lower extremity arterial calcification on computed tomography (CT) characteristics on both 7-years amputation-free survival and 10-years all-cause mortality in patients with CLI.

Method: Included were 89 CLI patients (mean age 73.1 ± 11.6 years) who underwent a CT angiography of the lower extremities. In the femoropopliteal and crural arteries based on a CT score the following calcification characteristics were assessed: severity, annularity, thickness and continuity. The predictive value of different arterial calcification characteristics was analysed by age- and sex-adjusted multivariate Cox regression analysis.

Results: Complete annular calcifications were common (femoropopliteal 43.7%, $n = 38$; crural, 63.2%, $n = 55$). Mean survival was 278.4 weeks (95% CI 238.77–318.0 weeks). Patients with complete annular calcifications had a higher all-cause 10-year mortality (femoropopliteal unadjusted HR 1.64, $p = 0.04$ and adjusted for age and sex HR 1.68, $p = 0.04$; crural unadjusted HR 1.92, $p = 0.02$, adjusted for age and sex HR 2.29, $p = 0.006$) than patients with other calcification characteristics.

Conclusions: Annularity of calcification of both femoropopliteal and crural arteries is a predictor for 10-year all-cause survival, its hazard being even higher than the traditional prognostic risk factors for CLI and therefore could be involved in the poor survival of these patients.

1. Introduction

Chronic limb-threatening ischemia (CLI) defined as Rutherford categories 4, 5 and 6 (corresponding with Fontaine 3 and 4) is associated with high rates of amputations (amputation rate at 1 year: 20.5–38.0%) and cardiovascular diseases [1–4], and this contributes greatly to a high mortality in CLI patients. Within five years after presentation 50–60% of patients will have died [5–8]. The burden of CLI is likely to increase due to increasing age of the western population, the increasing prevalence of diabetes mellitus, chronic kidney disease, metabolic syndrome and the continuing habits of smoking [9–12].

Why the prognosis of these patients is so poor is still not well understood. Many studies in CLI focus on the outcome of treatment strategies of the legs (PREVENT III score, Finnvasc score, BASIL prediction model) [13–19] or risk factors [20], but prognostic studies are still limited. In a previous study we showed that a high/immeasurable ankle-brachial index (ABI) is an independent risk factor for poor amputation-free survival in patients with CLI [20], and it is suggested that medial calcification is in part responsible for this stiffness [20–23].

Vascular calcifications have gained renewed attention in the last few years. The main approach to assess the role of calcifications has been to quantify the amount of calcification [24], but there has been much less interest in imaging characteristics of these calcifications as seen on computed tomography (CT) scans. A CT imaging score was proposed to analyse the carotid siphon on three imaging characteristics; annularity, thickness and continuity and these characteristics were used to improve

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prediction models [25]. Recently, one of our recent studies showed that in the lower extremities different types of arterial calcifications can be distinguished on CT [26].

Different arterial calcification patterns have also proven to have different risk factors and treatment outcome, which may indicate different pathophysiological mechanisms [27–31]. We hypothesized that the specific arterial calcification characteristics on CT scan can have a significant influence on the prognosis in CLI patients, but up to now this has not been proven.

Hence, the aim of this study was to assess the predictive value of CT characteristics of lower extremity arterial calcification on both 7-years amputation-free survival and 10-years all-cause mortality in patients with CLI.

2. Materials and methods

2.1. Study approval

The Percutaneous transluminal Angioplasty versus Drug-eluting stents for Infrapopliteal lesions (PADI) trial was registered in the ClinicalTrials.gov trial register under the number NCT00471289 and informed consents were obtained. The study was conducted according to the Declaration of Helsinki. The present study is a post-hoc analysis of this multi-centre trial.

2.2. Patients

Data from the PADI trial which included patients with CLI, were used. Detailed study design and results of this study have been published elsewhere [32–35]. In short, the PADI trial is a randomized controlled trial to investigate drug eluting stents (DES) for the treatment of infrapopliteal lesions in patients with CLI in comparison with the current reference treatment. Patients ($n = 149$) were included between October 2007 and February 2013. At 6 months after primary treatment, patency results were imaged by CT angiography, digital subtraction angiography or duplex sonography. A CT angiography was performed in 87 patients who are the subject of this study.

