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Low-Density Lipoprotein Lowering Does Not Improve Calf Muscle Perfusion, Energetics, or Exercise Performance in Peripheral Arterial Disease

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Objectives We hypothesized that low-density lipoprotein (LDL) reduction regardless of mechanism would improve calf muscle perfusion, energetics, or walking performance in peripheral arterial disease (PAD) as measured by magnetic resonance imaging and magnetic resonance spectroscopy.

Background Statins improve cardiovascular outcome in PAD, and some studies suggest improved walking performance.

Methods Sixty-eight patients with mild to moderate symptomatic PAD (age 65 ± 11 years; ankle-brachial index [ABI] 0.69 ± 0.14) were studied at baseline and annually for 2 years after beginning simvastatin 40 mg (n = 20) or simvastatin 40 mg/ezetimibe 10 mg (n = 18) if statin naïve, or ezetimibe 10 mg (n = 30) if taking a statin. Phosphocreatine recovery time was measured by ^{31}P magnetic resonance spectroscopy immediately after symptom-limited calf exercise on a 1.5-T scanner. Calf perfusion was measured using first-pass contrast-enhanced magnetic resonance imaging with 0.1 mM/kg gadolinium at peak exercise. Gadolinium-enhanced magnetic resonance angiography was graded. A 6-min walk and a standardized graded Skinner-Gardner exercise treadmill test with peak Vo_2 were performed. A repeated-measures model compared changes over time.

Results LDL reduction from baseline to year 2 was greater in the simvastatin 40 mg/ezetimibe 10 mg group (116 ± 42 mg/dl to 56 ± 21 mg/dl) than in the simvastatin 40 mg group (129 ± 40 mg/dl to 90 ± 30 mg/dl, $p < 0.01$). LDL also decreased in the ezetimibe 10 mg group (102 ± 28 mg/dl to 79 ± 27 mg/dl, $p < 0.01$). Despite this, there was no difference in perfusion, metabolism, or exercise parameters between groups or over time. Resting ABI did improve over time in the ezetimibe 10 mg group and the entire study group of patients.

Conclusions Despite effective LDL reduction in PAD, neither tissue perfusion, metabolism, nor exercise parameters improved, although rest ABI did. Thus, LDL lowering does not improve calf muscle physiology or functional capacity in PAD. (Comprehensive Magnetic Resonance of Peripheral Arterial Disease; NCT00587678) (J Am Coll Cardiol 2011; 58:1068–76) © 2011 by the American College of Cardiology Foundation

Peripheral arterial disease (PAD) is an independent predictor of cardiovascular disease morbidity and mortality (1) and is associated with a decrease in functional ability over time (2). Accordingly, for patients with PAD, it is critical to focus medical therapy on reducing their underlying cardiovascular risk as well as improving their functional status. Despite great strides in medical progress for the treatment of coronary artery disease, the therapeutic options and corresponding evidence base remain limited in PAD (3).

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Lipid-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in PAD reduces all-cause and cardiac mortality (4), and the benefit is related to both the dose of statin and degree of low-density lipoprotein (LDL) lowering. As a result, it is recommended

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that patients with PAD (5) receive statins with a goal LDL level of <100 mg/dl. Statins have been shown to improve pain-free walking performance in patients with PAD (6); however, the mechanisms remain unclear. Additional studies have failed to corroborate an improvement in functional ability in patients with PAD treated with statins; however, there was evidence of less decline in walking performance in this group (7). Ezetimibe, a nonstatin drug, is effective in lowering LDL cholesterol when added to statin therapy (8) but is of uncertain value in PAD. Ezetimibe has been studied in atherosclerotic plaque regression trials involving carotid artery intimal medial thickness (9–11); however, it has not previously been evaluated in a clinical trial in lower extremity PAD.

