Peripheral Arterial Disease and Progression of Coronary Atherosclerosis

Ayman A. Hussein, MD,* Kiyoko Uno, MD,* Kathy Wolski, MPH,* Samir Kapadia, MD,*
Paul Schoenhagen, MD,* E. Murat Tuzcu, MD,* Steven E. Nissen, MD,*
Stephen J. Nicholls, MBBS, PHD*†

Cleveland, Ohio

Objectives   The purpose of this analysis was to characterize the progression of coronary atherosclerosis in patients with concomitant peripheral arterial disease (PAD).

Background   Peripheral arterial disease is associated with adverse cardiovascular outcomes. The impact of concomitant PAD on coronary atherosclerosis progression in patients with coronary artery disease has not been well established.

Methods   The burden and progression of coronary atherosclerosis was investigated in 3,479 patients with coronary artery disease with (n = 216) and without (n = 3,263) concomitant PAD who participated in 7 clinical trials that employed serial intravascular ultrasound imaging.

Results   Patients with PAD had a greater percent atheroma volume ($40.4 \pm 9.2\%$ vs. $38.5 \pm 9.1\%$, p = 0.002) and percentage of images containing calcium ($35.1 \pm 26.2\%$ vs. $29.6 \pm 24.2\%$, p = 0.002), in association with smaller lumen volume (275.7 ± 101.6 mm^3 vs. 301.4 ± 110.3 mm^3, p < 0.001) and vessel wall volume (467.7 ± 166.8 mm^3 vs. 492.9 ± 169.8 mm^3, p = 0.01). On serial evaluation, patients with PAD demonstrated greater progression of percent atheroma volume ($+0.58 \pm 0.38$ vs. $+0.23 \pm 0.3\%$, p = 0.009) and total atheroma volume (-0.17 ± 2.69 mm^3 vs. -2.05 ± 2.15 mm^3, p = 0.03) and experienced more cardiovascular events (26.3% vs. 19.8%, p = 0.03). In patients with PAD and without PAD, respectively, achieving levels of low-density lipoprotein cholesterol <70 mg/dl was associated with less progression of percent atheroma volume ($+0.16 \pm 0.27\%$ vs. $+0.76 \pm 0.20\%$, p = 0.04; and $+0.05 \pm 0.14\%$ vs. $+0.29 \pm 0.13\%$, p < 0.001) and total atheroma volume (-3.0 ± 1.9 mm^3 vs. $+1.0 \pm 1.4$ mm^3, p = 0.04; and -3.3 ± 1.1 mm^3 vs. -1.6 ± 1.0 mm^3, p < 0.001).

Conclusions   Patients with concomitant PAD harbor more extensive and calcified coronary atherosclerosis, constrictive arterial remodeling, and greater disease progression. These changes are likely to contribute to adverse cardiovascular outcomes. The benefit for all patients achieving low levels of low-density lipoprotein cholesterol supports the need for intensive lipid lowering in patients with PAD.   (J Am Coll Cardiol 2011;57:1220–5) © 2011 by the American College of Cardiology Foundation

The adverse cardiovascular outcomes observed among patients with peripheral arterial disease (PAD) (1–3) highlight the need for intensive risk factor modification (4). However, only one-quarter of PAD patients receive guideline-recommended

therapies (5). Most of these clinical events are attributed to the coronary vasculature (1–3), regardless of whether a diagnosis of coronary artery disease (CAD) is already established (6). While the underlying mechanisms remain incompletely understood, it is unknown whether coronary disease progression is different in the setting of concomitant PAD.

Intravascular ultrasound (IVUS) has been increasingly employed in clinical trials and has enabled investigation of the clinical factors associated with disease progression. Accordingly, the objective of the current analysis was to assess the impact of an established clinical diagnosis of PAD on the burden and progression of coronary atherosclerosis.

Methods

Study population. This analysis included 3,479 CAD patients who underwent serial IVUS examinations in 7

clinical trials (7–13). PAD was determined on the basis of 1) symptoms of intermittent claudication with a documented low ankle-brachial index (<0.9); 2) obstructive disease on femoral angiography; or 3) a history of arterial revascularization within the lower limbs. Each of the trials was approved by the institutional review board at the participating sites, and all patients provided informed written consent before enrollment.