2.3. Clinical parameters and definitions

Patients were included with a Rutherford score of 4, 5 or 6. These patients suffer from ischemic rest pain, forefoot ulceration and ulceration with tissue necrosis. Symptoms had to be present longer than 2 weeks [5]. The following patient characteristics were recorded; sex, age, smoking status, diabetes mellitus (DM), coronary artery disease (CAD), stroke, the use of anticoagulant medication, hematocrit value and estimated Glomerular Filtration Rate (eGFR per mL/min/1.73 m^2). Regarding smoking status, patients were classified as smokers, ex-smokers or non-smokers. Chronic kidney disease (CKD) was defined as an eGFR < 45 mL/min/1.73 m^2. This is consistent with CKD stage 3B, 4 and 5: mild to moderate decrease in renal function to renal failure. In specific, dialysis dependent renal function was stated CKD class 5 (eGFR < 15 mL/min/1.73 m^2), which selects patients with the most severe degree of renal failure [36]. An experienced nurse measured blood pressures. Hypertension was defined as a systolic blood pressure $\geq$ 140 mmHg or if the patient was taking antihypertensive medication. The ankle-brachial index was calculated from the highest systolic blood pressure of the dorsalis pedis and posterior tibial arteries divided by the highest systolic blood pressure on the ipsilateral or contralateral brachial arterial systolic pressure. Overall, a single pressure measurement of each limb artery was performed.

2.4. Follow-up criteria and definitions

Follow-up consisted of annual assessments up to 7 years after treatment or until a clinical end-point was reached; amputation (through or above the ankle) or death. Regarding the completion of follow-up data until April 2019 (520 weeks) for this current study, municipal basic records were checked regarding death and date of death. Major amputation was defined as amputation through or above the ankle joint. Amputation-free survival was defined as survival free of amputations in the follow-up period.

2.5. Systematic assessment of calcification patterns

All 87 patients were evaluated on a CT angiography with 3 mm slice thickness reconstructions. Measurements were done by a radiology resident with extensive experience with the scoring system (LK), who was blinded to the patients' clinical data and outcome.

Bone window settings were used for evaluation of arterial calcifications (Window Settings: Window = 300 Hounsfield Units; Width = 1600 Hounsfield Units). This made it possible to distinguish well between calcium and other densities on the CT angiography. Calcification measurements were also not hindered by an acute occluded artery, because the thrombi responsible for these occlusions have lower densities than calcifications. If a stent was present due to previous treatment, this part of the artery was not included in the scoring of calcifications.

The calcification measurements were done according to the recently developed and CT-histologically validated score for the carotid siphon (inter-observer kappa 0.54−0.99) [25,37]. This scoring system has recently been applied in a study of the peripheral arteries and has shown that it makes a good distinction between different calcification characteristics on CT in the peripheral arteries. Extensive information and details about the CT calcification measurement procedure and the associated scoring system are also described herein [26].

In short, CT calcification characteristics were measured on the affected leg with CLI. Both the femoropopliteal and crural arteries were scored. Arterial calcification patterns were examined in a semi-quantitative way; severity (absent, mild, moderate, severe), annularity (absent, dot(s), $<90°$, $90-270°$, $270-360°$), thickness (absent, ≥ 1.5 mm, <1.5 mm), and continuity (indistinguishable, irregular/patchy or continuous). See Fig. 1 for examples of different calcifications of the arteries involved.

2.6. Statistical analysis

Baseline characteristics as well as CT imaging characteristics of arterial calcifications were used to describe the characteristics of the study populations; means with standard deviations (SD) for continuous variables, counts and percentages for categorical variables. Normal distribution was tested by QQ-plots.

The variables severity, annularity, thickness and continuity were converted into dichotomous variables due to the relatively low patient numbers in the 'less severe' categories, into severe vs non-severe, annular vs non-annular, thick vs thin and continuous vs non-continuous. Survival of patients was calculated up to ten years after the first inclusion; 7-year amputation-free survival and 10-year all-cause mortality for all patients were presented using Kaplan-Meier plots. Comparisons between the different characteristics were assessed based on the Log-Rank/Mantel Cox test for significance.

