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Tibial Artery Calcification as a Marker of Amputation Risk in Patients With Peripheral Arterial Disease

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Objectives The purpose of this study was to evaluate the relationship between calcification in tibial arteries, the degree of limb ischemia, and the near-term risk of amputation.

Background Determining the amputation risk in patients with peripheral arterial disease (PAD) remains difficult. Developing new measures to identify patients who are at high risk for amputation would allow for targeted interventions and focused trials aimed at limb preservation.

Methods Two hundred twenty-nine patients underwent evaluation by history, arterial Doppler, and multislice computed tomography of the lower extremities. We then explored the relationship between a tibial artery calcification (TAC), traditional risk factors for PAD, limb status at presentation, and near-term amputation risk.

Results Increased age and traditional atherosclerosis risk factors were associated with higher TAC scores. Patients with critical limb ischemia had the highest TAC scores, and increasing TAC scores were associated with worsening levels of limb ischemia in ordinal regression analysis. Receiver-operator characteristic analysis suggested that the TAC score predicted amputation better than the ankle-brachial index (ABI). Symptomatic patients with a TAC score greater than 400 had a significantly increased risk of amputation. In Cox regression analysis, there was a strong association between the TAC score and the risk of major amputation that remained after adjustment for traditional risk factors and the ABI.

Conclusions In patients presenting with PAD, the TAC score is associated with the stage of disease and it identifies those who are at high risk for amputation better than traditional risk factors and an abnormal ABI. (J Am Coll Cardiol 2008;51:1967–74) © 2008 by the American College of Cardiology Foundation

Peripheral arterial disease (PAD) affects approximately 5 million Americans (1), and it is associated with decreased quality of life (2,3), increased risk of death (4,5), and increased risk of limb-threatening ischemia (6). The majority of patients with symptoms of early PAD remain stable; over time, however, 15% to 25% develop progressive disease requiring vascular intervention and 1 in 25 will require amputation (7,8). Despite our skill in identifying lower extremity arterial disease using exam and noninvasive testing, our ability to identify the subset of patients with PAD who will ultimately require amputation remains limited.

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While extensive investigations on the role of coronary artery calcification and its use as a marker of coronary disease have been made over the last 15 years (9–11), similar studies using computed tomographic (CT)-based methods that focus on lower extremity calcification have not been undertaken. When lower extremity arterial calcification is

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visible on conventional X-rays, it is associated with an increased risk of amputation (12–15). However, arterial calcification is thought to begin insidiously, and it may progress over years or decades before becoming apparent (16,17). Recent advances in CT imaging technology and software have made it possible to rapidly distinguish between minimal, early calcification that is difficult to detect, and the late, systemic calcification that is easily seen on conventional X-rays (18).

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Abbreviations and Acronyms

ABI = ankle-brachial index
CLI = critical limb ischemia
CT = computed tomography
PAD = peripheral arterial disease
TAC = tibial artery calcification

We, thus, established an algorithm for measuring tibial artery calcification (TAC) using multidetector CT scanning. We evaluated the relationship between the TAC score and the severity of symptoms. We then evaluated the association between the TAC score and the near-term amputation risk in patients presenting with symptomatic PAD. Our results suggest that evaluation of tibial calcification by multislice CT scan may be a useful method for identifying those patients who are at high risk for amputation.

Methods

Subjects. Between January 2004 and October 2006, 118 patients with symptomatic lower extremity PAD were recruited from the vascular clinics of Vanderbilt University Hospital and the Nashville Veterans'Administration Hospital. In addition, we recruited a control group of 111 community volunteers without symptomatic PAD. In order to exclude the known effects of renal insufficiency and renal failure on arterial calcification, patients with a creatinine greater than 1.7 were excluded from this study. Also excluded were patients with type I diabetes, patients who did not ambulate, patients who had previously undergone a major amputation, patients with acute limb ischemia, patients who had previously undergone multiple (greater that 2) lower extremity revascularization procedures, and patients presenting with severe ischemia associated with gangrene or tissue loss (Rutherford category 6).

Patient assessment and group assignments. Patients were asked about symptoms of PAD including claudication, ischemic rest pain, and ulcers. A further medical history was obtained that involved assessment of vascular risk factors including a self-reported history of tobacco use, hyperlipidemia, hypertension, and diabetes. Patients then underwent evaluation by pulse exam and noninvasive arterial Doppler testing. Lower extremity physical exam findings and arterial Doppler findings were then used to assign a limb ischemia category according to the criteria set forth by Rutherford et al. (19).

Biochemical measurements. Patients underwent standard laboratory evaluation for measurement of total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides.

