Aortic calcification index predicts mortality and cardiovascular events in operatively treated patients with peripheral artery disease: A prospective PURE ASO cohort follow-up study

Ville Rantasalo, MD,[a] Dan Laukka, MD,[a,b,c] Veikko Nikulainen, MD, PhD,[a,d] Juho Jalkanen, MD, PhD,[a,d] Jarmo Gunn, MD, PhD,[a] *and* Harri Hakovirta, MD, PhD,[a,d,e] *Turku and Pori, Finland*

ABSTRACT

Objective: The present study evaluates the association of aortic calcification with mortality and major adverse cardiovascular and leg events (MACEs and MALEs) in patients with peripheral artery disease (PAD). The risk for mortality and MACEs and MALEs is considered in clinical decision-making.

Methods: This cohort found in 2012-2013 consists of 226 patients with symptomatic PAD referred to Turku University Hospital for invasive treatment. Follow-up data about mortality and survival without MACEs and MALEs were collected up to 5 years from the inclusion date, and aortic calcification index (ACI) was measured from patients with available imaging studies (164 of 226). ACIs' association with events and mortality was evaluated in Cox regression, Kaplan-Meier, and classification and regression tree analysis.

Results: All-cause mortality at 1, 3, and 5 years was 13.7% (31), 26.1% (59), and 46.9% (106), respectively. In multivariable Cox regression analysis, ACI and ACI $>$ 43 were independent risk factors for all-cause mortality (hazard ratio [HR]: 1.13 per 10 units, 95% confidence interval [CI]: 1.00-1.22 and HR: 1.83, 95% CI: 1.01-3.32, respectively) and for MACEs (HR: 1.10 per 10 units, 95% CI: 1.00-1.22 and HR: 3.14, 95% CI: 1.67-5.91, respectively), but not for MALEs. Classification and regression tree analysis showed that ACI $=$ 43 best divides cohort in relation to mortality. Kaplan-Meier analyses showed that ACI $>$ 43 is associated with greater mortality and occurrence of MACEs compared with those who have ACI $\leq$ 43 (log-rank *P* value .005 and .0012, respectively).

Conclusions: Risk for mortality and MACEs is associated with high ACI. ACI can expose the risk in patients with PAD for further cardiovascular events and mortality. (J Vasc Surg 2022;■:1-10.)

Keywords: Atherosclerosis; Peripheral artery disease; Aortic calcification; Aortic calcification index

Patients with peripheral artery disease (PAD) carry heavy atherosclerotic burden and suffer from cardiovascular diseases manifestations.[1-3] Lower limb amputations, myocardial infarcts (MIs), and strokes are the common causes of death and disability.[2] It is crucial to assess perioperative risk in patients with PAD for significant morbidity (major adverse leg events [MALEs] and major adverse cardiovascular events [MACEs]) and mortality when revascularization and preventive treatment is planned.

There are few tools for this kind of risk evaluation. Crural artery atherosclerosis and low ankle-brachial index (ABI) are associated with poor survival and cardiovascular events in patients with PAD.[4-7] Recently, our group reported that PAD lesions of different levels correlate with carotid and intracranial artery atherosclerotic lesions, and certain cytokine levels are higher in patients with more severe PAD.[8,9] Current guidelines point out risk factors on a broad scale mainly based on demographic factors.[10,11]

From the Department of Surgery[a] and Department of Clinical Neurosciences,[b] University of Turku, Turku; the Department of Neurosurgery, Neurocenter,[c] and Division of Gastroenterology and Urology,[d] Turku University Hospital, Turku; and the Department of Surgery, Satasairaala, Pori.[e]

V.R. and D.L. shared first authorship.

J.G. declares unrestricted research grants from Vifor Pharma Ltd and Finnish Foundation for Cardiovascular Research. These entities had no involvement in the study design, collection, data analysis, or interpretation of the data. Vifor Pharma Ltd was not involved in the decision to submit the manuscript for publication. H.H. declares federal support from the Culture Foundation Varsinais-Suomi and the Culture Foundation Satakunta and federal support for the present article. These entities were not involved in the decision to submit the manuscript for publication. V.R. declares research support grant from the foundation of Paavo Ilmari Ahvenainen. This foundation was not involved in the decision to submit the manuscript for publication.

Author conflict of interest: none.

Additional material for this article may be found online at www.jvascsurg.org.

Correspondence: Ville Rantasalo, MD, University of Turku Faculty of Medicine, Kiinamyllynkatu 4-8, PL 52, 20521 Turku, Finland (e-mail: vheran@utu.fi).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214

https://doi.org/10.1016/j.jvs.2022.07.001

Abdominal aortic calcification index (ACI) represents the degree of calcification of the abdominal aorta. ACI is measured from computed tomography (CT) studies. ACI is associated with cardiovascular diseases and their manifestations.[12-14] It summarizes atherosclerotic burden regardless of recorded risk factors. In this study, we investigated if ACI associates with invasively treated PAD patients' all-cause mortality or MACEs.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center, prospective peripheral artery disease patient cohort study
- **Key Findings:** Aortic calcification index is associated with mortality (hazard ratio [HR]: 1.13) and cardiovascular adverse events (HR: 1.10) in a cohort of 226 patients. Kaplan-Meier analysis showed that aortic calcification index over the threshold value of 43 was associated with mortality ($P = .005$) and adverse cardiovascular events ($P = .0012$).
- **Take Home Message:** Increased aortic calcification is associated with outcomes in patients with peripheral artery disease and could be useful in risk assessment.

METHODS

This is a prospective registry-based subgroup analysis study based on the PURE ASO (The Role of Purinergic Signaling in Atherosclerosis) follow-up cohort conducted at the Department of Vascular Surgery at the Turku University Hospital, Finland.[8] This study was approved by the local institutional review board and the ethical committee of the Hospital District of Southwestern Finland. This study is based on an already formed registry. New patient consent was waived based on the study design.

