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Research paper

Systemic arterial calcium burden in patients with chronic limb-threatening ischemia

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ABSTRACT

Introduction: 5-year mortality of chronic limb-threatening ischemia (CLTI) is 50–60% and coronary artery disease (CAD) is the main cause of death of CLTI patients, followed by stroke. The aim of this study is to quantify and qualify the calcium load in different arterial territories in patients with CLTI.
Methods: Prospectively, 60 patients with CLTI were included and received a full-body CT scan. 6 patients were excluded. Different arterial territories (the peripheral lower extremity arteries, coronary arteries, extracranial and intracranial carotid arteries, thoracic and abdominal aorta) were analyzed. Analysis and interrelations of both quantitative and semi-quantitative CT measurements was performed.
Results: Mean age was 72 years (range 47–95; SD 11.4). Almost all CLTI patients had calcified arterial beds (femoropopliteal 100%, crural 98.1%, coronary 100%, carotid bifurcation 96.2%, internal carotid artery 98.1%, thoracic aorta 96.2%, abdominal aorta 92.3%). Nearly all arterial territories had severe calcifications. 57% had a very high coronary Agatston score (>1000), and 35% extremely high (>2000). Calcifications in the lower extremity were significantly correlated to CAC score, carotid artery bifurcation calcification score, and to a lesser extent correlated to annular calcifications in the aorta. Very high and extremely high total CAC scores were strongly correlated with severe lower extremity arterial calcifications and severe carotid and intracranial internal carotid artery, thoracic and abdominal aorta calcifications in patients with CLTI patients.
Conclusions: In CLTI patients nearly all arterial territories are severely calcified, suggesting that systemic calcification plays an important role in the poor outcome of this disease.

1. Introduction

Although chronic limb-threatening ischemia (CLTI) is considered the most severe stage of peripheral arterial disease (PAD) leading frequently to lower extremity amputation, data suggest that it is a systemic cardiovascular disease since acute coronary syndrome, stroke and heart failure are leading to a high morbidity and mortality. A recent systematic review and meta-analysis showed that in patients with non-reconstructible CLTI in the year of diagnosis 27% had a major amputation and 18% died. The five-year mortality of CLTI patients is 50–60%[1–11] and coronary artery disease (CAD) is the main cause of death followed by stroke.[11,12] The prevalence of PAD including CLTI is still increasing to date.[13,14] Mortality rates in patients with CLTI improved somewhat in the last decade, probably due to more systematic use of anti-atherosclerotic and anti-hypertensive medication but the prognosis of patients with CLTI still remains very poor. Given the effective drugs it may well be that the high residual risk is not fully explained by atherosclerosis.

Evidence is accumulating that, at least in the lower extremities, a distinct process co-occurs with atherosclerosis, which is medial arterial calcification (MAC). In MAC deposits of hydroxyapatite occur in the medial layer of the arterial wall. These calcifications are increasingly recognized as being prevalent in PAD and they maybe an independent cause of vascular events. The typical concentric calcifications in MAC contribute to arterial stiffening and thereby contribute to hypertension, heart failure and pulse pressure related organ damage in susceptible organs like the kidneys

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and brain. We hypothesized that extensive calcifications would be present in the arterial tree of CLTI patients. If so, they could be responsible for some of the remaining vascular disease burden after adequate anti-atherosclerotic and anti-hypertensive treatment.

Therefore, the aim of this current study is to quantify and qualify the calcium load in different arterial territories (the peripheral lower extremity arteries, coronary arteries, extracranial and intracranial carotid arteries, thoracic and abdominal aorta) on full-body computed tomography (CT) scans in patients with CLTI and assess interrelations.

2. Materials and methods

2.1. Ethical approval

The medical Ethical Committee Zuid-West Holland Leiden/The Hague gave approval to perform the prospective PADI Imaging Trial in the Haga Teaching Hospital, the Hague, the Netherlands (Unique identifier number: NL64059.098.17) as well as the institutional board of the Haga Teaching Hospital. Written informed consent for the PADI Imaging Trial was obtained in all participants.

2.2. Study population

60 CLTI patients with a Rutherford 4, 5 and 6 (Fontaine 3 and 4) were recruited in the outpatient clinic by the vascular surgeon and were included in this study. Six patients were excluded; two patients due to low Fontaine stage (IIB) and four patients due to incomplete scanning. The remaining 54 patients were included for analysis. Extensive clinical assessment contained the following variables: age, gender, diabetes mellitus (DM), weight, current smoking status, systolic blood pressure, diastolic blood pressure, and renal function expressed in electronic glomerular filtration rate (eGFR). Obesity was defined as a body mass index (BMI) $\geq$ 30 kg/m^2. Hypertension was defined as a systolic blood pressure at admission >140 mmHg or diastolic blood pressure of >90 mmHg. Chronic kidney disease (CKD) was defined as an eGFR <60 ml/min/1.73 m^2, mildly decreased kidney function to renal failure (G3a-G5).[15] Severely decreased kidney function (G4-G5) was defined as a cut-off value of <30 ml/min/1.73 m^2,.[16]

For 5 years we will report the major complications and death. Major complications are; cerebrovascular events, cardiac events, undergoing intervention for peripheral vascular disease and kidney failure. Since this follow-up is still ongoing, this is outside the scope of this current article.