Univariate analyses and age- and sex-adjusted effects were calculated by hazard ratios with 95% confidence intervals (CI) for the different CT imaging characteristics for both 7-year amputation-free survival and 10-year all-cause mortality. A full univariate model and age- and sex-adjusted was created including the CT calcification characteristics and the factors of the known best performing prognostic model for CLI (the prevent III model). The factors of the prevent III model include dialysis-dependent renal function, tissue loss at baseline, advanced age (>75 year), history of coronary disease and hematocrit ($\leq$ 30%). A p-value of less than 0.05 was considered to be significant. Data analysis was carried out using SPSS version 24.0 (IBM Corporation, New York, United States).

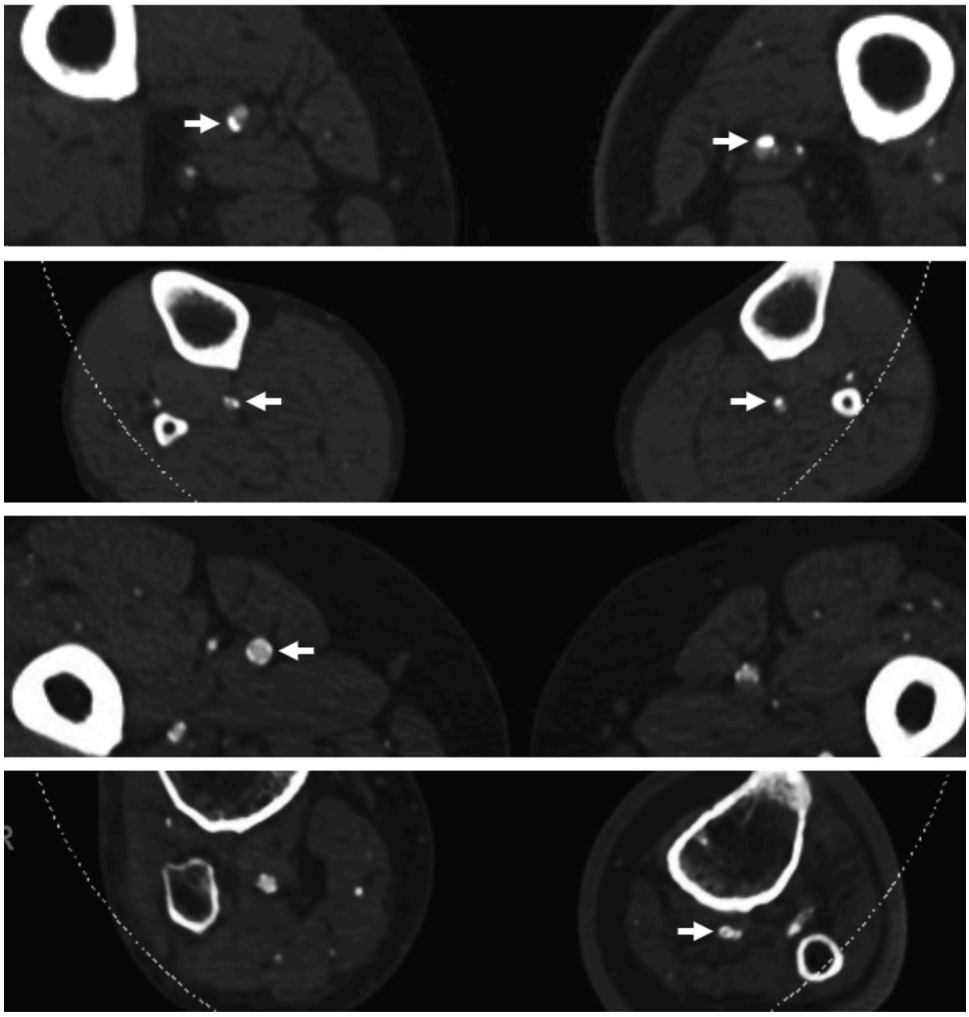

Fig. 1. Axial CT angiography slides at the level of the femoral and crural arteries. Top two figures: examples of incomplete annular (<270°) and thick calcifications (indicating dominant intimal calcifications). Bottom two figures: examples of complete annular (>270°) calcifications and thin calcifications (indicating dominant medial calcifications).