Imaging. Patients underwent noncontrast CT scanning of the lower extremities on a single 16-slice CT scanner (MX8000 IDT, Philips Medical, Cleveland, Ohio) that was calibrated daily and twice monthly using standardized protocols. Scans were performed using a 3-mm increment, mAs = 200, and kV = 120 with a field of view of 350 to 380 mm yielding typical spatial resolution $0.7 \times 0.7 \times 3.0$ mm^3. The scan duration was approximately 15 s. From the acquired raw data, the scan was reconstructed in 3-mm slices. The average number of slices was 135 ± 43 slices. Sample images from patients without (A) and with (B) tibial artery calcium are demonstrated in Figure 1.

Tibial artery calcium scoring. Tibial artery calcium scoring was performed using standardized calcium scoring software (Phillips Medical Systems, Amsterdam, the Netherlands) by investigators who were blinded to the results of the clinical assessment and Rutherford categories. Automated image analysis was performed using the software on a Dell dual processor computer. On cross-sectional images through the lower extremities, areas of calcification along the tibial arteries with a cross-sectional area greater than 1 mm^2 and with a density of >130 Hounsfield units (HU) were identified automatically. Regions of interest along the distal popliteal, anterior tibial, posterior tibial, and peroneal arteries were manually selected and labeled. Measurements were started at the bottom of the patella and ended at the widest portion of the tibial and fibular malleoli at the ankle. This usually included the bottom half of the popliteal artery and the entire length of the 3 tibial arteries down to the ankle. This also allowed us to include all anatomical variants of tibial artery origins. Calcium scores were determined according to the method described by Agatston et al. (9). This method was chosen because it is currently in widespread use and because it provides a simple transition from

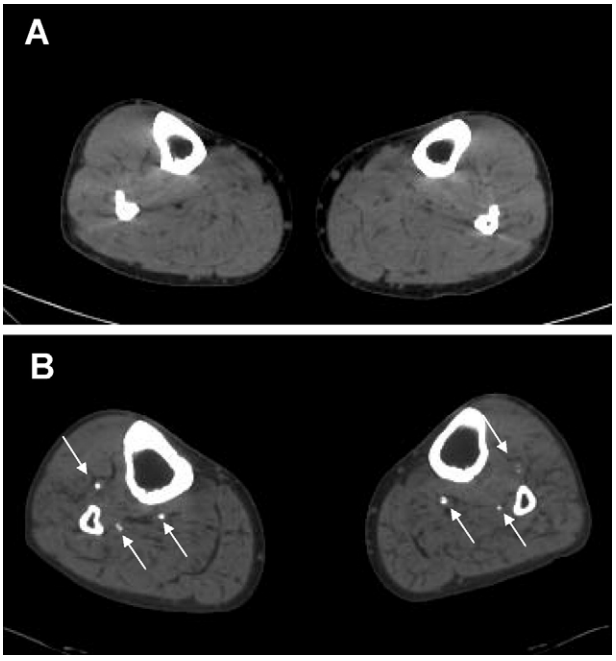

Figure 1 TAC

Noncontrasted multislice computed tomography showing a patient without **(A)** and with **(B)** significant tibial artery calcification (TAC). **Arrows** identify calcified tibial arteries.

coronary calcium scoring. Individual calcium values for each artery in each lower extremity were added together to derive a single combined TAC score for each patient. Interobserver variability was evaluated by 2 readers in a randomly selected list of 39 scans. The Spearman correlation coefficient was 0.98 with a value of $p < 0.001$.

Follow-up. Outcomes were determined from patient interviews during routine clinical follow-up. Patients presenting with critical limb ischemia (CLI) were followed at least monthly until symptoms resolved, healing was complete, or amputation occurred. Additional follow-up data were obtained through an institutional review board–approved chart review and through a follow-up completion survey performed by phone. Time to follow-up or event was calculated from the date of the CT scan. We were unable to obtain follow-up on 2 patients (1 patient with claudication and 1 patient with CLI) who did not return for management after their CT scan (98% follow-up). The control population was contacted 1 time for follow-up by phone questionnaire. We were unable to contact 4 patients in this group (96% follow-up). Follow-up of at least 3 months was available in 223 patients, and the mean follow-up time was 13.8 ± 7.7 months. Minor amputation was defined as any amputation limited to the distal forefoot up to the transmetatarsal level. Major amputation was defined as any amputation above the ankle.