2.3. CT scanning protocol

All included CLTI patients were scanned on a 256-slice CT scanner (Siemens Definition Flash Scanner, Siemens Healthineers, Forchheim, Germany). The scanning protocol consisted a full-body protocol divided into two scans. At first, a low-dose prospective ECG-triggered coronary CT without contrast (flash) was performed from the vertex of the skull to the pubic bone. The arms were placed next to the body in slender patients, in large patients the arms were stretched on the abdomen to get as much of the arms as possible in the field-of-view. Patients were scanned with a standard 80 and 120 keV with dose modulation on. The rotation time was 0.28, pitch 3.4 and collimation 0.6). Slice thickness was set on 0.65 mm.

The second scan was from the vertebral body L1 to the feet. The scan was performed with intravenous contrast (90 ml Xenetix, 300/100 ml NaCl), with an injection time of 5 ml/s. Contrast timing was triggered on the aorta with a test bolus of 15 ml contrast mixed with 40 ml NaCl with a delay of 18 s. The standard kV was 80 and 120 with dose modulation. The rotation time was 0.5, pitch 0.6 and collimation 0.6.

2.4. Overview of arterial calcification assessment

For this study, we used quantitative calcium score as well as a semi-quantitative morphologic CT score. When achievable, both were performed. A radiology resident (LCDK) with more than four years of experience in both quantitative as semi-quantitative score was blinded to the patient's clinical data during the scoring process and performed all measurements. Independently of this, a subset of 30 patients was scored with the semi-quantitative morphologic CT score by a senior radiologist (WPThM) with more than 40 years of experience to evaluate test-retest reproducibility.

Calcifications were measured in the femoropopliteal and crural arteries, coronary arteries, carotid artery bifurcation and intracranial carotid arteries, thoracic and abdominal aorta.

2.5. Quantitative calcium score

Quantitative arterial calcium scores were measured by the method described by Agatston et al.[17] The software package Syngo.Calcium Scoring (Siemens Healthineers, Erlangen, Germany) was used. Calcium was detected with a Hounsfield Units (HU) above 130 on a non-contrast CT. Total volume/mm^3 and calcium scores were calculated. Stents can cause metal artifacts, however, in bone setting we were able to locate calcium outside the stents and this was measured by hand as accurately as possible.

2.6. Semi-quantitative morphologic CT score

Semi-quantitative morphological calcification measurements were done according to the recently developed and CT-histological validated score for the carotid siphon (inter-observer kappa 0.54–0.99).[18,19] This scoring system has recently been applied in a study of the peripheral arteries of the lower extremities and has shown that these characteristics for intima and media calcifications cluster in the same way in the femorocrural arteries as in the carotid syphon.[20,21] Severity was scored as absent, mild, moderate and severe. Annularity was scored as absent, dot(s), <90°, 90–270°, 270–360°. Thickness as absent, $\geq$1.5 mm and 1.5 mm. At last, continuity was scored as absent/indistinguishable, irregular/patchy and continuous.

2.6.1. Lower extremity artery calcification measurements

The femoropopliteal artery was defined as the superficial femoral artery in direct continuation with the popliteal artery. The crural arteries were defined as the tibioperoneal trunk and the anterior tibial artery.

Due to the presence of intravenous contrast no quantitative measurements could be obtained. Semi-quantitative measurements were performed on the affected leg with CLTI. See Fig. 1 for examples of extensive calcifications in the femoropopliteal and crural arteries.

2.6.2. Coronary arterial calcification measurements

All coronary arteries were measured independently as well as added up to a total score. Quantitative Agatston scores and total calcium scores were measured. Coronary arterial calcium (CAC) scores were divided into 0, 0–100, 101–400, 401–1000, according to Rumberger et al.[22] Very high and extremely high CAC scores were defined as total CAC $\geq$1000 and total CAC $\geq$2000, respectively.[23,24] See Fig. 2A for examples of severely calcified coronary arteries. Semi-quantitative measurements were not performed.

2.6.3. Carotid artery calcification measurements

The extracranial carotid artery was measured within 3 cm proximal and distal at the carotid bifurcation (CB). Both left and right arteries were measured. Semi-quantitative and quantitative scores were used. CB scores were classified into terciles (0–800, 801–1600, 1601–2400) to perform logistic regression analyses. See Fig. 2B for examples of calcifications at the carotid artery bifurcation.

The intracranial internal carotid artery (iICA) (frequently known as carotid syphon) was measured with the semi-quantitative score. Quantitative measurements could not be done in this software package because of the adjacent petrous bone. See Fig. 2C.