3. Results

3.1. Study population

In total there were 87 patients with a mean age of 73.11 ± 11.63 years. There were 73.6% male patients. Baseline characteristics are shown in Table 1. Mean survival was 278.4 weeks (95% CI 238.77–318.0 weeks) with a maximum follow-up of 520 weeks. After 10 years, the majority of CLI patients had died 67/87 (77.0%). 7-year amputation-free survival was 23/87 (26.2%). Mean amputation-free survival was 215.1 (95% CI 185.1–245.1 weeks). See Fig. 2A and 2B for all-cause mortality and amputation-free survival Kaplan-Meier curves.

3.2. CT imaging calcification patterns

The results of the assessment of calcification CT imaging characteristics (severity, annularity, thickness and continuity) for both femoropopliteal and crural arteries are presented in Table 2.

The majority of the femoropopliteal and crural arterial calcifications were severe. Thickness, annularity and continuity could already be present at lower age but increased considerably with age. See stacked Figs. 3A and 3B, age divided into strata of 20 years. There were no significant differences in calcification patterns between initial treatment strategy (PTA ± BMS / paclitaxel-coated DES).

3.3. Prognostic value of calcification characteristics and factors from the prevent III model

Age- and sex-adjusted effects were calculated for both 7-years amputation-free survival and 10-years all-cause mortality (see Table 3).

Severity of calcification showed in the univariate analysis a higher hazard ratio (HR) than the classic prognostic factors used for CLI as reported in the prevent III model (10-year survival rate: femoropopliteal HR 2.75, 95% CI 1.09–6.91, $p = 0.01$ and crural HR 2.13, 95% CI 1.00–4.51, $p = 0.03$). After adjusting for age and sex, these differences lost significance. Also, for 7-year amputation-free survival, severity did not influence the outcome significantly. Thickness and continuity had no significant HR for both univariate and age- and gender-adjusted.

For annularity of calcifications in the femoropopliteal arteries, both univariate and age- and sex-adjusted HR showed significant HR for predicting 10-year all-cause mortality (unadjusted HR 1.64, 95% CI 0.99–2.73, $p = 0.04$, adjusted for age and sex HR 1.68, 95% CI 1.01−2.80, $p = 0.04$; crural unadjusted HR 1.92, 95% CI 1.01–3.34, $p = 0.02$, adjusted for age and sex HR 2.29, 95% CI 1.28−4.13, $p = 0.006$). Crural calcifications also had a significant predictive value on 7-years amputation-free survival after adjusting for age and sex (see Table 3).

Of the prevent III factors, only advanced age was significant for both 7-year amputation-free survival (HR 1.40, 95% CI 1.05–1.9, $p = 0.02$) and 10-year all-cause mortality (HR 1.38, 1.06–1.80, $p = 0.02$).

Table 1
Baseline clinical characteristics of all included patients.

Variables		N (%)/mean ± SD
Age (years)		73.1 ± 11.6
40–59 y		10 (11.5%)
60–79 y		47 (54.0%)
80–99 y		30 (34.5%)
Sex (male)		64 (73.6%)
Smoking habit	Smoker	21 (24.1%)
	Ex-smoker	20 (23.0%)
Hypertension		39 (70.9%)
History of CAD		33 (37.9%)
History of stroke		9 (10.3%)
History of DM		53 (60.9%)
eGFR (mL/min/1.73 m^2)		59 ± 27
CKD (eGFR<45 mL/min/1.73m^2)		26 (30.2%)
Dialysis-dependent renal function (eGFR<15 mL/min/1.73m^2)		4 (4.6%)
Rutherford category at baseline	4	15 (17.2%)
	5	55 (63.2%)
	6	16 (18.4%)
ABI at baseline		0.85 ± 0.27
ABI at baseline (categorized)	ABI<0.7	41 (47.1%)
	0.7 < ABI<1.4	37 (42.5%)
	ABI>1.4 or immeasurable	9 (10.3%)
Initial treatment (PTA ± BMS or DES)	PTA ± BMS	45 (51.7%)
	DES	42 (48.3%)

Abbreviations: CAD = coronary artery disease, DM = diabetes mellitus, eGFR = glomerular filtration rate (mL/min/1.73m^2), CKD = chronic kidney disease, ABI = ankle-brachial index, PTA = percutaneous transluminal angioplasty, BMS = bare-metal stents, DES = drug-eluting stents.