PAD patient cohort. All patients admitted to this tertiary center for elective invasive treatment for PAD were screened (227 patients) for this study cohort; 226 were included, and one patient declined. The cohort did not include initially conservatively treated patients. The included patients were diagnosed with PAD by a vascular surgeon at the department's outpatient clinic. Patients gave informed consent at the time of enrollment, which took place between February 2012 and March 2013. The cohort data contained baseline demographics and clinical data for evaluation at the time of initial treatment. Initially, patients were categorized by the state of lower extremity ischemia using ABI, toe-brachial index (TBI), and Rutherford classification. Rutherford classes I-III were noted as intermittent claudication (IC) and IV-VI as critical limb ischemia (CLI). Lowest measurement of ABI and TBI was noted.[8]

Follow-up data. In addition to baseline and clinical data of the cohort, we collected data on overall survival and occurrence of cardiovascular (MACEs) or leg-related (MALEs) adverse events after initial treatment by reviewing patient records. Patients were not contacted by us during the follow-up because our tertiary center is responsible for the invasive treatment of PAD and other events we investigated on its catchment area and therefore record data are complete for assessing these outcomes. Also, national conjoined patient records information on mortality is available via records. Cohort mortality and events were recorded until December 2020, but we limited the follow-up period to 5 years from the individual inclusion date. MACEs were categorized as MI (MACE MI), heart failure (MACE HF), ischemic stroke (MACE IS), and all combined (MACE). MALEs are major amputation (MALE amputation, above the ankle level) or revascularization (MALE revascularization) or MALE (amputation and revascularization, either or both). MALE revascularization is either open bypass surgery, endovascular percutaneous transluminal angioplasty, or endovascular stent-graft placement. Analyses in subcategories (MACE MI, IS, HF and MALE amputation and MALE revascularization) are presented in Supplementary Material (online only).

Aortic calcification index. Records were reviewed for CT studies showing abdominal aorta. We measured abdominal ACI manually from those who had sufficient imaging data available. Studies were performed both with and without contrast enhancement. Patients were not categorized in relation to imaging with or without contrast enhancement. Abdominal ACI was calculated from axial CT slices 5 mm apart from renal arteries to aortic bifurcation. Iliac arteries were not included in measurements, and degree of stenosis was not measured. Each slice was given a value from 0 to 12 depending on how vastly calcification covered each axial view of the abdominal aorta. That is, the value of 6 meant that half of such slice was covered in atherosclerotic plaque and 12 meant that the whole circumference of the axially viewed aorta was covered in atherosclerotic plaque. The number of these 5 mm slices was recorded (n in the formula below), and the sum of these calcification values was calculated. Aortic calcification (=atherosclerotic plaque) is defined as a white, dense plaque over 1 mm^2 and over 300 Hounsfield units on CT scan. Thus, atherosclerotic plaques were distinguished from contrast and adjacent anatomical structures. ACI was calculated using the following formula:

$$\text{ACI} = \frac{\text{total sum of calcification in all slices}}{12 \times \text{n}} \times 100$$

The illustration of the method is available in our last publication with this same method.[15]

The first authors measured all patients' ACIs unblinded. The first authors' inter-rater reliability has been assessed with good agreement for this same ACI measurement method earlier in our previous study.[15] In this study, a

Table I. Baseline demographics of the study cohort and all the univariates for mortality

	Alive (n = 100, 44.2%)	SD	Dead (n = 126, 55.8%)	SD	*P* value
Overall survival mean, years	5	–	2.91	1.85	–
Mean age at the imaging	67.30	9.31	75.06	8.57	**<.001**
Mean ACI	46.05	25.73	57.43	23.43	**.003**
Mean serum creatinine, μmol/L	80.36	25.51	106.61	83.34	**.003**
Low-density lipoprotein, mmol/L	2.29	0.98	2.19	0.89	.4589
Toe-brachial index	0.34	0.16	0.25	0.17	**<.001**
Mean ABI	0.60	0.31	0.71	0.65	.106
	N	%	N	%	
ABI <0.5	41	43.2	59	48.8	**.022**
ABI 0.5-0.9	44	46.3	42	34.7	**.022**
ABI 0.9-1.4	9	9.5	8	6.6	**.022**
ABI >1.4	1	1.1	12	9.9	**.022**
Men	57	57.0	71	56.3	.922
Intermittent claudication	66	66.0	28	30.2	**<.001**
Critical limb ischemia	34	34.0	88	69.8	**<.001**
Hypertension	64	64.0	103	81.7	**.003**
Asthma	1	1	13	10.3	**.004**
Coronary artery disease	22	22	45	35.7	**.025**
Congestive heart failure at the presentation	0	0.0	37	29.4	**<.001**
Atrial fibrillation	8	8.0	34	27.0	**<.001**
Previous ischemic stroke	9	9	19	15.1	.168
Hypercholesterolemia	32	32	40	31.7	.968
Type 1 diabetes	7	7.0	7	5.6	.655
Type 2 diabetes	24	24.0	41	32.5	.159
No diabetes	69	69.0	78	61.9	.267
Renal insufficiency	9	9.0	45	35.7	**<.001**
Uremia	0	0.0	12	9,5	**.002**
Rheumatoid arthritis	4	4.0	14	11.1	**.050**
Pharmacotherapy					
Statin prescribed	66	66.0	77	61.1	.449
Aspirin use	64	64	76	53.2	.102
Clopidogrel use	11	11.0	9	7.1	.311
Any antiplatelet therapy	71	71.0	72	57.1	**.032**
Warfarin	12	12.0	37	29.4	**.002**
β-Blocker	43	43.0	85	67.5	**<.001**
Any renin-angiotensin system inhibitor	58	58.0	82	65.1	.276
Calcium channel blockers	29	29.0	41	32.5	.568
Diuretics	11	11.0	53	42.1	**<.001**
Nitroglycerin	12	12.0	33	26.2	**.008**
Glucocorticoids	12	12.0	30	23.8	**.023**
Metformin	21	21.0	20	15.9	.321
Bisphosphonates	3	3.0	12	9.5	**.050**

ABI, Ankle-brachial index; *ACI*, aortic calcification index; *SD*, standard deviation.
Boldface *P* values represent statistical significance.

random subset of measurements by V.R. and D.L. were compared with each other with good agreement (see also Supplementary Material, online only). Measurements were conducted after all patients' follow-up had ended. Measurements are reproducible easily and carry low risk of bias due to the simple method. Manual measurements avoid the risk of inconsistency between automated and semiautomated methods. Manual measurements are available when CT imaging is available without additional diagnostic software/hardware.

Table II. Demographics and significant univariates in proportion for major adverse cardiovascular events (*MACEs*)

	No MACE (n = 129, 57.1%)	SD	MACE (n = 95, 42.0%)	SD	*P* value
Overall survival mean, years	3.72	1.83	3.97	1.57	.287
Mean age	70.06	9.56	73.20	9.73	.032
Mean ACI	46.31	27.13	59.70	20.38	**.001**
TBI	0.30	0.18	0.27	0.16	.154
Low-density lipoprotein, mmol/L	2.29	0.91	2.16	0.97	.331
Creatinine, μmol/L	90.17	40.23	101.36	89.98	.212
Mean ABI	0.70	0.57	0.62	0.47	.252
	N	%	N	%	
ABI <0.5	51	41.5	49	53.8	.322
ABI 0.5-0.9	52	42.3	32	35.2	.322
ABI 0.9-1.4	11	8.9	6	6.6	.322
ABI >1.4	9	7.3	4	4.4	.322
Survived	67	51.9	31	32.6	**.004**
Deceased	62	48.1	64	67.4	**.004**
Male	66	51.2	60	63.2	**.074**
Female	63	48.8	35	36.8	**.074**
Carotid stenosis	3	2.3	9	9.5	**.019**
Previous ischemic stroke	11	8.5	17	17.9	**.036**
Coronary artery disease	29	22.5	36	37.9	**.012**
Intermittent claudication	68	52.7	35	36.8	**.018**
Critical limb ischemia	61	47.3	60	63.2	**.018**
Beta blocker	65	50.4	62	65.3	**.026**
Nitroglycerin	14	10.9	31	32.6	**<.001**
MALE revascularization	43	33.3	47	49.5	**.015**

ABI, Ankle-brachial index; *ACI*, aortic calcification index; *MALE*, major adverse leg event; *SD*, standard deviation; *TBI*, toe-brachial index.
Boldface *P* values represent statistical significance.