Statistical analysis. Statistical computations were carried out using the SPSS version 15.0 (SPSS Inc., Chicago, Illinois) and GraphPad Prism 5 (GraphPad Software Inc., San Diego, California). Continuous variables were summarized via mean and SD, and dichotomous variables were summarized via counts and percents. The normality of continuous variables was checked using the Kolmogorov-Smirnov test. Due to non-normal distributions, comparisons of continuous variables across TAC groups and across limb ischemia categories were performed using the Kruskal-Wallis test, and post-hoc comparisons were performed using Dunn's post-test. For comparison of dichotomous variables across TAC groups and limb ischemia categories, we used the chi-square test for trend followed by pairwise comparisons using the chi-square test. Values for TAC scores were significantly skewed, and for this reason statistics were performed on log-transformed TAC + 1 scores. Associations of clinical variables with severity of limb ischemia at presentation were assessed using ordinal logistic regression and expressed as hazard ratios with 95% confidence intervals. Receiver-operator characteristic curves were generated for TAC and ankle-brachial index (ABI) versus major and major plus minor amputation. Event-free curves for major amputation were generated using Kaplan-Meier analysis and compared using the log-rank test. Predictors of major amputation in patients with PAD were evaluated using Cox proportional hazards regression. Hazard ratios, 95% confidence intervals, and p values are listed. In order to maintain the predictive accuracy of different ranges of ankle pressures for limb ischemia, ABIs were categorized according to the following scale: 0 for normal ABIs of 0.9 to 1.4; 1 for diminished ABIs of 0.6 to 0.9; 2 for ABIs between 0.3 to 0.6; and 3 for ABIs below 0.3 and for noncompressible vessels.

Results

Patient characteristics at baseline. A total of 229 patients completed the study and were included in the initial analysis of risk factors for TAC (Table 1). Interestingly, total cholesterol levels and low-density lipoprotein were inversely related to the tibial calcification score; however, there was a trend toward increased statin use in patients with higher TAC scores. Patients with higher TAC scores had a higher incidence of PAD symptoms.

Table 1 Patient Characteristics According to TAC Score

	TAC = 0 (n = 83)	TAC = 1 to 503 (n = 72)	TAC >503 (n = 74)	p Value
Age, yrs	57 ± 7	60 ± 8	67 ± 10	<0.0001
Men, %	41	69	76	<0.0001
Caucasian, %	89	85	74	0.1128
Type 2 diabetes, %	46	68	74	0.0004
Hypertension, %	55	72	78	<0.0001
Hyperlipidemia, %	57	63	72	0.0010
Smoking history	45	74	81	0.0004
Total cholesterol	187 ± 35	178 ± 43	162 ± 42	0.0002
HDL cholesterol	54 ± 17	46 ± 14	44 ± 14	0.0003
LDL cholesterol	99 ± 39	88 ± 29	79 ± 29	0.0026
Triglycerides	194 ± 115	213 ± 150	204 ± 137	0.6054
BMI	30.6 ± 7.3	29.1 ± 5.4	28.7 ± 7.5	0.1658
Statin use, %	51	61	65	0.0667
PAD symptoms, %	22	53	85	<0.0001

BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PAD = peripheral arterial disease; TAC = tibial artery calcification.

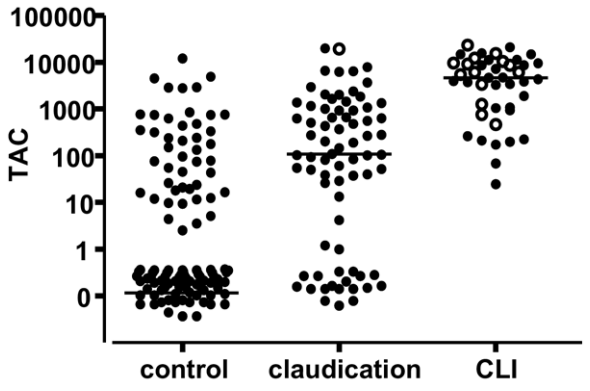

Figure 2 TAC Scores by Limb Status

Tibial artery calcification (TAC) scores in patients without (control group) and with peripheral arterial disease (claudication and critical limb ischemia [CLI]). Each **dot** represents a single patient. **Open circles** represent patients who subsequently underwent major amputation. **Lines** represent median for each group.

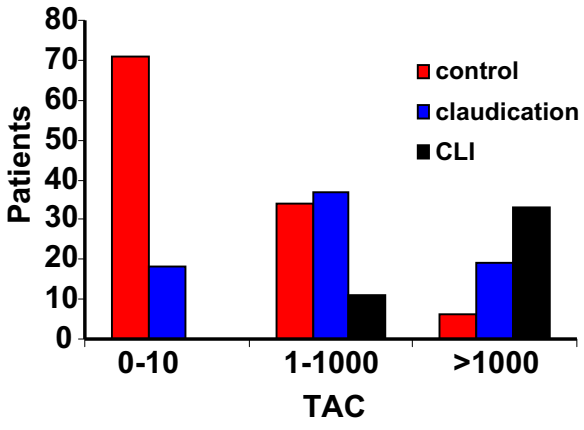

Figure 3 Clinical Presentation by TAC Range

Patients were divided according to tibial artery calcification (TAC) categories (0 to 10, 10 to 1,000, and >1,000). **Bars** represent the number of patients with no disease (**red bars**, control group), claudication **(blue bars)**, or critical limb ischemia (CLI) **(black bars)**.