4. Discussion

4.1. Principal findings

In this present study, CT imaging characteristics of calcifications of the femoropopliteal and crural arteries in a cohort of CLI patients were investigated. Annularity was a good predictor for 10-year all-cause survival in both femoropopliteal and crural arteries and for 7-year amputation-free survival only in the crural arteries. Severity, thickness and continuity of calcifications were of no predictive value. Already in our youngest age category 40–59 years, the majority of femoropopliteal and crural arteries had severe calcifications, which increased gradually per age group. Calcifications were also thicker, more annular and more continuous on a higher age.

These findings provide insights into the importance of CT imaging characteristics of arterial calcifications compared to the classical known risk factors of CLI and can contribute to improving prognostic modelling for CLI patients.

4.2. Different arterial calcifications and locations

Histologic studies show two different types of calcifications; medial and intimal. Where in earlier days was thought that arterial intimal calcifications were present in only the most severe (type 5b lesions) [38], we now know that arterial calcification can be present in all forms of atherosclerosis, despite its severity. Medial arterial calcification is hydroxyapatite deposited along elastin fibers in the medial wall where vascular smooth muscle cells undergo transdifferentiation to an osteo/chondrogenic cell type [39]. One of the calcification characteristics of medial calcification is annularity. The predictive value of annular calcifications for mortality found in this study is therefore most likely caused by these medial calcifications [40].

Femoropopliteal and infrapopliteal/below-the knee arteries seem to differ in pathology with significantly more atherosclerosis in the SFA than the BTK arteries. Hunter's canal, through which the femoral artery runs, is a location prone to atherogenesis [41]. Therefore, more intimal wall calcifications can be expected. Recently, a histopathologic post-mortem study that analysed especially CLI patients showed that medial calcifications are significantly more common in the crural than in femoropopliteal arteries (OR 2.89, $p = 0.08$) [42].

Our current study result fits well with these observations. Since we can expect full annular calcification, which is more common in the crural arteries, can lead to a higher odds ratio on survival compared to the femoropopliteal arteries where less complete annular calcification occurs.

4.3. Annularity of arterial calcifications

Annularity of calcifications, probably localized in the medial layer of the arterial wall, as a predictor for all-cause mortality has been described in other arterial locations previously. Hendriks et al. showed that a greater annularity of the calcifications in the aorta-iliac arteries is associated with a higher mortality risk [28]. In addition, in another study conducted in the common carotid artery, carotid bulb, and proximal internal carotid artery it was shown that greater annularity was associated with less neurological symptoms [43].

Annularity of the vascular calcifications has also been studied by correlating histology with CT imaging characteristics. Kockelkoren et al. showed in the intracranial internal carotid artery that complete annularity was mainly located in the medial layer of the vessel wall [25]. However, CT–histologic correlation studies for the arteries of the lower extremity are lacking.

How annular vascular calcifications can influence all-cause mortality is not completely understood but it has been thought that annular calcifications can damage the elasticity and cause stiffening of the vessel wall. This in turn can cause an increase in pulse wave velocity and damage the small vessels of organs such as kidney and brain [44,45]. Furthermore, it has been postulated that annular calcifications can prevent vascular remodelling making coping with concomitant atherosclerotic disease much more difficult [40].

4.4. Arterial calcification and aging

We showed that in CLI the calcifications were more severe in older patients which increased gradually by age group. Previously we also showed that in asymptomatic patients, arterial calcifications gradually increased per age group [26]. Zettervall et al. showed that patients with CLI had much more severe calcifications than patients with intermittent claudication independent of the severity of the disease [46]. So, it seems likely that asymptomatic patients, patients with claudication and CLI patients have increasingly more severe calcifications and that calcifications are more severe with a higher age.