ACI measurements require only minimal resources and can be conducted by researchers, and numeric results are still comparable.

Statistical analysis. Statistical analysis was carried out using IMB SPSS Statistics 27 software for windows (IBM). The hypothesis is that ACI is higher in patients with MALEs or MACEs or in deceased patients, and it would increase risk for these events. A *P* value of less than .05 was the threshold for statistical significance. Continuous variable normal distribution assumption was tested with the Kolmogorov-Smirnov test, Shapiro-wilk test, and visually. Analysis for means and differences in groups was performed with an independent-samples *t*-test with the assumption of equal variances. Equality of variances was tested with Levene's test. Continuous variables are reported as mean and standard deviation. Categorical variable between-group differences are evaluated using the χ^2 test for proportions. Survival analysis for MACEs, MALEs, and mortality was conducted using Cox regression analysis. Models included clinically relevant risk factors and statistically significant differing univariates for each event. The log-rank test and respective Kaplan-Meier analysis were conducted for survival free of mortality, MACEs, and MALEs.

Classification and regression tree (CART) analysis was used to find a cutoff value for ACI to categorize patients in relation mortality. ACI was forced as the first variable in tree to find the threshold value of ACI. This value was used further to categorize patients in relation to this value. Also survival of these patients was investigated as patients who had ACI over or under this threshold value.

Validation was assessed by cross-validation through 10-folds. The minimum number of patients for a parent node was set at 100 and at 50 for child nodes, and the maximum tree depth was set at 5. Gini's method was used to measure impurity, and the minimum change in improvement was set at 0.0001. CART analysis uses surrogates as substitutes for missing values. To discriminate the relevance of ACIs, ABIs, and TBIs in total survival prediction models, Concordance or Harrel's C (C-index) statistical analysis was carried out. The same Cox proportional hazard model for total survival was included with ACI or ABI or TBI, one at the time. Respective C-indexes were calculated and compared with each other to find out their relevance in the model. C-index was interpreted as less than 0.5 (very poor), 0.5-0.7 (reasonable), 0.7-0.8

Table III. Demographics and significant univariates in proportion for major adverse leg events (*MALEs*)

	No MALE (n = 123, 54.4%)	SD	MALE (n = 103, 45.6%)	SD	*P* value
Aortic calcification index	49.45	27.28	54.78	22.43	.175
Serum creatinine, μmol/L	89.89	35.12	101.18	89.32	.200
Age at the imaging	70.76	10.23	71.87	9.16	.443
Low-density lipoprotein level, mmol/L	2.36	0.87	2.09	0.99	**.046**
TBI	0.31	0.18	0.26	0.16	**.032**
ABI	0.68	0.56	0.64	0.50	.521
	N	%	N	%	
ABI <0.5	50	43.1	50	50.0	.742
ABI 0.5-0.9	49	42.2	37	37.0	.742
ABI 0.9-1.4	9	7.8	8	8.0	.742
ABI >1.4	8	6.9	5	5.0	.742
Survived	55	44.7	44	42.7	.763
Deceased	68	55.3	59	57.3	.763
Men	62	50.4	66	64.1	**.039**
Women	61	49.6	37	35.9	**.039**
Type 2 diabetes mellitus	24	19.5	41	39.8	**.001**
Uremia	3	2.4	9	8.7	**.035**
MACE MI	21	17.1	33	32.0	**.009**
Intermittent claudication	66	53.7	38	36.9	**.012**
Critical limb ischemia	57	46.3	65	63.1	**.012**
Statin	70	56.9	73	70.9	**.030**
Clopidogrel	4	3.3	16	15.5	**.001**
Antiplatelet therapy	68	55.3	75	72.8	**.006**
Gliptin	9	7.3	17	16.5	**.031**

ABI, Ankle-brachial index; *MACE*, major adverse cardiovascular event; *MI*, myocardial infarct; *SD*, standard deviation; *TBI*, toe-brachial index.
Boldface *P* values represent statistical significance.

(good), and >0.8 (excellent).[16,17] This analysis sought to find out whether C-indexes for each model would differ greatly from each other. Cases were not excluded due to user missing values. The regression model in SPSS uses listwise deletion.

RESULTS

Demographics and ACI. The study included 226 patients (male: n = 128, mean age: 71.3 years). A total of 126 patients (55.8%) died during follow-up. The mean survival time (nonsurvivors) was 2.91 years (8 days to 5 years) and the median survival was 3.27 years. The mean follow-up time was 3.82 years (all patients). A total of 122 (54.0%) had CLI and 104 (46.2%) had IC. There was no significant difference in mean ACI between patients with IC and those with CLI (48.7 vs 44.4, $P = .251$). From 226 patients, 164 patients had available imaging for ACI measurements. Baseline characteristics presented in Tables I to III were noted at the time of enrollment. Further details are presented in Supplementary Material (online only).

Total survival. Cumulative all-cause mortality at 1, 3, and 5 years was 13.7% (31), 26.1% (59), and 46.9% (106), respectively (standard error: 0.003 years, overall Kaplan-Meier analysis). ACI was higher in nonsurvivors (57.71 vs 45.59, $P = .002$). TBI was significantly lower in nonsurvivors (0.343 vs 0.2489, $P < .001$). Coronary artery disease (CAD), renal insufficiency, congestive HF, atrial fibrillation, CLI, and hypertension at the presentation were more common with nonsurvivors (Table I).

ACI > 43 was associated with greater mortality in the log-rank test ($P = .005$) (Fig 1). The value of 43 is derived from CART analysis (Fig 2). Total mortality was 65.0% in patients with ACI > 43 vs 34.8% in patients with ACI ≤ 43. In multivariate Cox regression analysis, statistically significant risk factors for mortality were ACI (hazard ratio [HR]: 1.13, 95% confidence intervals [CI]: 1.01-1.26 for 10 units), age (HR: 1.05 per year, 95% CI: 1.02-1.08), previous HF (HR: 4.53, 95% CI: 2.59-7.91), renal insufficiency (HR: 2.19, 95% CI: 1.27-3.79), and asthma (HR: 2.86, 95% CI: 1.23-6.61). ACI > 43 HR for mortality was 1.83 (95% CI: 1.01-3.32) (Fig 3).