TAC score is associated with severity of limb ischemia at presentation. The control population was generally well matched with the claudication group, but patients presenting with CLI were older, more likely to be men, and more likely to have type 2 diabetes, hypertension, and a history of tobacco use. The TAC score increased significantly between the control and claudication groups and between the claudication and CLI groups (Fig. 2, Table 2).

We next assessed the association between the TAC score and the level of ischemia at presentation. When we divided patients according to TAC ranges, the proportion of patients presenting with CLI increased from 0% in the lowest group to 57% for patients with a TAC score of greater than 1,000 (Fig. 3). In order to adjust for the possible confounding effects of demographic and risk factors, we used ordinal logistic regression to evaluate the association between the TAC score and limb status at presentation (control, claudication, or CLI). After correcting for age, male gender, type II diabetes, hypertension, hyperlipidemia, and tobacco use, the TAC score continued to have a strong association with worsening ischemia (Table 3).

TAC score predicts amputation. During follow-up, a total of 28 amputations occurred in our vascular patient population while no amputations occurred in the control patient population. In the group of 74 patients initially presenting with claudication, there were 3 amputations (2 minor and 1 major). In the group of 45 patients presenting with CLI, there were 25 amputations. Of these, 15 were major and 10 were minor amputations. Receiver-operator characteristic curves were generated to evaluate the predictive value of TAC for amputation and to compare it with the ABI. When we evaluated these measures versus major amputation, the area under the curve for TAC was greater than that for the ABI (Fig. 4A). When we evaluated these measures versus the combined end point of major and minor amputation, the area under the curve for TAC remained greater than that for ABI (Fig. 4B). Thus, receiver-operator

Table 2 Patient Characteristics According to Severity of Limb Ischemia at Presentation

	Control Group (n = 111)	Claudication (n = 74)	CLI (n = 44)	p Value
Age (yrs)	59 ± 7	60 ± 10	67 ± 11*†	0.0001
Men (%)	54	65	73*	0.0223
Caucasian (%)	89	77*	77	0.0314
Type 2 DM (%)	59	55	82‡§	0.0263
Hypertension (%)	59	72	86‡	0.0006
Hyperlipidemia (%)	53	77‡	66	0.0267
Tobacco use (%)	47	81‡	86‡	<0.0001
BMI (kg/m^2)	30.3 ± 6.7	29.4 ± 6.5	27.7 ± 7.7	0.3914
TAC‖	0 (0, 12,093)	107 (0, 19,848)‡	4,475 (24, 23,392)‡§	<0.0001

*$p < 0.05$ versus control group; †$p < 0.05$ versus claudication group; ‡$p < 0.01$ versus control group; §$p < 0.01$ versus claudication group; ‖Tibial artery calcification (TAC) scores are expressed as median (minimum, maximum).
BMI = body mass index; CLI = critical limb ischemia; DM = diabetes mellitus.

Table 3 Adjusted HR for Increasing Severity of Limb Ischemia at Presentation*

	HR (95% CI)	p Value
Age	1.003 (0.970–1.037)	0.8611
Men	0.814 (0.426–1.555)	0.5327
Caucasian	1.065 (0.486–2.336)	0.8746
Type 2 diabetes	0.809 (0.430–1.519)	0.5091
Hypertension	1.833 (0.930–3.614)	0.0800
Hyperlipidemia	1.229 (0.662–2.282)	0.5131
Smoking history	3.683 (1.886–7.194)	0.0001
TAC score†	2.548 (1.945–3.340)	<0.0001

*Control, claudication, and critical limb ischemia groups; †log-transformed tibial artery calcification (TAC) values were used for statistics.
CI = confidence interval; HR = hazard ratio; TAC = tibial artery calcification.

characteristic curves, while not corrected for possible confounders, indicate that the TAC score is a better marker of amputation risk than the ABI. We identified a TAC cutoff value of 400 which, when applied to our symptomatic vascular patient population, yielded a sensitivity of 94%, a specificity of 46%, a positive predictive value of 23% (15 of 65), and a negative predictive value of 98% (1 of 59) for major amputation.

Kaplan-Meier curve analysis was performed using a cutoff TAC value of 400 for the prediction of major amputation in symptomatic vascular patients. The log-rank test showed that patients presenting with vascular symptoms and a TAC score >400 had a significantly higher major amputation rate compared with patients with a TAC score <400 (Fig. 5).