4.5. Strengths and limitations

This study has several strengths. To our knowledge, this study is the first prognostic cohort which studied calcification patterns as seen on CT scans in CLI patients in relation to long-term survival. Other strengths include the high event rate and completeness of the mortality data at 10-year follow-up.

This study also has its limitations to mention. First, since this study is a follow-up study of a randomized clinical trial (PADI trial), the treatment strategy may have affected our outcome. The initial PADI Trial has randomized for PTA ± BMS and paclitaxel-coated DES. We are aware of the current warnings by amongst others the FDA given after a meta-analysis concerns paclitaxel-coated DES and DEB. Therefore, we conducted an additional study investigating 10-year follow-up, this showed no significant difference in survival between our PTA ± BMS and DES patients. Also, we did not observe any dose-related adverse effects on survival of CLI patients treated with paclitaxel-coated DES in a recently published additional analysis [35]. We also rigorously searched the

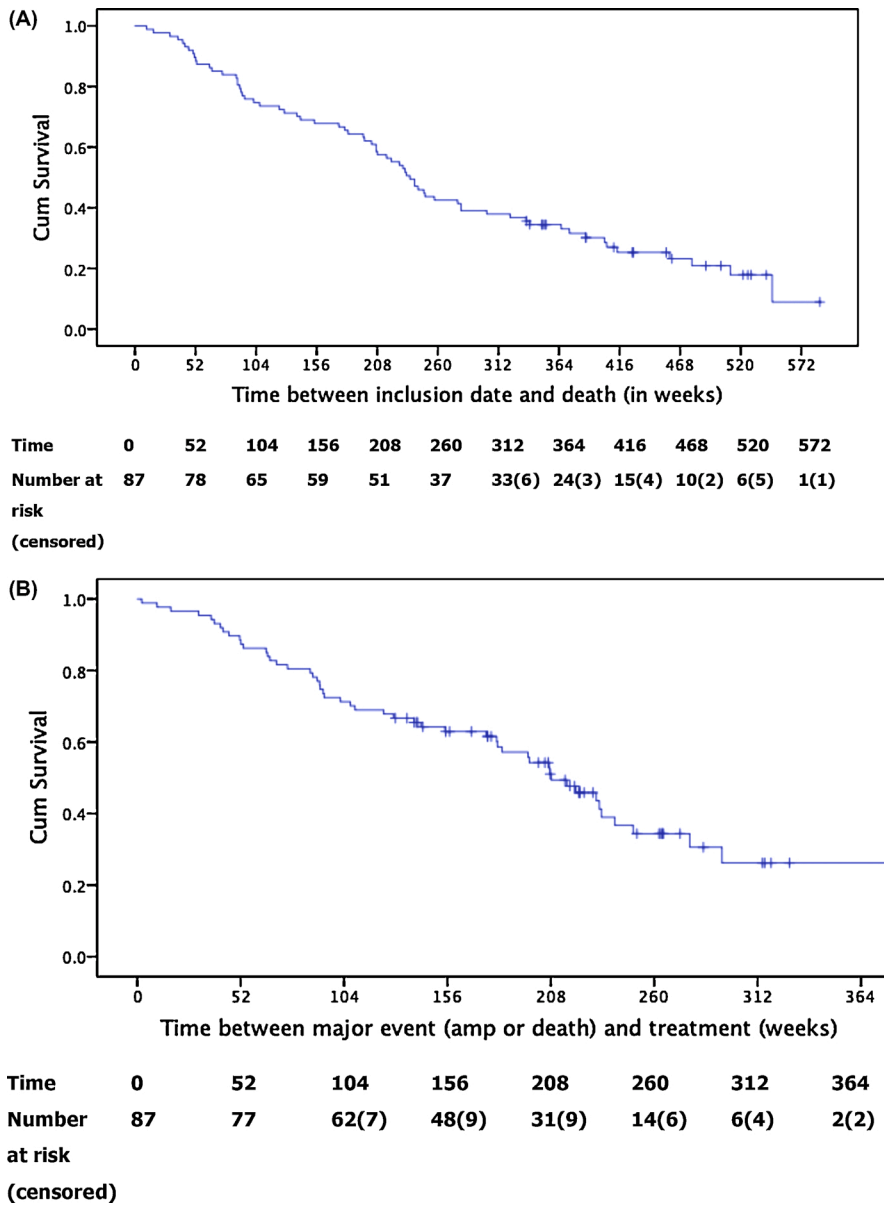

Fig. 2. A. 10-years Kaplan Meier all-cause survival curve of all CLI patients. B. Kaplan Meier amputation-free survival of all CLI patients.

Table 2
Severity, annularity, thickness and continuity of calcifications in femoropopliteal and crural arteries.

		Femoropopliteal N (%)	Crural N (%)
Severity	Absent	2 (2.3%)	2 (2.3%)
	Mild	5 (5.7%)	4 (4.6%)
	Moderate	6 (6.9%)	10 (11.5%)
	Severe	74 (85.1%)	71 (81.6%)