Patients with highest (>1.4) and lowest (<0.5) ABI had highest mortality (59.0% and 92.3%, respectively, $P = .028$) compared with other ABI categories. TBI was significantly lower in patients who died (0.249 vs 0.343, $P < .001$). Harrel's C for the Cox model including ABI as

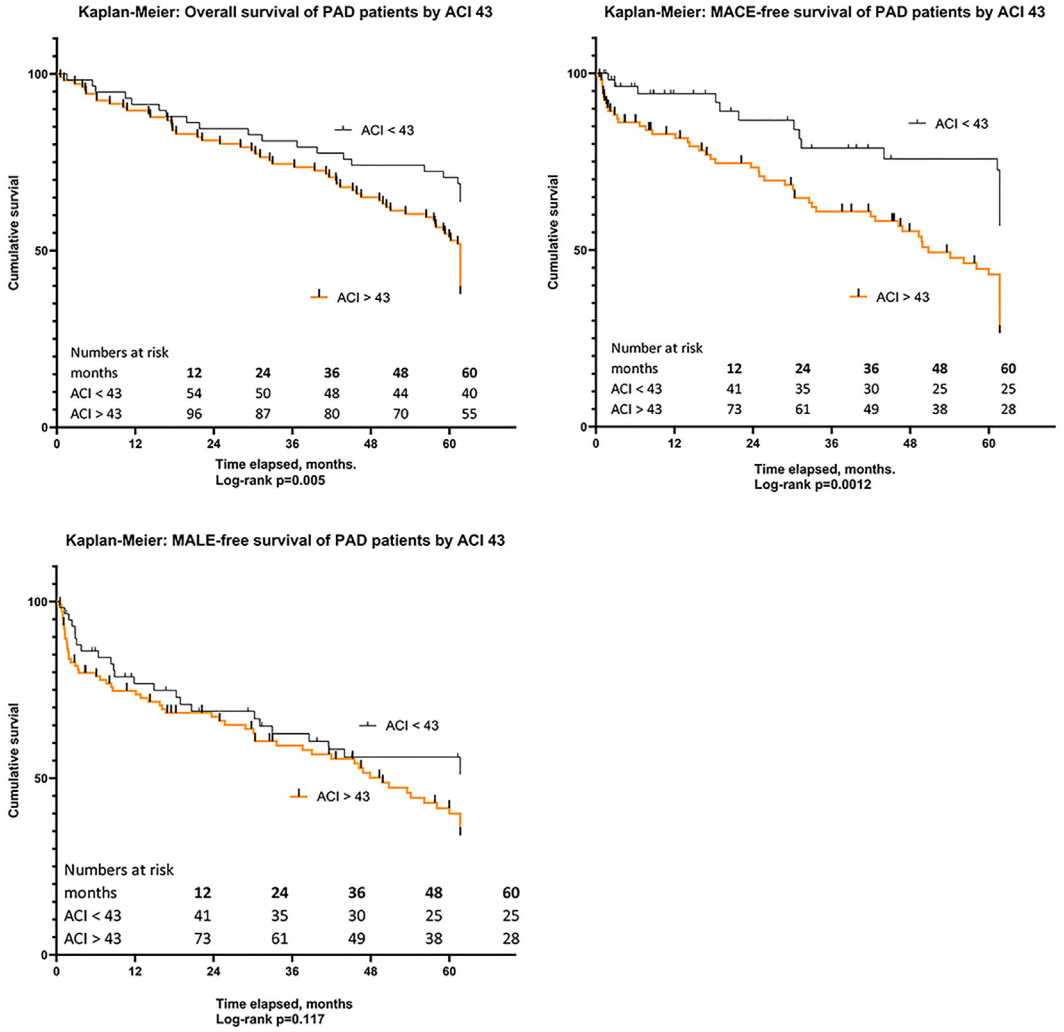


Fig 1. Survival by aortic calcification index (*ACI*) > 43. Peripheral artery disease (*PAD*) patients' survival by ACI > 43 and ACI ≤ 43 in Kaplan-Meier curves. Mortality and occurrence of major adverse cardiovascular events (*MACEs*) was greater with patients who had ACI > 43. Occurrence of major adverse leg events (*MALEs*) was similar with patients who had ACI > 43 and ACI ≤ 43.

variable instead of ACI was 0.75. Harrel's C for the same model with TBI instead of ACI was 0.74. Harrel's C for the same model with ACI was 0.72. The C-index for ACI as only variable in the Cox model was 0.58. For TBI, the C-index was 0.61 and for ABI 0.52.

MACE. MACE occurred with 95 (42.0%) patients. The mean ACI was higher with patients who suffered MACEs during follow-up (59.69 vs 46.31, $P = .001$). Patients who died had more often MACE (48.8% vs 34.4%, $P = .029$) than those who did not. Patients with MACE had more often carotid stenosis, previous IS, CAD, or CLI than those who had no MACE (Table II).

Risk for MACE was associated with ACI (HR: 1.10 per 10 units, 95% CI: 1.00-1.22) and ACI > 43 (HR: 3.14, 95% CI: 1.67-5.91). The occurrence of MALE revascularization (HR: 5.033, 95% CI: 3.016-8.401) increased the risk for MACE (Fig 3). In the log-rank test (Kaplan-Meier), ACI > 43 was associated with MACEs compared with MACE-free survival, $P = .0012$ (Fig 1).

MALE. MALE occurred with 103 patients (92 revascularizations and 27 major amputations). ACI was not statistically significantly higher in patients with MALE (54.65 vs 49.32, $P = .176$). Patients with MALE more often had type 2 diabetes (19.5% vs 39.8%, $P = .001$), MACE MI (17.1% vs 32.0%, $P = .009$), and CLI (46.3% vs 63.1%, $P = .012$) than those who survived without MALE (Table III).

ACI was not associated with increased risk for any MALE (Fig 3). In the log-rank test (Kaplan-Meier), ACI > 43 was not significantly associated with MALE-free survival, $P = .117$ (Fig 1). Mean TBI was lower (0.26 vs 0.31, $P = .032$) in patients with MALEs. Risk for MALE was associated with the use of clopidogrel (HR: 2.17, 95% CI: 1.19-3.93) and type 2 diabetes (HR: 1.66, 95% CI: 1.05-2.63).