In our final analysis, we used Cox proportional hazards analysis to evaluate predictors of major amputation including TAC >400 in our symptomatic vascular patient population (Rutherford categories 1 to 5). Interestingly, in univariate analysis, traditional risk factors and the ABI lost their predictive value while a TAC >400 remained predictive. In multivariate analysis, after adjusting for age and ABI, the hazard ratio for a TAC >400 was 11.27 ($p = 0.025$) (Table 4). These findings suggest that in patients presenting to the vascular service with symptomatic PAD, a TAC score >400 predicts amputation better than demographics, risk factors, and the ABI.

Discussion

Our study showed for the first time that multislice CT can be used to quantify calcification in the tibial arteries and that TAC is strongly associated with the stage of lower extremity vascular disease and the near-term risk of major amputation. This association was preserved after correction for traditional risk factors and the ABI, an indirect measure of pedal perfusion. Patients without tibial calcification did not require amputation, while 1 in 5 patients presenting with ischemic symptoms and a TAC score >400 underwent major amputation. Our study suggests that tibial artery calcium may be a useful measure to stratify patients into risk categories and to guide therapy aimed at limb preservation.

The initial diagnosis of PAD in patients is uncomplicated. Once the diagnosis of PAD is made, however, determining which patients have a poor limb prognosis with ultimate need for major amputation remains problematic. While an abnormal ABI can predict all-cause and cardiovascular-specific mortality (20), it correlates poorly with symptoms (21), can give misleading results in patients with calcified vessels (22), and cannot predict healing after forefoot amputation (23). Our results suggest that the TAC score may be most useful in this at-risk patient cohort with known vascular disease. Patients with low or normal TAC scores could be safely managed with conventional medical management, whereas patients with a TAC score above a certain threshold might benefit from more intensive medical therapy, custom shoes, and more frequent foot examination, and they may also be more suitable for participation in clinical trials aimed at preventing amputation.

Abdominal, pelvic, and lower extremity calcification have previously been shown to reflect advanced occlusive disease and increased risk of cardiovascular events (12–15,24–27).

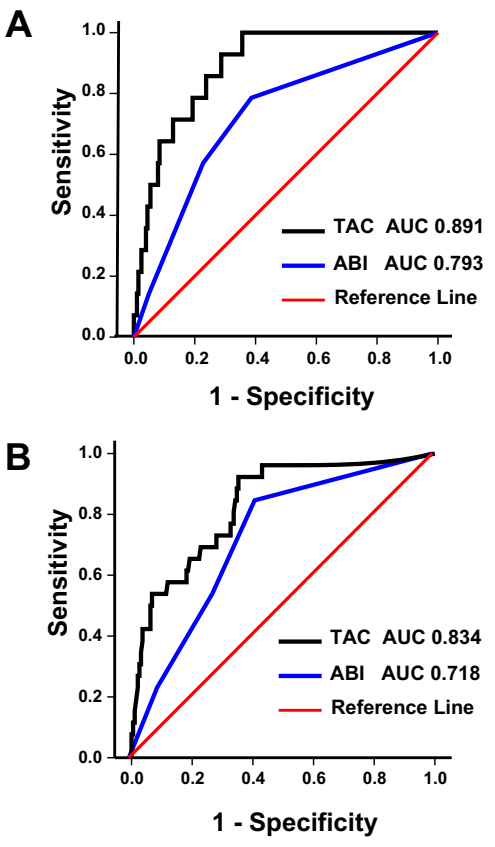

Figure 4 ROC Analysis

Receiver-operator characteristic (ROC) curves for the predictive value of tibial artery calcification (TAC) and ankle-brachial index (ABI) on major amputation **(A)** and on major and minor amputation **(B)**. The **black line** represents the ROC curve for TAC score. The **blue line** represents ROC curve for ABI. The **red line** represents no effect. AUC = area under the curve.

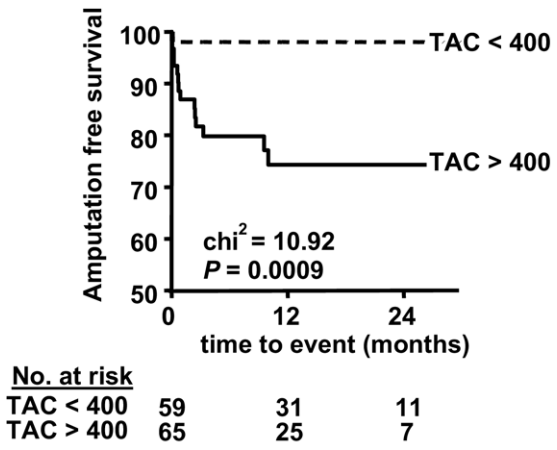

Figure 5 **Major Amputation Events According to TAC Score for Patients With PAD**

Symptomatic vascular patients were stratified by tibial artery calcification (TAC) scores >400 or <400. Kaplan-Meier curves were derived for major amputation-free survival. The p value is derived using the log-rank test. Number of patients at risk at each time point is listed on the **bottom**. PAD = peripheral arterial disease.