Annularity	No calcifications	2 (2.3%)	2 (2.3%)
	Dot(s)	8 (9.2%)	6 (6.9%)
	< 90	10(11.5%)	18 (20.7%)
	90–269	29 (33.3%)	6 (6.9%)
	270–360	38 (43.7%)	55 (63.2%)
Thickness	0mm	2 (2.3%)	2 (2.3%)
	>1.5 mm	60 (69.0%)	63 (72.4%)
	≤1.5 mm	25 (28.7%)	22 (25.3%)
Continuity	Dot/indefinable	6 (6.9%)	3 (3.4%)
	Irregular/patchy	58 (66.7%)	49 (56.3%)
	Continuous	23 (26.4%)	35 (40.2%)

Values were presented as number (percentages).

current literature to a possible influence of paclitaxel on (arterial) calcium. However, we found no evidence in current literature that calcifications are affected by these low doses of paclitaxel. Therefore, we do not expect the previous treatment strategies in this study cohort to have affected our current study results.

The second limitation of the study is that the PADI study has used as exclusion criterium an impaired renal function (eGFR<20 mL/min/1.73 m^2), excluding patients with a likely high calcification load that, if included, may have increased our odds ratios for calcification in our study. If so, the reported association and findings could be stronger.

4.6. Conclusions

In conclusion, annularity of calcifications in the arterial wall is a good predictor for 10-year all-cause mortality and 7-year amputation-free survival of CLI patients, especially in the crural arteries and is easy to use in daily clinical practice. Severity, thickness and continuity of calcifications are not predictive for survival. The predictive value of annularity is higher than the traditional prognostic risk factors for CLI.