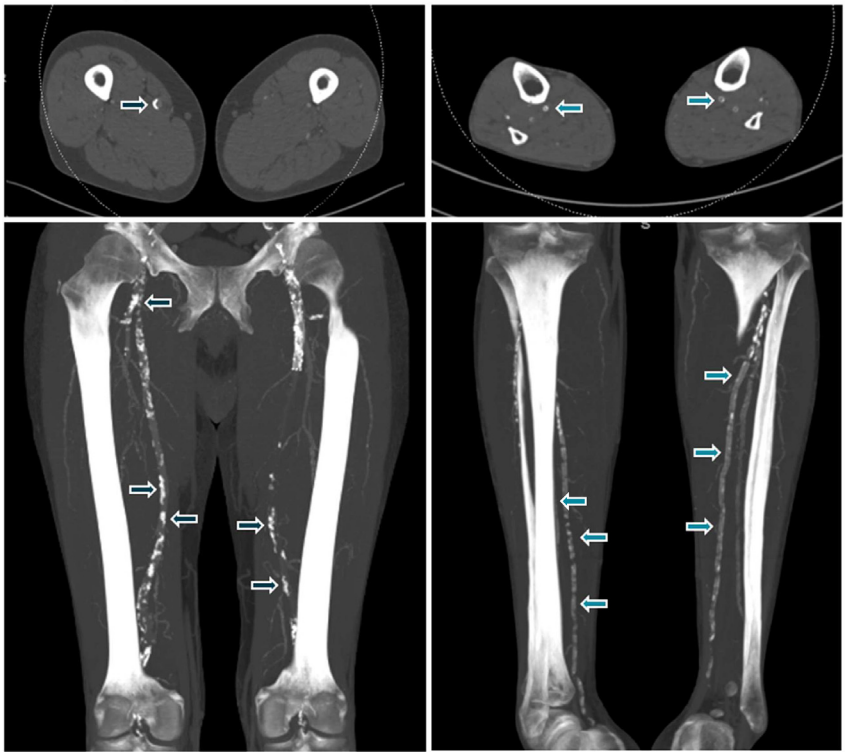

Fig. 1. Examples of calcification measurements in the arteries of the lower extremities. Axial thin and coronal maximum intensity projection (MIP) images. **Left two images**: Severe patchy femoropopliteal calcifications (dark blue arrows). N.B. a stent has been placed in the left proximal femoral artery. **Right two images:** Severe continuous circular and thin crural calcifications (light blue arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

2.6.4. Aortic calcification measurements

Of the semi-quantitative scores only annularity of the aorta was assessed at two levels. The ascending thoracic aorta was measured just before the origin of the left subclavian artery. Second, the abdominal aorta was measured below the level of the diaphragm, above the run-off of the celiac trunk.

Quantitative scores could not be assessed in the aorta, because the particles of calcium were too large for the calcium scoring software since this was developed for the coronary arteries and a cut-off was used for the detection of calcium. See Fig. 2D for examples of calcifications of the thoracic and abdominal aorta.

2.7. Statistical considerations

2.7.1. Interrater reliability

Test - retest reproducibility was assessed for the semi-quantitative score (severity, circularity, thickness and continuity) in the lower extremities. Since the data to be tested consisted of ordinal data, the weighted Cohen's Kappa test (K_w) was used to compare the reliability of the two observers of calcification measurements. K_w values were interpreted based on the guidelines of Landis and Koch.[25]

2.7.2. Statistical analysis

All continuous variables were presented as means and standard deviations if normal distributed. Normal distribution was tested with QQ-plots. If not normally distributed, for example CAC scores, data were presented as medians with quartiles (P25–P75). Categorical data are presented as frequencies and percentages (%).

Correlation was assessed by Spearman's correlation coefficients (since the data were not normally distributed) of calcifications of the femoropopliteal and crural arteries compared to the coronary, carotid arteries and aorta. We interpreted a negligible Spearman's correlation between 0.00 and 0.20, weak between 0.21 and 0.40, moderate between 0.41 and 0.60, strong between 0.61 and 0.80 and very strong between 0.81 and 1.00.

Additional analyses were performed for the very high and extremely high CAC scores using binary logistic regression analysis, shown in odds ratios (OR). A p-value less than 0.05 was considered to be significant.

Statistical analyses were conducted using SPSS Statistics version 27.0 (IBM Corporation, Armonk, New York).

3. Results

3.1. Interrater reliability of morphologic calcification measurements in the lower extremities

Cohen's weighted Kappa tests showed good agreement of inter reader test-retest reproducibility for the morphologic calcification measurements in the lower extremities. K_w values were for severity 0.72 (95%CI 0.55–0.90, $p < 0.001$), annularity 0.77 (95% CI 00.58–0.95, $p < 0.001$), thickness 0.65 (95% CI 0.29–1.01, $p < 0.001$) and continuity 0.62 (95% CI 0.31–0.94, $p < 0.001$).

3.2. Baseline characteristics

Baseline characteristics and comorbidities of the included CLTI patients are shown inTable 1. As can be expected with these CLTI patients, 58.5% (31/54) had a history of PAD, 38.9% (21/54) of CAD, 13.2% (7/54) of stroke. Patients in these cohort were treated according to the current guidelines amongst others of best pharmacological therapy and treated, if necessary, with statins (78%), anti-hypertensive medication (67.3%) and 30.2% of patients were taking oral coumarin anticoagulants (acenocoumarol or phenprocoumon).