Recent studies have focused on patients with chronic kidney disease (28), and there is a well-known association of increased systemic vascular calcification in patients on dialysis (29–33). Relationships between the macroscopic arterial calcification that is visible on conventional X-rays and glucose tolerance (34), neuropathy (35), mortality rates, and complications of diabetes including amputation have also been demonstrated (12). However, the utility of quantitative assessment of vascular calcification by multislice CT has not been evaluated.

We propose a scoring protocol for lower extremities based on the extensive investigations previously performed on coronary artery calcium (9). Our rationale for assessing arterial calcification in the tibial vessels was related to previous work suggesting an association between distal calcific disease and amputation (12). It was also based on the known relationships between diabetes, tibial atherosclerosis, and limb loss (36). While there are significant risk factor associations for calcified atherosclerosis in different vascular beds (37), we suspected that the amount of calcific disease in the tibial vessels would most strongly reflect the degree of blood-flow impairment to the foot. We excluded calcification in the aortoiliac and femoral regions based on the fact that chronic, single-level disease above the knee is infrequently associated with CLI (38), while tibial artery disease, even in an isolated form, can lead to amputation (39). Additionally, the risk factors for aortoiliac and femoropopliteal disease are known to be different from those for tibial occlusive disease (40), and we did not want to confound the associations between the TAC score, risk factors, and end stage events.

In order to remain consistent with the methods used for scoring coronary calcium, we did not attempt to distinguish between intimal and medial calcification. Previous studies have suggested that medial, but not intimal, calcification predicts cardiovascular events (12–14). We are unable to determine if our results would have been different had we focused on medial calcification; however, the predictive ability of the TAC score remains strong. A comparison of the total calcification score with a scoring system based solely on medial calcification may yield insight into the pathophysiological importance of the 2 types of calcification. Finally, the progression rate of TAC is unknown. It was previously thought that PAD patients progressed consecutively through the stages of ischemia from mild to severe claudication then to rest pain or ulceration. However, we now know that many patients presenting with CLI progressed rapidly, and previous studies suggest that more than one-half of CLI patients are asymptomatic 6 months prior (41). Our data show that many patients with high TAC scores had minimal symptoms of lower extremity vascular disease. Further studies will be needed to determine if this subgroup of patients with high TAC and minimal or no symptoms are indeed the same patients who will go on to develop CLI.

Study limitations. Our study has several limitations. First, we chose to modify the Agatston scoring system for use in the tibial arteries because of its widespread integration in

Table 4 **HRs for Major Amputation in Patients Presenting With PAD**

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age	1.04 (0.996–1.086)	0.079	1.001 (0.955–1.049)	0.980
Men	2.27 (0.645–7.965)	0.202		
Caucasian	0.87 (0.281–2.705)	0.813		
Type 2 diabetes	1.04 (0.390–2.771)	0.938		
Hypertension	1.42 (0.406–5.002)	0.581		
Hyperlipidemia	1.63 (0.466–5.737)	0.443		
Smoking history	0.82 (0.232–2.865)	0.751		
ABI	1.73 (0.971–3.084)	0.063	1.33 (0.732–2.433)	0.346
TAC >400	14.40 (1.90–109.112)	0.010	11.27 (1.353–93.842)	0.025

ABI = ankle-brachial index; PAD = peripheral arterial disease; other abbreviations as in Table 3.

coronary artery scoring; however, it is possible that other scoring methods such as the volumetric method of Callister (42) or the mass scoring method initially suggested by Detrano et al. (43) would be better for comparing scores at different centers and for tracking calcium changes over time. Future work will be needed to address this issue. We have not fully addressed the variability in the performance or interpretation of scans. However, our interobserver variability was excellent with a Spearman correlation coefficient of 0.98, and in coronary arteries, the technique is remarkably robust (44). We chose to use parameters similar to those used for coronary artery calcium scoring including a 3-mm slice thickness and nonoverlapping segments; however, optimization of parameters for efficient comparison and tracking of TAC scores will be needed. The scoring method will also need to be validated against other calcium assessment systems and against the total amount of occlusive disease. We did not demonstrate utility of the TAC score in patients within specific Rutherford groups owing to the limited number of events; however, when we assessed the predictive value of TAC for major and minor amputations in patients presenting with Rutherford categories 1 to 4, TAC was a significant factor ($p = 0.010$), although there were only 3 amputations in this group (2 minor and 1 major). When we included the presence or absence of CLI as a variable in logistic regression analysis, the p value for TAC approached significance ($p = 0.060$). Larger and longer-term studies will be needed to determine the associative and predictive aspects of TAC scoring in individual patient subpopulations. There was selection bias in our population in that over one-half of our subjects came from a referral vascular surgery practice. While we tried to compensate for this by recruiting asymptomatic volunteers from the community, our results cannot be extrapolated to the overall population. We did not include toe pressures or a toe-brachial index in our analysis of predictors for major amputation, and this may be a better measure of limb ischemia in patients with calcified vessels (22). Additionally, our study does not take into account the various efforts at limb salvage, and, in particular, we have not categorized the attempts at revascularization, wound care, or other treatments that were offered to the patients in our study. Tibial artery calcification scores, however, were unknown to physicians recommending amputation, and they were not used for clinical decision-making.

