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Femoral Plaque Echogenicity and Cardiovascular Risk in Claudicants

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OBJECTIVES The present study was designed to verify whether the evaluation of femoral plaque echogenicity might be a useful tool for cardiovascular risk assessment in patients affected by lower extremity peripheral arterial disease.

BACKGROUND Lower extremity peripheral arterial disease is a common manifestation of atherosclerosis and is associated with a high risk of developing major cardiovascular events. Vulnerable atherosclerotic plaque plays a central role in the occurrence of acute ischemic events in different vascular territories. Furthermore, atherosclerosis is a systemic disease, and the presence of an unstable atherosclerotic plaque in a certain vascular district, characterized by low echogenicity at B-mode ultrasound, is associated to a greater prevalence of unstable plaques in other vascular beds.

METHODS Femoral plaque echogenicity of 246 claudicants with ankle/brachial index $\leq$0.90 was evaluated at B-mode ultrasound by visual analysis and by calculating the grayscale median (GSM) value. In these patients, the occurrence of myocardial infarction and stroke was prospectively assessed.

RESULTS Femoral GSM values and plaque types assessed by visual analysis were highly correlated by Spearman analysis (rho = 0.905, $p < 0.001$). During a median follow-up of 30 months, 32 patients (13%) had a major cardiovascular event. Compared with patients without events, those who experienced an event during the follow-up had a lower femoral plaque GSM value (42.9 $\pm$ 26.2 vs. 58.8 $\pm$ 19.3, $p = 0.002$) and a higher prevalence of hypoechoic femoral plaque at visual analysis (68.8% vs. 19.6%, $p < 0.001$). At Cox analysis, femoral GSM showed an inverse relationship with cardiovascular risk, even after adjustment for possible confounders (hazard ratio: 0.96, 95% confidence interval [CI]: 0.95 to 0.98, $p < 0.001$). Furthermore, patients with hypoechoic femoral plaques at visual analysis had a 7.24-fold increased cardiovascular risk compared with patients with hyperechoic plaques after adjustment for possible confounders (95% CI: 3.23 to 16.22, $p < 0.001$).

CONCLUSIONS This study demonstrates that the presence of hypoechoic atherosclerotic femoral plaques is associated with higher cardiovascular risk in lower extremity peripheral arterial disease patients. (J Am Coll Cardiol Img 2012;5:348–57) © 2012 by the American College of Cardiology Foundation

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Vulnerable atherosclerotic plaque plays a central role in the occurrence of acute ischemic events in different vascular districts (1–4). Culprit lesions responsible for acute coronary syndromes most commonly result from disruption of vulnerable plaques that are angiographically modest in severity (5–8). These rupture-prone plaques have certain characteristics, such as: a thin cap; a large lipid core composed of cholesterol, lipids, and dead foam cells; and increased inflammatory activity (1,3,4,8,9). Similarly, histopathological studies demonstrated that certain morphological features of carotid atheroma, such as a large lipid core separated from the lumen by a thin or ruptured fibrous cap and the presence of intraplaque hemorrhage, are associated with increased stroke risk (2). To date, little is known about the pathophysiological implication and the impact on clinical outcome of unstable plaques in the lower limbs of patients affected by lower extremity peripheral arterial disease (LE-PAD), a common manifestation of atherosclerosis characterized by a high risk of developing ischemic vascular events and death (10,11).

Plaque echogenicity, evaluated by B-mode ultrasound imaging, has been found to be a simple and reliable tool in predicting plaque composition. Plaques that appear hypoechoic present an inflammatory infiltration and are lipid-rich (12,13), whereas those with high echogenicity have more fibrous tissue and calcific components, which make them more stable (12,13). It is noteworthy that atherosclerosis is a systemic disease that commonly involves several vascular territories, and recent studies indicate that plaque instability may not be confined to a single vascular bed and may involve different arterial districts simultaneously (14,15). Thus, the early noninvasive visualization of "sensitive" hypoechoic spots in the arterial tree might have important clinical implications, potentially identifying a subgroup of patients exposed to a higher cardiovascular risk. Indeed, patients with unstable femoral or carotid plaques are more likely to have unstable plaques in the contralateral artery (14,15). In LE-PAD patients, the presence of hypoechoic femoral plaques is associated with a greater prevalence of hypoechoic carotid plaques (16). Furthermore, subjects with history of cerebrovascular disease and hypoechoic carotid plaques are at increased risk not only of developing an acute cerebrovascular event, but also an acute coronary syndrome (17,18). However, to date, little is known about the prognostic implications of a hypoechoic plaque in the lower limbs on cardiovascular events. This is particularly unfortunate because LE-PAD has a widespread impact on health beyond the lower extremity circulation (10,11). Accordingly, we conducted a prospective study aimed at evaluating the prognostic impact of femoral plaque echogenicity on the incidence of myocardial infarction and stroke in a homogeneous cohort of LE-PAD patients.

METHODS

Patients. A total of 410 consecutive subjects who were referred to our vascular laboratory for suspected intermittent claudication were screened for enrollment in the study. LE-PAD was diagnosed on the basis of an ankle-brachial index (ABI) ≤0.90 associated with 1 or more stenoses of lower extremity arteries at B-mode ultrasound. According to these criteria, 43 subjects were classified as not having LE-PAD. In addition, 14 claudicants with ABI >1.4 were excluded because these values may be falsely elevated due to severe arterial calcification, and 11 patients were excluded because they were affected by critical limb ischemia. Thus, 342 patients affected by intermittent claudication were initially selected. Of these, 24 were excluded for 1 of the following exclusion criteria: acute coronary syndromes, cerebrovascular events, or revascularization procedures during the previous 6 months; abnormal myocardial ischemia stress test at enrollment; significant renal, hepatic, or inflammatory disease; decompensated heart failure; or malignant neoplasia. Therefore, 318 patients affected by LE-PAD at stage II of Fontaine classification were potentially suitable to be enrolled in the study. To be included, claudicants should have at least an atherosclerotic plaque in 1 or both femoral arterial districts within 4 cm proximal and 1 cm distal to the femoral bifurcation. Thus, 72 patients were excluded for 1 of the following reasons: absence of femoral plaque (n = 3); presence of plaque in femoral arteries <1.3 mm because such plaque could not be clearly separated from diffused thickened intima-media complex (n = 4) (19); presence of calcified femoral plaque with an acoustic shadow because it was technically not reliable to determine its echogenicity (n = 34); previous femoral revascularization procedure (n = 20), under the assumption that the revascularized artery might be that at higher risk; occlusion of femoral arteries in the tract

ABBREVIATIONS AND ACRONYMS

ABI = ankle-brachial index
CI = confidence interval
GSM = grayscale median
HR = hazard ratio
ICC = intraclass correlation coefficient
IMT = intima-media thickness
IQR = interquartile range
LE-PAD = lower extremity peripheral arterial disease
ROC = receiver-operating characteristic