3.3. Calcifications in different locations in CLTI patients

3.3.1. Lower extremity arterial calcifications

Results of the semi-quantitative assessment of the femoropopliteal and crural arteries are given in Table 2. Calcifications in the femoral arteries were mostly severe (70.4%), 90–270° (50.0%), thick (83.3%) and irregular/patchy in 74.9%. There were no patients without calcifications in the femoropopliteal arteries. In the crural arteries, there was only one patient without calcifications (1.9% of all patients).

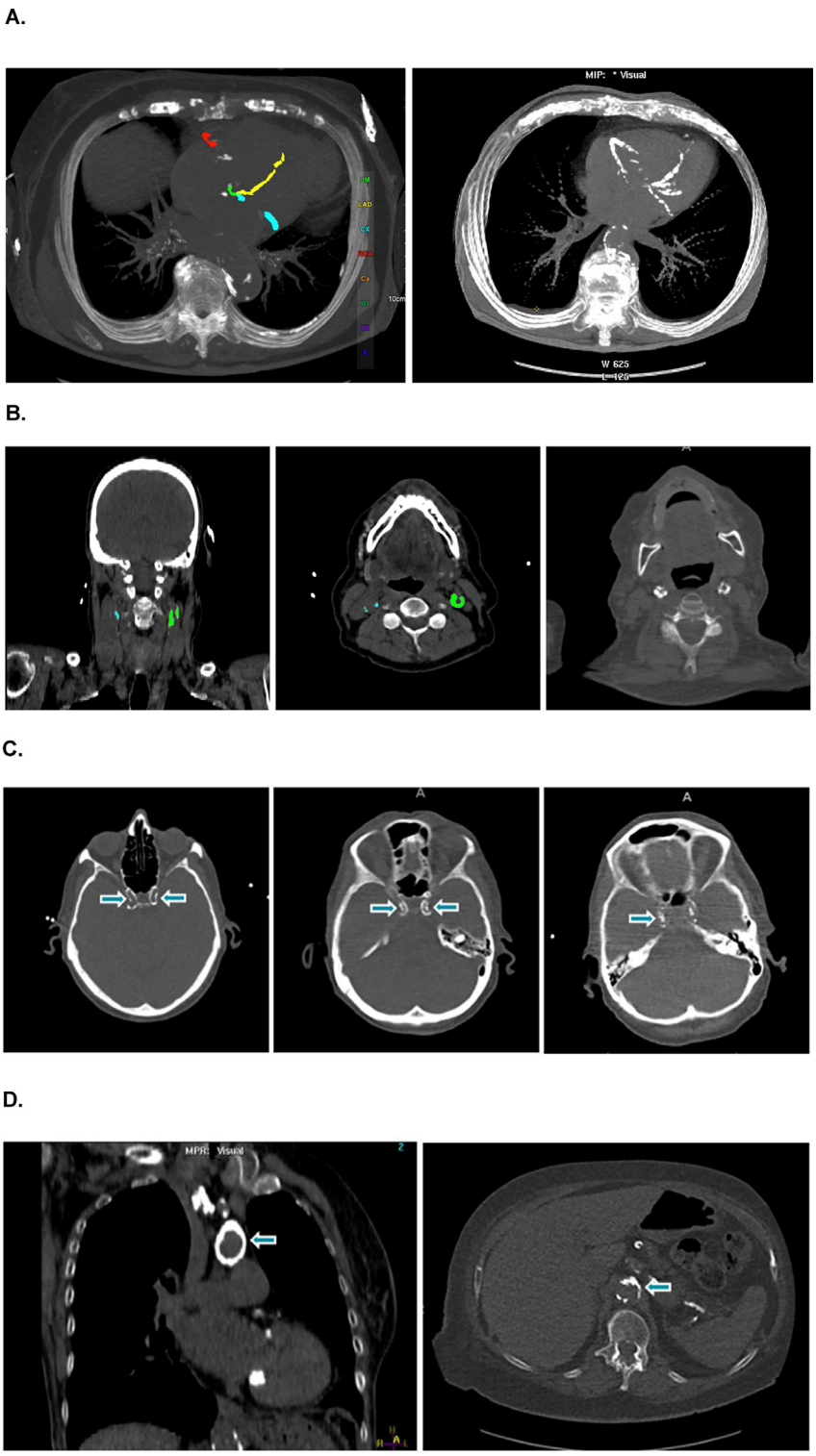

Fig. 2. Examples of calcification measurements in CLTI patients. **A.** Left: Maximum intensity projection (MIP) Image with marked calcium scores in the LM (green), LAD (yellow), CX (light blue) and RCA (red) in CLI patients. Right: complete MIP view of the heart with extensive calcifications. **B.** Extensive calcifications at the left (green) and right (blue) carotid artery at the level of the carotid bifurcation (axial and coronal planes). **C.** Examples of iICA calcification measurements at the level of the carotid syphon (axial CT planes). Left and middle image: continuous circular calcifications. Right image: non-continuous/patchy calcifications. See blue arrows. **D.** Examples of aorta calcification measurements. Left: the ascending thoracic aorta: at the level of the left subclavian artery. Right: abdominal aorta at the level of the diaphragm.