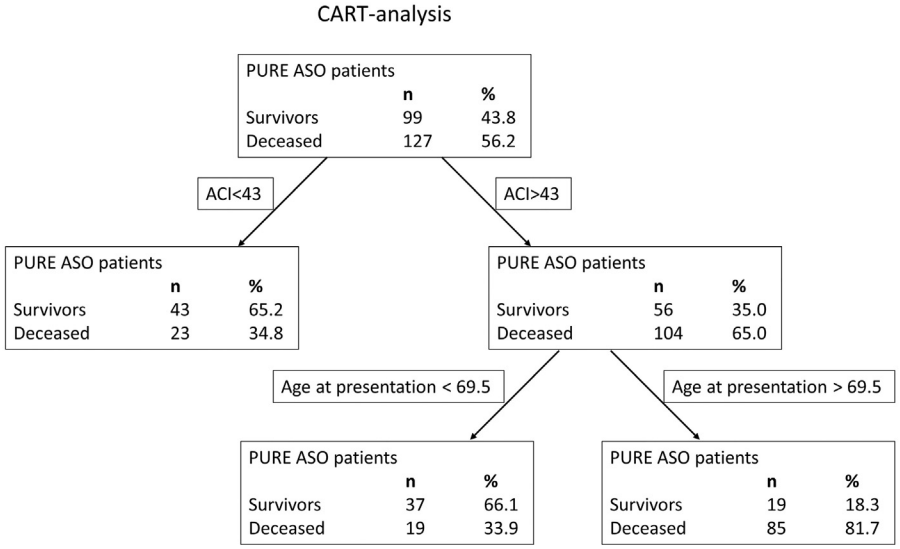


Fig 2. Classification and regression tree (*CART*) analysis of peripheral artery disease (PAD) patients' survival. CART analysis shows that the most significant combination of predictors for mortality is aortic calcification index (*ACI*) > 43 and age over 69.5 years. *PURE ASO*, Role of Purinergic Signaling in Atherosclerosis.

DISCUSSION

Mortality and cardiovascular morbidity of operatively treated patients with PAD are associated with ACI, but ACI is not associated with MALEs. CART analysis showed that patients with ACI > 43 had greater risk for mortality, and the same threshold value was related to lesser MACE-free survival in the multivariable regression model. Harrell's C showed similar results for ACI, TBI, and ABI regarding all-cause mortality analysis.[18] In this context, this means that none of these were greatly superior to each other.

The outcome in patients with PAD is assessed by estimating mortality, limb patency (after initial treatment), and the survival free of other cardiovascular events. Existing clinical classifications appear to be inadequate in assessing patient outcomes after the treatment. These classifications estimate disease severity by the distribution of stenoses and atherosclerotic lesions in the lower limb arteries, iliac arteries, and distal aorta. Latest classification, Global Anatomic Staging System (GLASS), offers guidance in choosing the revascularization method, but it does not reach very well in patient risk evaluation.[10,19-22] The same guidelines offer the PLAN (Patient risk estimation, Limb staging, and ANatomic distribution) strategy for risk assessment. PLAN is based on risk factors associated with reduced survival, but it does not include any patient-specific measurements.[10] Older but still more widely used Trans-Atlantic intersociety consensus for the management of PAD (TASC II staging) lacks information of infrapopliteal vasculature and describes survival narrowly. TASC II classes seem to have no association with PAD patients' overall survival or limb patency in the long term.[23,24] The wound, ischemia, and foot infection (WiFI) classification is more detailed in predicting PAD patients' risk for amputation and benefit from revascularization, but it does not offer tools for overall survival estimation. It is also noteworthy that survival in relation to MALEs, MACEs, and limb patency seems to depend on used antithrombotic and/or anticoagulative medication, and therefore prediction of outcomes is prone to uncertainty.[25]

Aortic calcification is associated with cardiovascular disease-related morbidity and mortality, such as ABI, which is used in diagnosing PAD.[13,26-31] A recently published study reveals that high abdominal aortic calcification and low ABI are both associated with higher total health care costs in risk patients.[32] ACI is higher in patients who have renal insufficiency, state known to accelerate vascular calcification.[33] Also, recently we published a study of ACIs' association with intracranial aneurysms.[15] Abdominal aortic calcification is associated with PAD incidence.[28] Aortic calcification is a marker of atherosclerotic disease that is caused by systemic low-grade inflammation that eventually builds calcification in arteries' walls.[34]

Our results serve ACI as a disease-specific method for visualizing patients' risk for cardiovascular events and mortality. Subsequent results could provide reference intervals for ACI, and then it could be used alongside other metrics and risk factors when patients' risk for morbidity and mortality is evaluated. ACI is easily achievable, noninvasive, and relatively free of bias. Diagnosis and classification in patients with PAD, CAD, and IS are usually based on vascular imaging, which sometimes includes

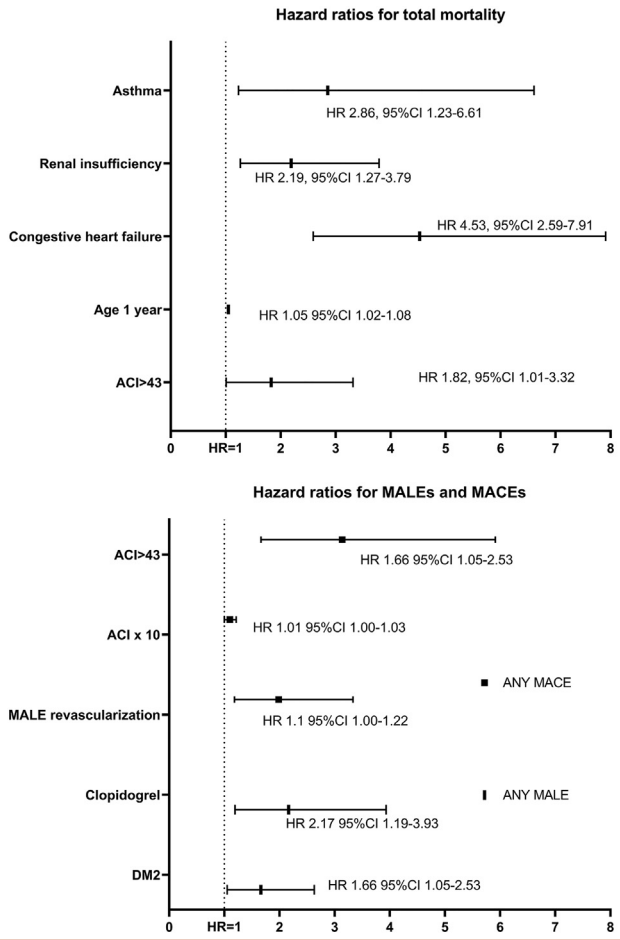


Fig 3. Hazard ratios (*HRs*) for total survival, major adverse cardiovascular events (*MACEs*), and major adverse leg events (*MALEs*). Adjusted multivariate Cox proportional hazard model showed significant predictors for MALEs, MACEs, and mortality, respectively. The model for mortality is adjusted for sex, serum creatinine, ankle-brachial index (ABI), hypertension, asthma, coronary artery disease, atrial fibrillation, use of bisphosphonates, and rheumatoid arthritis. The model for any MACE was adjusted for age, sex, and coronary artery disease. The model for any MALE was adjusted for age, sex, toe-brachial index (TBI), aortic calcification index (*ACI*), stage of peripheral artery disease (PAD) (intermittent claudication [IC]/critical limb ischemia [CLI]), uremia, use of statins, type 2 diabetes, and the use of clopidogrel. Each model included statistically significant univariate variables, but those with clinically or statistically relevant or suspected multicollinearity were left out of the models. Results present the last step of the backward stepwise Wald method. *CI*, Confidence interval; *DM2*, type 2 diabetes mellitus.

abdominal aorta. Also, abdominal CT is quite common in population level.[35] In clinical practice, ACI can be used to obtain additional information when assessing patients' risk when imaging has been performed. ACIs' accuracy in relation to current risk assessment tools is yet to be established.