Previous work by our group (12) used magnetic resonance imaging (MRI) techniques to demonstrate the multiple determinants of functional status in patients with PAD. We found that abnormal mitochondrial function is independent of calf muscle tissue perfusion; however, both correlate with impaired exercise capacity in patients with PAD and symptomatic claudication. Given the complexity of functional capacity in PAD and the pleiotropic (noncholesterol lowering) effects of statins (13), including improved endothelial function, stabilization of atherosclerotic plaque, and decreased vascular inflammation, they may have particular therapeutic benefit in this disease. Our study of superficial femoral artery plaque volume in this patient group demonstrated plaque regression with new statin therapy with or without ezetimibe, but progression when adding ezetimibe to ongoing statin therapy, although there was no placebo for the latter group (14). The potential benefits of LDL lowering with statins and/or ezetimibe on the underlying physiology in PAD remain incompletely understood.

Thus, we aimed to investigate the role of LDL lowering on the following parameters in PAD patients: 1) calf muscle perfusion with first-pass contrast-enhanced MRI; 2) calf muscle energetics with measurement of phosphocreatine (PCr) recovery time constant by ^{31}P magnetic resonance spectroscopy (MRS); 3) macrovascular disease measured with magnetic resonance angiography (MRA); and 4) exercise capacity with functional testing. Two parallel studies were performed with the same primary endpoints. In the first study, statin-naïve patients were randomized to receive either simvastatin or a combination of simvastatin plus ezetimibe. The second part of the study evaluated patients already taking a statin with LDL >80 mg/dl who received open-label ezetimibe in addition to ongoing statin therapy.

Methods

Study design. Patients between the ages of 30 and 85 years with symptoms of intermittent claudication and an ankle-brachial index (ABI) between 0.4 and 0.9, based on vascular laboratory testing done during the screening period, were eligible. Exclusion criteria included rest pain, critical limb ischemia, contraindication to MRI, pregnancy, and comorbidities that severely limited the patient's ability to perform a walking treadmill test. Approximately 350 vascular laboratory patients were screened for participation over the 15-month recruitment period. Screened patients who did not enroll in the study refused to participate due to travel concerns, the extended nature of the study, or anticipated difficulty with functional testing due to musculoskeletal issues or frailty. Patients provided written informed consent before study enrollment. The study protocol was approved by the Human Investigation Committee at the University of Virginia. The present study was performed as a pre-specified secondary endpoint in a study of atherosclerotic plaque regression.

Abbreviations and Acronyms

- **ABI** = ankle-brachial index
- **E group** = study group treated with usual statin and open-label ezetimibe added
- **LDL** = low-density lipoprotein
- **MRA** = magnetic resonance angiography
- **MRI** = magnetic resonance imaging
- **MRS** = magnetic resonance spectroscopy
- **PAD** = peripheral arterial disease
- **PCr** = phosphocreatine
- **S group** = study group treated with simvastatin
- **S + E group** = study group treated with simvastatin + ezetimibe

In the randomized study, statin-naïve patients (no statin therapy for at least the previous 6 months) regardless of baseline LDL cholesterol underwent a double-blind randomization to simvastatin 40 mg (S group) or a combination pill of simvastatin 40 mg + ezetimibe 10 mg (S + E group) daily using a block randomization scheme. For the parallel direct treatment study, patients were enrolled already on statin therapy but with LDL >80 mg/dl and had open-label ezetimibe 10 mg/day added (E group) to their usual statin. For the randomized study, the investigators and study subjects were blinded to therapy, and all results until follow-up studies and data analysis were complete.

Study protocol. As previously described, the study was divided over 2 days to allow sufficient time between exercise portions of the protocol to avoid fatigue and ischemic pre-conditioning. Patients were admitted overnight to the General Clinical Research Center. Due to imaging time constraints, only the more symptomatic leg was studied by MRI/MRS. Patients returned at yearly intervals twice and underwent repeat testing each year using the same protocols.

Magnetic resonance protocols. MRI protocols were completed on an Avanto 1.5-T scanner and MRS protocols on a Sonata 1.5-T scanner (both Siemens Healthcare, Erlangen, Germany) because MRS hardware and software were only available for the latter. Calf muscle perfusion was immediately measured at peak plantar flexion exercise using a magnetic resonance–compatible foot pedal ergometer at a rate of 10 to 12 rpm with first-pass gadolinium-enhanced imaging as previously described (15) (Fig. 1). Time-intensity curves were generated with Argus software (Siemens Healthcare) for a region of interest in the calf muscle