Calcifications varied in severity. Calcifications were mostly thin in 74.1% of patients. There was no clear pattern with annular, continuous or irregular/patchy calcifications.

3.3.2. *Coronary arterial calcifications*

The results of the semi-quantitative and quantitative calcification assessments of the coronary arteries are presented in Table 3. There were no patients without coronary calcifications. The coronary arteries of CLTI patients are severely calcified. The median total CAC score is 1484.9 (P25–P75: 342.6–2386.8), with 16 lesions (SD 9) per patient. In descending order, the left anterior descending (LAD) artery was the most severe calcified artery with a CAC score of 499.5 (94.5–875.5), followed by the right coronary artery (RCA) with a CAC score of 222.0 (16.58–936.0), the circumflex (Cx) artery with a CAC score of 134.1 (8.2–466.5) and the left main (LM) artery with a CAC score of 63.9 (0–185.4).

Table 1
Baseline table of the included patients with CLTI (n = 54).

Baseline characteristics		Mean (SD)	N (%)
Age (years)		72 (11)	
Gender (male)			36 (66.7%)
Length (cm)		172 (10)	
Weight (kg)		74.7 (17.4)	
BMI (kg/m^2)		25.05 (4.08)	
Diabetes Mellitus			24 (44.4%)
Stroke			7 (13.2%)
CAD			21 (38.9%)
History of PAD			31 (58.5%)
Smoking	No smoking		2 (3.8%)
	Former smoker		18 (34.6%)
	Smoker		32 (61.5%)
Current usage of warfarin			16 (30.2%)
Current usage of antihypertensive medicine			35 (67.3%)
Current usage of statins			32 (78.0%)
Fontaine baseline	3		22 (40.7%)
	4		32 (59.3%)
Systolic blood pressure upper extremity (mmHg)		162 (27)	
Diastolic blood pressure upper extremity (mmHg)		84 (22)	
Systolic blood pressure ankle (mmHg)		84 (58)	
Hypertension (mmHg)	<140		7 (13.5%)
	≥140		45 (86.5%)
eGFR (ml/min/1.73m^2)		72 (27)	
CKD (eGFR <60 ml/min/1.73m^2)		17 (31.5%)	
CKD (eGFR <30 ml/min/1.73 m^2)		5 (9.3%)	
ABI categorized	<0.7		42 (77.8%)
	0.7–1.40		3 (5.6%)
	>1.40/immeasurable		9 (16.7%)

Abbreviations: BMI = body mass index; PAD = peripheral arterial disease; CAD = coronary artery disease; eGFR = estimated glomerular filtration rate(mL/min/1.73 m^2); CKD = chronic kidney disease; ABI = ankle-brachial index.

Table 2
Semi-quantitative calcification measurements in the femoropopliteal and crural arteries.

Artery	Calcification characteristic		N	%
Femoropopliteal arteries	Severity	Absent	0	0.0%
		Mild	8	14.8%
		Moderate	8	14.8%
		Severe	38	70.4%
	Annularity	Absent	0	0.0%
		Dot(s)	5	9.3%
		<90°	11	20.4%
		90–270°	27	50.0%
		271–360°	11	20.4%
	Thickness	Absent	0	0.0%
		Thick ≥1.5 mm	45	83.3%
		Thin <1.5 mm	9	16.7%
	Continuity	Indistinguishable	7	13.0%
		Irregular/patchy	41	75.9%
		Continuous	6	11.1%
Crural arteries	Severity	Absent	1	1.9%
		Mild	16	30.2%
		Moderate	20	37.7%
		Severe	16	30.2%
	Annularity	Absent	1	1.9%
		Dot(s)	13	24.5%
		<90°	15	28.3%
		90–270°	10	18.9%
		271–360°	14	26.4%
	Thickness	Absent	2	3.7%
		Thick ≥1.5 mm	12	22.2%
		Thin <1.5 mm	40	74.1%
	Continuity	Indistinguishable	24	44.4%
		Irregular/patchy	12	22.2%
		Continuous	18	33.3%

Table 3
Calcifications at the coronary arteries and the aorta.

Arterial territory	Arterial calcification characteristic	Median (P25–P75)	N (%)
Coronary arteries	Total calcium volume (mm^3)	1216.3 (290.9–1891.8)	
	Total CAC score	1484.9 (342.6–2386.8)	
	Subcategorized total CAC scores		
	0		0 (0.0%)
	1–100		6 (11.1%)
	101–400		8 (14.8%)
	401–1000		8 (14.8%)
	1001–2000		14 (25.9%)
	>2000		18 (33.3%)

Abbreviations: CAC = coronary arterial calcifications.
Continuous variables are reported as median (P25–P75) and categorical variables as n(%).

3.3.3. Carotid bifurcation (CB) and intracranial internal carotid artery (iICA)

The CB was assessed quantitative and semi-quantitative and the results are given in Table 4. Most of the calcifications consisted of 2 pieces for both left and right. The CB had a high calcification score with a relatively higher left-side calcification score of 472.6 (P25–P75: 107.8–874.8) versus right with 282.9 (P25–P75: 96.7–605.9). Most calcifications at the CB were almost annular (between 90 and 270°) in 41.5%, thick in 84.3% and irregular/patchy in 59.6%. Only 11.8% were thin.