In conclusion, we found that ACI is associated with PAD patients' overall survival and MACE-free survival. Based on our study results, ACI can improve risk assessment of patients with PAD.

Limitations. There are limitations to this study. There were 62 cases with missing ACI measurements. However, cohort demographics do not alter the availability of imaging studies. Patients are not categorized by the invasive treatment they received (open bypass surgery or endovascular treatment) because we think that such categorization would interfere with our method—categorization by operation strategy would emphasize the effect of current strategies on the possible outcome in follow-up and simultaneously undermine the relevance of ACI. Also, ACI did not affect the treatment strategy. This cohorts' mean ACI is a lot higher with patients with PAD than with subjects in our recent study of ACIs' association with intracranial aneurysms.[15] As these subjects had already symptomatic atherosclerotic disease and they were older, it is credible that these patients' ACI was higher. Smoking was not associated with ACI even though it is a well-known risk factor for aortic calcification. We categorized patients as smokers, ex-smokers, and nonsmokers, and therefore burden of vascular disease caused by smoking cannot be established because we did not evaluate smoking duration, pack-years, and duration since cessation.

We did not categorize patients by the clinical presentation of PAD (IC or CLI) because latter describes a very broad spectrum of patients from ischemic rest pain to severe necrosis. All patients had PAD severe enough to be symptomatic and were treated invasively in the initial setting. Survival of patients with IC and CLI relative to the ACI cutoff value of 43 is presented in the Supplementary Material (online only). Total survival in relation to the ACI cutoff value was not significantly different in patients presented with IC, but based on the above-mentioned bias, we see that this statistical finding is not clinically significant in this setting. Interobserver reproducibility was not measured in this study. However, the observer's (V.R.) inter-rater reliability has been assessed with good agreement for this same ACI measurement method earlier, and a random subset of measurements were compared with other author D.L. (see Supplemental Material, online only).[15] ACI's cutoff value in CART analysis was determined using analysis that uses substitute values. This has no major effect on our results' utility as in this study's CART analysis merely indicates that a cutoff value for ACI that best divides population in relation to end points can be found. More data would be needed to distinguish diagnostic or prognostic values for ACI. Our center's geographic catchment area is mostly populous, and the cohort describes a typical demographic of patients with PAD in this area. We see that the population of this region and center is not heavily exposed to geographic bias. This approach exposes our study to bias generated by insufficient reporting in records, but

we estimate that this phenomenon is not significant and probably evenly distributed. We could not assess these patients in relation to two other major PAD classifications: WiFI and GLASS, because these classifications were introduced after this study cohort was found. Our approach does not allow us to evaluate these patients afterward efficiently and reliably in relation to these classifications.

The data underlying this article cannot be shared publicly due to the privacy of the study subjects of this cohort. The data will be shared on reasonable request to the corresponding author.

AUTHOR CONTRIBUTIONS

Conception and design: VR, DL, VN, JJ, JG, HH
Analysis and interpretation: VR, DL, VN, JG, HH
Data collection: VR, DL, VN, JJ, JG, HH
Writing the article: VR, DL, VN, JJ, JG, HH
Critical revision of the article: VR, DL, VN, JJ, JG, HH
Final approval of the article: VR, DL, VN, JJ, JG, HH
Statistical analysis: VR, DL, VN, JJ, JG, HH
Obtained funding: Not applicable
Overall responsibility: VR