IVUS imaging. The details on IVUS image acquisition and analysis have been previously reported in detail (7–13). The percent atheroma volume (PAV), total atheroma volume (TAV), and volumes occupied by lumen and external elastic membrane were calculated (14). Substantial plaque progression and regression were defined as at least a 5% relative increase or decrease in PAV, respectively.

Statistical analysis. Patients were stratified according to the presence (n = 216) or absence (n = 3263) of PAD. Results are presented as percentages for categorical variables and mean ± SD for continuous variables. When variables were not normally distributed, their results are expressed as median (interquartile range). Clinical and plaque characteristics were compared by the Student *t* test or analysis of variance for continuous variables as appropriate. For categorical variables, the chi-square test or Fisher's exact test was used. Changes in measures of risk factors, atheroma burden, and vascular dimensions were compared by analysis of covariance, after controlling for baseline values, and expressed as least squared mean ± SE. In a secondary analysis, which aimed to assess the potential independent association of PAD with CAD progression, a propensity analysis was performed, in which every PAD patient was matched to non-PAD patients in a 1:3 ratio on the basis of the predicted probability for PAD. The propensity match-ing process accounted for base-line characteristics including age, sex, race, current smoking status, body mass index, hypertension, diabetes mellitus, hyperlipid-emia, heart failure, baseline risk factor control, medications use (as-pirin, beta-blockers, angiotensin-converting enzyme inhibitor, statins, oral antidiabetic, study medications), history of stroke, and myocardial infarction. A 2-sided p value <0.05 was con-sidered statistically significant. All statistical analyses were performed with SAS version 9.1 (SAS Institute, Cary, North Carolina).

Abbreviations and Acronyms

CAD = coronary artery disease

IVUS = intravascular ultrasound

PAD = peripheral arterial disease

PAV = percent atheroma volume

TAV = total atheroma volume

Results

Patient characteristics. Clinical characteristics of patients with PAD and without PAD are summarized in Table 1. The PAD patients were older (p < 0.001), more likely to be smokers (p < 0.001), and had more diabetes (p < 0.001), hyperlipidemia (p < 0.001) and heart failure (p < 0.001). There was no difference between the groups with regard to use of cardioprotective therapies at baseline. Fewer patients with PAD were treated with a statin (p = 0.01). Risk factor control at baseline and during the course of the studies is summarized in Table 2. PAD patients were more likely to experience a cardiovascular event (death/myocardial infarction/revascularization/stroke: 26.3% vs. 19.8%, p = 0.03).
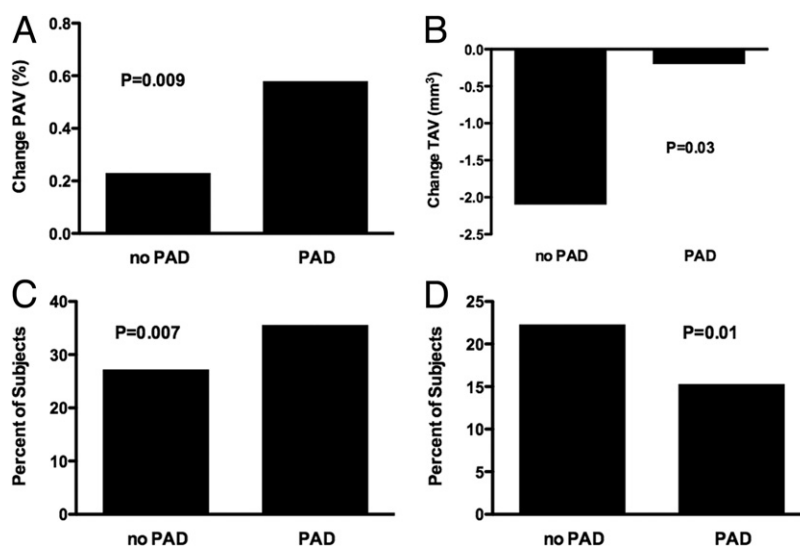

Figure 1   Disease Progression in PAD Patients

Changes in **(A)** percent atheroma volume (PAV) and **(B)** total atheroma volume (TAV), and percent of patients with **(C)** disease progression and **(D)** regression, according to the presence or absence of peripheral arterial disease (PAD).