Most of the calcifications in the iICA were 90–270° in 48.1% (26/54) or complete annular in 27.8% (17/54), and thick in 68.7% (37/54).

3.3.4. Aorta calcifications

The semi-quantitative data are given in Table 5. In the thoracic aorta there were only 3.8% of patients (n = 2) without calcifications. Many of the calcifications were annular (36.5%, n = 19). The same pattern could be seen in the abdominal aorta with only 7.7% of patients without calcifications (n = 4) and a substantial proportion of patients with annular calcifications (30.8%).

3.4. Correlation analysis

3.4.1. Lower extremities: correlations between lower extremity arteries and different arterial territories

Spearman's correlation coefficients were calculated between the semi-quantitative calcification scores in the arteries of the lower extremities and the quantitative and semi-quantitative calcification measurements in the coronary arteries, carotid arteries and aorta. See Supplemental Tables 1–4.

Femoropopliteal and crural calcification severity both had a moderate to strong correlated with coronary calcifications (R = 0.60 and R = 0.53 respectively). Both femoropopliteal and crural severity was also moderate to strong correlated to carotid bifurcation calcification (R = 0.62 and R = 0.53 respectively). Interestingly, crural severity had a moderate correlation with annularity of calcifications in the iICA (R = 0.55, p < 0.001).

With regard to annularity of calcifications in the lower extremities, particularly moderate correlations were found in the crural arteries when compared to total CAC scores (total CAC volume R = 0.47, p < 0.001). The calcification load at the left carotid bifurcation had a stronger correlation than the right carotid bifurcation for both femoropopliteal and crural arteries. A moderate correlation of crural annularity with annularity was also found in the iICA (R = 0.48, p < 0.001).

Table 4
Arterial calcifications in the carotid arteries at the carotid bifurcation and the carotid siphon in patients with CLTI (n = 54 patients).

Arterial territory	Arterial calcification characteristic		Median (P25–P75)	N (%)
Carotid bifurcation	Annularity	Absent		2 (3.8%)
		Dot(s)		4 (7.5%)
		<90°		10 (18.9%)
		90–270°		22 (41.5%)
		271–360°		15 (28.3%)
	Thickness	Absent		2 (3.9%)
		Thick ≥1.5 mm		43 (84.3%)
		Thin <1.5 mm		6 (11.8%)
	Continuity	Indistinguisable		15 (28.8%)
		Irregular/patchy		31 (59.6%)
		Continuous		6 (11.5%)
	Left volume (mm^3)		375.7 (94.0–741.3)	
	Left score		472.6 (107.8–874.8)	
	Right volume (mm^3)		248.1 (83.8–505.4)	
	Right score		282.9 (96.7–605.9)	
iICA	Annularity	Absent		1 (1.9%)
		Dot(s)		1 (1.9%)
		<90°		9 (16.7%)
		90–270°		26 (48.1%)
		271–360°		17 (31.5%)
	Thickness	Absent		1 (1.9%)
		Thick ≥1.5 mm		37 (68.5%)
		Thin <1.5 mm		16 (31.5%)
	Continuity	Indistinguisable		7 (13.0%)
		Irregular/patchy		24 (44.4%)
		Continuous		23 (42.6%)

Abbreviations: CB = external carotid artery at the carotid bifurcation; iICA = intracranial internal carotid arteries.
Continuous variables are reported as median (P25–P75) and categorical variables as n (%).

Table 5
Annularity of arterial calcifications in the aorta in patients with CLTI (n = 54).

Arterial territory	Arterial calcification characteristic		Median (P25–P75)	N (%)
Aorta	Thoracic aorta annularity	Absent		2 (3.8%)
		Dot(s)		4 (7.7%)
		<90°		10 (19.2%)
		90–270°		17 (32.7%)
		271–360°		19 (36.5%)
	Abdominal aorta annularity	Absent		4 (7.7%)
		Dot(s)		8 (15.4%)
		<90°		14 (26.9%)
		90–270°		10 (19.2%)
		271–360°		16 (30.8%)

Continuous variables are reported as median (P25–P75) and categorical variables as n(%).

Correlations between thickness of calcifications in the lower extremities were negligible to weak (see Supplemental Table 3).

Continuity of calcifications in the femoropopliteal artery showed significantly higher correlations than crural arteries (femoropopliteal 0.45, $p < 0.001$ vs crural 0.22, $p = 0.11$). Next to the earlier described strong correlation for crural severity and annularity, crural continuity of calcifications were also moderately associated with annular iICA calcifications (0.51, $p < 0.001$).

3.4.2. Coronary arteries: very high and extremely high CAC score

Additionally, patients with high and extremely high CAC scores were evaluated. Patients were stratified according coronary arterial calcification (CAC) scores; CAC <1000, very high with a CAC score of 1000–2000 and extremely high with a CAC score >2000. For baseline characteristics of these sub categories, see Supplemental Table 5. Patients with an extremely high CAC score (CAC >2000) had the highest percentage of CAD, PAD, CKD and high or immeasurable ankle-brachial index (ABI).