Recognizing the influence of arterial calcifications on long-term

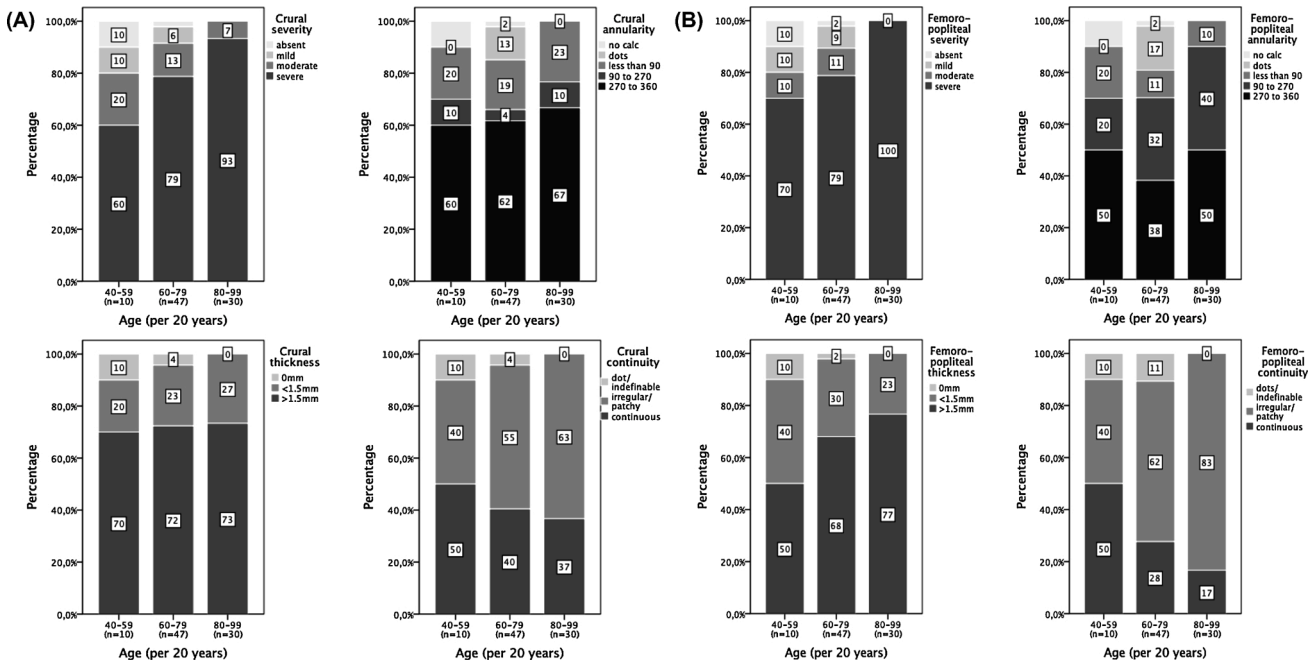

Fig. 3. A. Stacked graphs showing the different calcification characteristics, divided into age-strata per 20 years for the crural arteries. B. Stacked graphs showing the different calcification characteristics, divided into age-strata per 20 years for the femoropopliteal arteries.

Table 3
Cox Regression analyses for 7-years amputation-free survival and 10-year all-cause mortality, multivariate corrected for age and sex.

		7-years amputation-free survival			10-year all-cause mortality		
		HR	950% CI	P	HR	950% CI	P
Severity	Femoropopliteal	0.78	0.34–1.77	0.50	2.03	0.79–5.13	0.14
	Crural	1.00	0.47–2.15	0.99	1.55	0.71–3.35	0.26
Annularity	Femoropopliteal	1.54	0.88–2.71	0.13	1.68	1.01–2.80	0.04*
	Crural	1.96	1.05–3.65	0.03*	2.29	1.28–4.13	0.006*
Dialysis-dependent renal function		1.27	0.88–1.83	0.20	0.85	0.52–1.40	0.53
Tissue loss at baseline		1.08	0.84–1.39	0.56	1.16	0.91–1.47	0.23
Advanced age (>75 year) †		1.37	1.02–1.85	0.04*	1.38	1.05–1.82	0.02*
History of coronary disease		1.42	0.80–2.55	0.89	1.26	0.74–2.16	0.39
Hematocrit (≤ 30%)		1.80	0.67–4.89	0.24	1.05	1.02–1.08	0.84

* p-value < 0.05.
† Advanced age (>75 year) only adjusted for sex.

survival in CLI patients adds to the current prognostic risk factors known in this poorly performing patient cohort.

Statement of originality

The authors hereby declare to take full responsibility for the contents of this article. The authors declare that the text presented is original and that the only sources used were the sources we have quoted and mentioned in my reference list.

Declaration of Competing Interest

All authors declare that they have received no grants, contracts, other forms of financial supports or relationships with the industry relevant to this paper.

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AUTHORSHIP All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

CRediT authorship contribution statement

Louise CD Konijn: Conceptualization, Methodology, Formal analysis, Validation, Investigation, Writing - original draft, Writing - review & editing. **Richard AP Takx:** Conceptualization, Methodology, Validation, Writing - review & editing, Supervision. **Pim A de Jong:** Conceptualization, Methodology, Validation, Investigation, Writing - review & editing, Supervision. **Marlon I Spreen:** Investigation, Resources. **Hugo TC Veger:** Writing - review & editing. **Willem PThM Mali:** Conceptualization, Methodology, Investigation, Writing - review & editing, Supervision. **Hendrik van Overhagen:** Conceptualization, Writing - review & editing, Supervision.

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