REFERENCES

1. van Haelst STW, Koopman C, den Ruijter HM, Moll FL, Visseren FL, Vaartjes I, et al. Cardiovascular and all-cause mortality in patients with intermittent claudication and critical limb ischaemia. Br J Surg 2018;105:252-61.
2. Golomb BA, Dang TT, Criqui MH. Peripheral arterial disease: morbidity and mortality implications. Circulation 2006;114:688-99.
3. Sampson UKA, Fowkes FGR, McDermott MM, Criqui MH, Aboyans V, Norman PE, et al. Global and regional burden of death and disability from peripheral artery disease: 21 world regions, 1990 to 2010. Glob Heart 2014;9:145-58.e21.
4. Zheng ZJ, Sharrett AR, Chambless LE, Rosamond WD, Nieto FJ, Sheps DS, et al. Associations of ankle-brachial index with clinical coronary heart disease, stroke and preclinical carotid and popliteal atherosclerosis: the Atherosclerosis Risk in Communities (ARIC) study. Atherosclerosis 1997;131:115-25.
5. Wickström J-E, Jalkanen JM, Venermo M, Hakovirta HH. Crural index and extensive atherosclerosis of crural vessels are associated with long-term cardiovascular mortality in patients with symptomatic peripheral artery disease. Atherosclerosis 2017;264:44-50.
6. Jalkanen JM, Wickström JE, Venermo M, Hakovirta HH. Data on amputation free survival of patients with lower limb peripheral artery disease classified according TASC II classification and a new crural index. Data Brief 2016;8:242-6.
7. Jalkanen JM, Wickström J-E, Venermo M, Hakovirta HH. The extent of atherosclerotic lesions in crural arteries predicts survival of patients with lower limb peripheral artery disease: a new classification of crural atherosclerosis. Atherosclerosis 2016;251:328-33.
8. Jalkanen J, Yegutkin GG, Hollmén M, Aalto K, Kiviniemi T, Salomaa V, et al. Aberrant circulating levels of purinergic signaling markers are associated with several key aspects of peripheral atherosclerosis and thrombosis. Circ Res 2015;116:1206-15.
9. Virtanen J, Varpela M, Biancari F, Jalkanen J, Hakovirta H. Association between anatomical distribution of symptomatic peripheral artery disease and cerebrovascular disease. Vascular 2020;28:295-300.
10. Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. J Vasc Surg 2019;69:3S-125S.e40.
11. Aboyans V, Ricco JB, Bartelink MLEL, Björck M, Brodmann M, Cohnert T, et al. Editor's Choice—2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2018;55:305-68.
12. Zettervall SL, Marshall AP, Fleser P, Guzman RJ. Association of arterial calcification with chronic limb ischemia in patients with peripheral artery disease. J Vasc Surg 2018;67:507-13.
13. Oishi H, Horibe H, Yamase Y, Ueyama C, Takemoto Y, Shigeta T, et al. Predictive value of abdominal aortic calcification index for mid-term cardiovascular events in patients with acute coronary syndrome. Heart Vessels 2020;35:620-9.
14. Tatami Y, Yasuda Y, Suzuki S, Ishii H, Sawai A, Shibata Y, et al. Impact of abdominal aortic calcification on long-term cardiovascular outcomes in patients with chronic kidney disease. Atherosclerosis 2015;243:349-55.
15. Rantasalo V, Gunn J, Kiviniemi T, Hirvonen J, Saarenpää I, Kivelev J, et al. Intracranial aneurysm is predicted by abdominal aortic calcification index: a retrospective case-control study. Atherosclerosis 2021;334:30-8.
16. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361-87.
17. Therneau T, Atkinson E. The concordance statistics method. 2021. Available at: https://cran.r-project.org/web/packages/survival/vignettes/concordance.pdf. Accessed October 13, 2021.
18. Longato E, Vettoretti M, Di Camillo B. A practical perspective on the concordance index for the evaluation and selection of prognostic time-to-event models. J Biomed Inform 2020;108:103496.
19. El Khoury R, Wu B, Edwards CT, Lancaster EM, Hiramoto JS, Vartanian SM, et al. The Global Limb Anatomic Staging System is associated with outcomes of infrainguinal revascularization in chronic limb threatening ischemia. J Vasc Surg 2021;73:2009-20.e4.
20. Liang P, Marcaccio CL, Darling JD, Kong D, Rao V, St John E, et al. Validation of the Global Limb Anatomic Staging System in first-time lower extremity revascularization. J Vasc Surg 2021;73:1683-91.e1.
21. Kodama A, Meecham L, Popplewell M, Bate G, Conte MS, Bradbury AW. Editor's Choice—Relationship between Global Limb Anatomic Staging System (GLASS) and clinical outcomes following revascularisation for chronic limb threatening ischaemia in the Bypass Versus Angioplasty in Severe Ischaemia of the Leg (BASIL)-1 trial. Eur J Vasc Endovasc Surg 2020;60:687-95.
22. Hicks CW, Zhang GQ, Canner JK, Weaver ML, Lum YW, Black JH, et al. The global anatomic staging system does not predict limb based patency of tibial endovascular interventions. Ann Vasc Surg 2021;75:79-85.
23. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR. Inter-society consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg 2007;45(Suppl S):5-67.
24. Kumakura H, Kanai H, Araki Y, Hojo Y, Iwasaki T, Ichikawa S. 15-year patency and life expectancy after primary stenting guided by intravascular ultrasound for iliac artery lesions in peripheral arterial disease. JACC Cardiovasc Interv 2015;8:1893-901.
25. Bauersachs RM, Szarek M, Brodmann M, Gudz I, Debus ES, Nehler MR, et al. Total ischemic event reduction with rivaroxaban after peripheral arterial revascularization in the VOYAGER PAD trial. J Am Coll Cardiol 2021;78:317-26.
26. Criqui MH, Denenberg JO, McClelland RL, Allison MA, Ix JH, Guerci A, et al. Abdominal aortic calcium, coronary artery calcium, and cardiovascular morbidity and mortality in the multi-ethnic study of atherosclerosis. Arterioscler Thromb Vasc Biol 2014;34:1574-9.
27. Lewis JR, Schousboe JT, Lim WH, Wong G, Wilson KE, Zhu K, et al. long-term atherosclerotic vascular disease risk and prognosis in elderly women with abdominal aortic calcification on lateral spine images captured during bone density testing: a prospective study. J Bone Miner Res 2018;33:1001-10.
28. Levitzky YS, Cupples LA, Murabito JM, Kannel WB, Kiel DP, Wilson PWF, et al. Prediction of intermittent claudication, ischemic stroke, and other cardiovascular disease by detection of abdominal aortic calcific deposits by plain lumbar radiographs. Am J Cardiol 2008;101:326-31.
29. Aboyans V, Lacroix P, Postil A, Guilloux J, Rollé F, Cornu E, et al. Subclinical peripheral arterial disease and incompressible ankle arteries are both long-term prognostic factors in patients undergoing coronary artery bypass grafting. J Am Coll Cardiol 2005;46:815-20.
30. Escofet Peris M, Alzamora MT, Valverde M, Fores R, Pera G, Baena-Díez JM, et al. Long-term morbidity and mortality after first and

recurrent cardiovascular events in the ARTPER cohort. J Clin Med 2020;9:4064.
31. Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, et al. Rivaroxaban in peripheral artery disease after revascularization. N Engl J Med 2020;382:1994-2004.
32. Schousboe JT, Vo TN, Langsetmo L, Adabag S, Szulc P, Lewis JR, et al. Abdominal aortic calcification (AAC) and ankle-brachial index (ABI) predict health care costs and utilization in older men, independent of prevalent clinical cardiovascular disease and each other. Atherosclerosis 2020;295:31-7.
33. Hanada S, Ando R, Naito S, Kobayashi N, Wakabayashi M, Hata T, et al. Assessment and significance of abdominal aortic calcification in chronic kidney disease. Nephrol Dial Transpl 2010;25:1888-95.
34. Raggi P, Genest J, Giles JT, Rayner KJ, Dwivedi G, Beanlands RS, et al. Role of inflammation in the pathogenesis of atherosclerosis and therapeutic interventions. Atherosclerosis 2018;276:98-108.
35. Pola A, Corbella D, Righini A, Torresin A, Colombo PE, Vismara L, et al. Computed tomography use in a large Italian region: trend analysis 2004-2014 of emergency and outpatient CT examinations in children and adults. Eur Radiol 2018;28:2308-18.

Submitted Apr 5, 2022; accepted Jul 1, 2022.

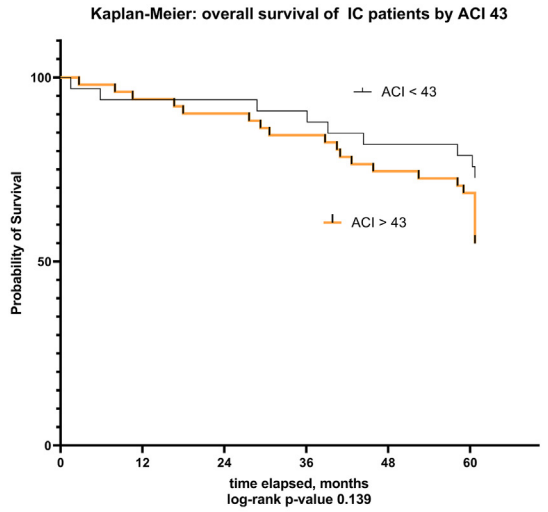
Additional material for this article may be found online at www.jvascsurg.org.