Binary logistic regression analysis was performed to determine the ORs between CAC<1000, CAC 1000–2000 and CAC >2000 and the calcium measurements of lower extremity calcification, carotid calcifications and aortic calcifications. See Supplemental Table 6. CAC<1000 had weak to moderate ORs with calcifications score and morphology in the different arterial territories.

Significantly higher ORs were found in patients with very high and extremely high CAC scores. In patients with the most severe calcifications in the femoropopliteal arteries the OR was 11.70 ($p < 0.005$), the most severe calcifications in the crural arteries 9.19 ($p = 0.007$) and the complete annular calcifications with an OR of 6.08, p-value 0.030. In the carotid bifurcation significant OR were found in the highest calcification categories of 1600–2400 for both left and right, however these were not significant.

Regarding CAC >1000, patients had higher OR for complete annular abdominal aortic calcifications (OR 4.44, $p = 0.04$).

In patients with an extremely high CAC score (CAC >2000), the OR did improve in the femoropopliteal arteries and aorta even more. For complete annular calcifications in the thoracic aorta, the OR went from 3.15 to 3.61 with a significant p-value of 0.036. For abdominal complete annular calcifications, the OR did even improve from 4.44 up to 7.50 (p-value = 0.0003). There was no improvement in the crural arteries or carotid arteries. The extremely high OR in severity of calcifications in the femoropopliteal arteries with a *rho* of 1.539, can be explained because all patients had severe calcifications. Coronary arterial calcifications were not correlated to Fontaine stage.

At last, we specifically looked at patients with a low CAC (<1000). There appeared to be no determinants associated with a CAC score below 1000. See Supplemental Table 7.

4. Discussion

This study provides an overview of systemic calcifications in patients with CLTI. The main finding of our study is that nearly all arterial beds are severely calcified in patients with CLTI and that there are moderate to high correlations between severe lower extremity arterial calcifications and severe systemic calcification. In addition, CLTI patients with very high CAC scores (>1000) were significantly correlated with most severe and complete annular calcifications in the crural and femoropopliteal arteries.

We will discuss our findings in the context of the different arterial territories.

4.1. Correlations lower extremities with systemic calcifications

4.1.1. High correlations between coronary arterial calcium and the aorta

In this study, we found high correlations between different central and peripheral arterial beds. We found no comparative in patients with CLTI or studies of this size of arterial beds in the current literature. However, there are studies in non-symptomatic adults. For example, one of the MESA studies found higher CAC in persons with thoracic aorta calcium.[26] We only found a high Spearman correlation between complete annular thoracic calcifications and a very high CAC (>2000) of 3.61 ($p = 0.04$). We found no correlation in patients with a low CAC score.

Another population-based study also found moderate to strong correlations between the coronary arteries, aortic arch and the carotid arteries.[27] Despite the fact that there were no comparable study cohorts, these findings support our hypothesis that atherosclerosis is a systemic/multi-arterial disease.

4.1.2. Very high and extremely high CAC scores

Recent results of the MESA cohort show a distinct group of patients at the highest risk for all-cause mortality and cardiovascular mortality, with a CAC score of >1000.[24] In this population of asymptomatic adults, only 4.3% had a CAC score >1000. When comparing these results to our CLTI patient group, 57% had an Agatston score of >1000 and even 35% an Agatston score >2000. High CAC scores have clear clinical implications as shown in the MESA study. Patients with an Agatston score of zero had a mortality rate per 1000 person years for coronary heart disease, cardiovascular disease, cancer and all-cause mortality of 0.1, 0.3, 0.8 and 1.6 compared with patients with an Agatston score of >1000 of 5.1, 8.0, 4.6 and 18.8 respectively.[24]

In general, calcifications in the coronary arteries are ascribed to atherosclerotic disease however in histologic-CT correlation studies cases with Agatston scores >1000 are generally lacking. So, in CLTI the high coronary disease burden can be explained by the extremely high calcium scores and the histologic nature of these calcifications is uncertain. In dialysis patients it has been described that the coronary calcification score is less related to obstruction and maybe the etiology of these high calcium scores is different.[28] In our logistic regression analysis, very high and extremely high were related to severe calcification in all arterial beds. This points at a common mechanism of calcification in these arterial beds.

4.1.3. Carotid arteries

In the carotid bifurcation we found thick annular calcifications in 40%, while thin ones were rare. This fits with atherosclerotic type of calcific lesions. However, calcification scores at the carotid artery bifurcation are not convincingly related to the degree of strokes.[29,30] It has been stated that the inverse relationship of calcifications at the carotid artery bifurcation and strokes indicates the stabilizing effect of calcifications to protect against stroke.[31]

Quantitatively, in the carotid bifurcation, we found a mean calcification load score on the left of 473, while on the right this was 283. Recently, in a cohort of patients with unstable angina or positive stress test for myocardial ischemia the quantitative carotid score was 59 and 23 respectively on the left and right side.[32] So, this score in CLTI patients is about 10 times higher, but the difference between left and right remains. This could mean that the mechanism by which calcification occurs remains similar but that the calcification process itself is much more unleashed in CLTI patients than in other atherosclerotic patients. In other words, CLTI patients may react much stronger with calcification on a certain stimulus than other vascular patients.