Conclusions

We have demonstrated that: 1) tibial artery calcium scores are higher in patients with PAD than in asymptomatic control subjects; 2) increasing calcium scores are associated with increasing severity of PAD; and 3) the TAC score predicts the short-term risk of amputation, independent of other risk factors and the ABI. Further efforts to evaluate the pathophysiological mechanisms relating tibial artery calcium accumulation to CLI are warranted, as are clinical investigations aimed at preventing lower extremity amputation in this high-risk population.

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REFERENCES

1. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. Circulation 2004;110:738–43.
2. Izquierdo-Porrera AM, Gardner AW, Bradham DD, et al. Relationship between objective measures of peripheral arterial disease severity to self-reported quality of life in older adults with intermittent claudication. J Vasc Surg 2005;41:625–30.
3. Long J, Modrall JG, Parker BJ, Swann A, Welborn MB 3rd, Anthony T. Correlation between ankle-brachial index, symptoms, and health-related quality of life in patients with peripheral vascular disease. J Vasc Surg 2004;39:723–7.
4. Feringa HH, Bax JJ, van Waning VH, et al. The long-term prognostic value of the resting and postexercise ankle-brachial index. Arch Intern Med 2006;166:529–35.
5. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992;326:381–6.
6. Dormandy J, Heeck L, Vig S. Predicting which patients will develop chronic critical leg ischemia. Semin Vasc Surg 1999;12:138–41.
7. Harris LM, Peer R, Curl GR, Pillai L, Upson J, Ricotta JJ. Long-term follow-up of patients with early atherosclerosis. J Vasc Surg 1996;23:576–80; discussion 581.
8. Weitz JI, Byrne J, Clagett GP, et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. Circulation 1996;94:3026–49.
9. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–32.
10. Bellasi A, Raggi P. Diagnostic and prognostic value of coronary artery calcium screening. Curr Opin Cardiol 2005;20:375–80.
11. Fuster V, Fayad ZA, Moreno PR, Poon M, Corti R, Badimon JJ. Atherothrombosis and high-risk plaque: part II: approaches by non-invasive computed tomographic/magnetic resonance imaging. J Am Coll Cardiol 2005;46:1209–18.
12. Everhart JE, Pettitt DJ, Knowler WC, Rose FA, Bennett PH. Medial arterial calcification and its association with mortality and complications of diabetes. Diabetologia 1988;31:16–23.
13. Niskanen L, Siitonen O, Suhonen M, Uusitupa MI. Medial artery calcification predicts cardiovascular mortality in patients with NIDDM. Diabetes Care 1994;17:1252–6.
14. Lehto S, Niskanen L, Suhonen M, Ronnemaa T, Laakso M. Medial artery calcification. A neglected harbinger of cardiovascular complications in non-insulin-dependent diabetes mellitus. Arterioscler Thromb Vasc Biol 1996;16:978–83.
15. Mayfield JA, Caps MT, Boyko EJ, Ahroni JH, Smith DG. Relationship of medial arterial calcinosis to autonomic neuropathy and adverse outcomes in a diabetic veteran population. J Diabetes Complications 2002;16:165–71.
16. Ardehali R, Nasir K, Kolandaivelu A, Budoff MJ, Blumenthal RS. Screening patients for subclinical atherosclerosis with non-contrast cardiac CT. Atherosclerosis 2007;192:235–42.
17. Kronmal RA, McClelland RL, Detrano R, et al. Risk factors for the progression of coronary artery calcification in asymptomatic subjects.