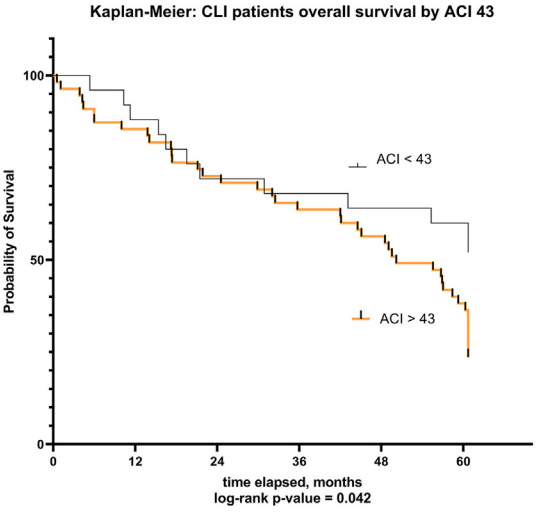
Journal of Vascular Surgery
Volume ■, Number ■

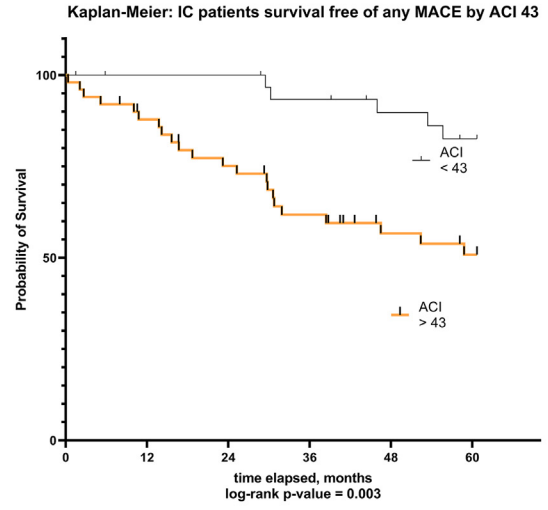
Supplementary Table (online only). Major adverse cardiovascular events (*MACEs*) and major adverse leg events (*MALEs*) between survivors and deceased patients

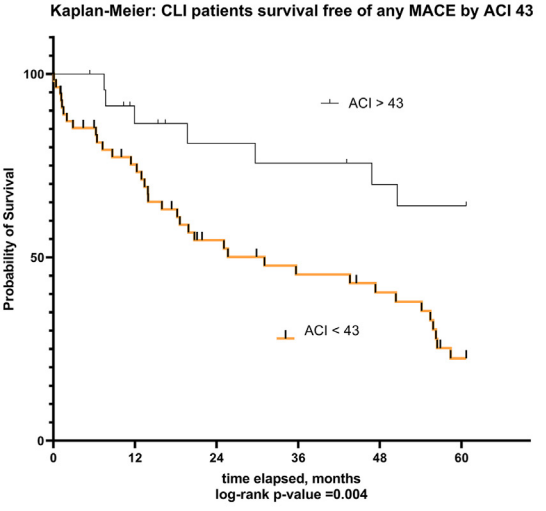
	Survivors (n = 100, 44.2%)		Nonsurvivors (n = 126, 55.8%)		
	N	%	N	%	*P*
MALE	49	49.49	60	47.24	.2708
No MALE	50	50.51	67	52.76	.2708
MACE	34	34.34	62	48.82	**.0290**
No MACE	65	65.66	65	51.18	**.0290**
MALE amputation	10	10.10	22	17.32	.1223
No MALE amputation	89	89.90	105	82.68	.1223
MALE revascularization	47	47.47	51	40.16	.2708
No MALE revascularizations	52	52.53	76	36.22	.2708
MACE myocardial infarct	23	23.23	32	25.20	.7328
No MACE myocardial infarct	76	76.77	95	74.80	.7328
MACE heart failure	13	13.13	45	35.43	**.0001**
No MACE heart failure	86	86.87	82	64.57	**.0001**
MACE ischemic stroke	14	14.14	12	9.45	.3039
No MACE ischemic stroke	75	75.76	99	77.95	.3039

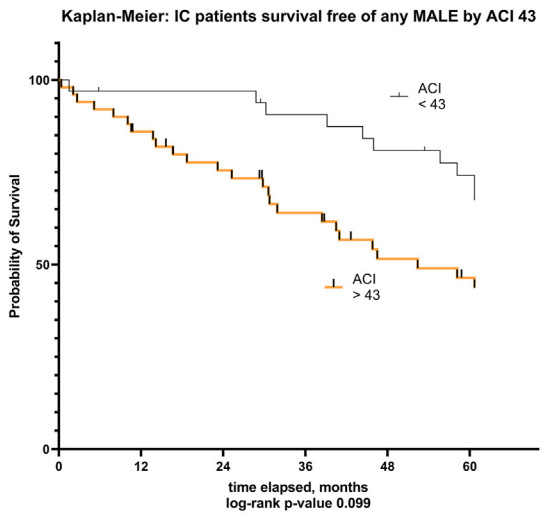
Boldface *P* values represent statistical significance.

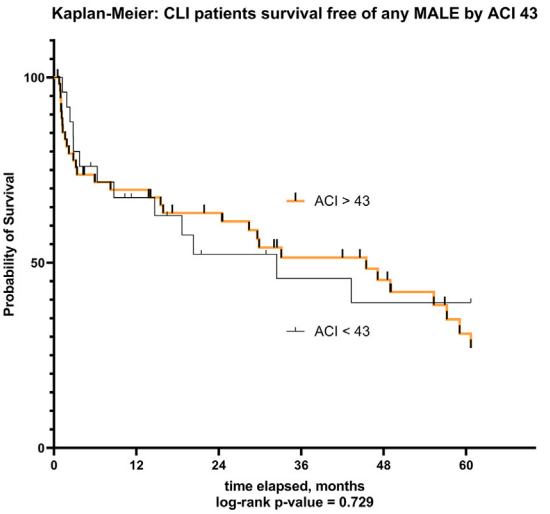












Supplementary Fig (online only). Mortality and survival without events (Kaplan-Meier curves) in intermittent claudication (*IC*) and critical limb ischemia (*CLI*) patients in relation to aortic calcification index (*ACI*) threshold value 43. Patients with IC had no significant difference in overall survival in relation to the ACI cutoff value 43, whereas patients with CLI had diminished survival with ACI 43 or greater. *MACE*, Major adverse cardiovascular event; *MALE*, major adverse leg event.