Calcifications in the iICA are prognostic for stroke.[33] In a recent study that also differentiated between media and intimal calcifications, a dominant media pattern was related to cardiovascular risk factors, as well as intimal iICA calcification.[34] Since we found high annular calcified iICAs indicative of MAC, our results are consistent with these results and may explain the high stroke rate.

Remarkably, there was a strong correlation between the lower leg calcifications and the iICA calcifications. In the lower leg, histological studies of amputated legs have shown extensive medial calcifications. In the iICA, it was shown in a CT-histology correlation study that more than 70% of the calcifications seen on CT in this region are due to internal elastic lamina calcification fitting medial calcifications. Perhaps a similar mechanism is here at play.

4.1.4. Annularity of the aorta

Complete annular calcification of the ascending (thoracic) aorta, also the definition porcelain aorta, was found in 36.5% of the CLTI patients. Due to lack of a clear definition, few data are available about the prevalence of these annular calcifications in the general population.[35] Recently, assessment of the extent of the calcification has become relevant for the transaortic valve replacement procedure and it was shown that in this severely cardiovascular compromised population 18% had a porcelain aorta. The calcifications seen in a porcelain aorta are thought to be caused by both atherosclerotic disease and by MAC frequently occurring simultaneously. The prognostic value of the complete annular thoracic aorta calcification is unknown at this time.

Complete annular calcification was also found in the abdominal aorta in 34% of our cases. Calcifications in the abdominal aorta have extensively been investigated on lateral x-rays made for bone mineral density assessment. These calcifications have been linked to all cardiovascular disease and mortality and incident coronary heart disease myocardial infarction and stroke.[36,37] Recently it was shown that abdominal aorta calcification was shown to be a better predictor than the Framingham risk score. Annularity of the calcification of the abdominal aorta adds to this risk.[38]

The purpose of our study was to investigate whether calcification could explain the residual disease burden after adequate treatment with anti-atherosclerotic and anti-hypertensive treatment. Patients in these cohort were treated according to the current guidelines amongst others of best pharmacological therapy and treated, if necessary, with statins (78%) and anti-hypertensive medication (67.3%).

We found convincing evidence that there is excessive systemic calcification. In most arterial territories these calcifications are linked to a high risk of cardiovascular disease or mortality.[33,34,38–47] So, these calcifications could explain the high residual cardiovascular disease burden in CLTI patients.

We cannot be sure about the type of the calcification. As of now probably both intimal and medial calcifications are involved and lead to excessive calcification.

Intimal calcifications are not only calcified lipid lakes of complex atherosclerotic lesions but also fibrocalcific type of lesions without lipids that play an important role in abdominal aorta, iliac and femoropopliteal artery calcifications and are probably present in the peripheral vessels in a very early stage.[48] Furthermore, medial calcifications can originate in the internal elastic lamina but also in the vascular smooth muscle cells and up to now the precise relation between both is uncertain.

Possibly in the very last phase of the calcification process, which is similar for intimal and medial calcifications, the inhibition of the calcification process is compromised in CLTI patients, leading to excessive calcification. A single systemic nature of the calcification process has been suggested before. Takx et al. showed in a cluster analysis that calcification of different vascular territories cluster very well, but do not cluster with traditional cardiovascular risk factors.[49]

For CLTI patients, therapies blocking calcifications are needed to test the hypothesis that the calcifications itself are a cause of disease. Recently it was shown that etidronate could halt calcifications in all arterial beds in patients with pseudoxantomata elastica.[50] This rare monogenetic vascular calcifying disease is like several other rare monogenetic calcifying diseases treated with etidronate or is subject of investigation with this medication. In all these diseases anorganic pyrophosphate (PPi), the strong calcification inhibitor is diminished causing vascular calcification. Etidronate, a stable PPi analogon, can replace PPi.

Several other non-surgical treatment strategies are currently being investigated and could in the future contribute to a better treatment of CLTI patients.[51,52]

4.2. Strengths and limitations

The main strength of this study is that we studied the calcification process in CLTI patients comprehensively in nearly all large vascular territories in the body. As far as we know, such assessment in CLTI patients has not occurred.

This study also has its limitations. There has not been a systematic quantitative assessment of all territories due to the use of contrast or lack of a good quantitative program. However, the semi-quantitative assessment was done in all territories and provided convincing evidence for extensive calcification in all territories. Second, we did not take into account renal function and diabetes as a possible cause of this calcification.

5. Conclusion

In conclusion, nearly all arterial territories are severely calcified in patients with CLTI and calcifications in the lower extremity were significantly correlated to CAC score, carotid artery bifurcation calcification score, and to a lesser extent correlated to the annular calcifications in the aorta. Secondly, very high and extremely high total CAC scores were strongly correlated with severe lower extremity arterial calcifications and severe carotid and intracranial internal carotid artery, thoracic and abdominal aorta calcifications in patients with CLTI patients.

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Declaration of competing interests

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcct.2023.03.003.

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