Results from the Multi-Ethnic Study of Atherosclerosis (MESA) screening patients for subclinical atherosclerosis with non-contrast cardiac CT. Circulation 2007;192:235–42.
18. Nasir K, Budoff MJ, Post WS, et al. Electron beam CT versus helical CT scans for assessing coronary calcification: current utility and future directions. Am Heart J 2003;146:969–77.
19. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg 1997;26:517–38.
20. Resnick HE, Lindsay RS, McDermott MM, et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart study. Circulation 2004;109: 733–9.
21. Szuba A, Oka RK, Harada R, Cooke JP. Limb hemodynamics are not predictive of functional capacity in patients with PAD. Vasc Med 2006;11:155–63.
22. Brooks B, Dean R, Patel S, Wu B, Molyneaux L, Yue DK. TBI or not TBI: that is the question. Is it better to measure toe pressure than ankle pressure in diabetic patients? Diabet Med 2001;18:528–32.
23. Nguyen TH, Gordon IL, Whalen D, Wilson SE. Transmetatarsal amputation: predictors of healing. Am Surg 2006;72:973–7.
24. Witteman JC, Kok FJ, van Saase JL, Valkenburg HA. Aortic calcification as a predictor of cardiovascular mortality. Lancet 1986;2: 1120–2.
25. Niskanen LK, Suhonen M, Siitonen O, Lehtinen JM, Uusitupa MI. Aortic and lower limb artery calcification in type 2 (non-insulin-dependent) diabetic patients and non-diabetic control subjects. A five year follow-up study. Atherosclerosis 1990;84:61–71.
26. Wilson PW, Kauppila LI, O'Donnell CJ, et al. Abdominal aortic calcific deposits are an important predictor of vascular morbidity and mortality. Circulation 2001;103:1529–34.
27. Reaven PD, Sacks J. Coronary artery and abdominal aortic calcification are associated with cardiovascular disease in type 2 diabetes. Diabetologia 2005;48:379–85.
28. Sigrist M, Bungay P, Taal MW, McIntyre CW. Vascular calcification and cardiovascular function in chronic kidney disease. Nephrol Dial Transplant 2006;21:707–14.
29. Moe SM, Chen NX. Pathophysiology of vascular calcification in chronic kidney disease. Circ Res 2004;95:560–7.
30. Shanahan CM. Vascular calcification. Curr Opin Nephrol Hypertens 2005;14:361–7.
31. Ketteler M, Westenfeld R, Schlieper G, Brandenburg V. Pathogenesis of vascular calcification in dialysis patients. Clin Exp Nephrol 2005; 9:265–70.
32. London GM, Marchais SJ, Guerin AP, Metivier F. Arteriosclerosis, vascular calcifications and cardiovascular disease in uremia. Curr Opin Nephrol Hypertens 2005;14:525–31.
33. Campean V, Neureiter D, Varga I, et al. Atherosclerosis and vascular calcification in chronic renal failure. Kidney Blood Press Res 2005;28: 280–9.
34. Neubauer B. A quantitative study of peripheral arterial calcification and glucose tolerance in elderly diabetics and non-diabetics. Diabetologia 1971;7:409–13.
35. Edmonds ME, Morrison N, Laws JW, Watkins PJ. Medial arterial calcification and diabetic neuropathy. Br Med J (Clin Res Ed) 1982;284:928–30.
36. Faglia E, Favales F, Quarantiello A, et al. Angiographic evaluation of peripheral arterial occlusive disease and its role as a prognostic determinant for major amputation in diabetic subjects with foot ulcers. Diabetes Care 1998;21:625–30.
37. Allison MA, Criqui MH, Wright CM. Patterns and risk factors for systemic calcified atherosclerosis. Arterioscler Thromb Vasc Biol 2004;24:331–6.
38. Martinez BD, Hertzer NR, Beven EG. Influence of distal arterial occlusive disease on prognosis following aortobifemoral bypass. Surgery 1980;88:795–805.
39. Wolfle KD, Bruijnen H, Reeps C, et al. Tibioperoneal arterial lesions and critical foot ischaemia: successful management by the use of short vein grafts and percutaneous transluminal angioplasty. VASA 2000; 29:207–14.
40. Vogt MT, Wolfson SK, Kuller LH. Segmental arterial disease in the lower extremities: correlates of disease and relationship to mortality. J Clin Epidemiol 1993;46:1267–76.
41. Dormandy J, Belcher G, Broos P, et al. Prospective study of 713 below-knee amputations for ischaemia and the effect of a prostacyclin analogue on healing. Hawaii study group. Br J Surg 1994;81:33–7.
42. Callister TQ, Cooil B, Raya SP, Lippolis NJ, Russo DJ, Raggi P. Coronary artery disease: improved reproducibility of calcium scoring with an electron-beam CT volumetric method. Radiology 1998;208: 807–14.
43. Detrano R, Kang X, Mahaisavariya P, et al. Accuracy of quantifying coronary hydroxyapatite with electron beam tomography. Invest Radiol 1994;29:733–8.
44. Lawler LP, Horton KM, Scatarige JC, et al. Coronary artery calcification scoring by prospectively triggered multidetector-row computed tomography: is it reproducible? J Comput Assist Tomogr 2004;28: 40–5.