Attainment of low-density lipoprotein cholesterol goal after endovascular treatment is associated with reduced cardiovascular events in patients with peripheral arterial disease

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Objective: **The relationship between attainment of low-density lipoprotein cholesterol (LDL-C) levels and clinical outcomes in patients with peripheral arterial disease (PAD) has received little attention. We sought to investigate clinical outcomes in relation to attainment of LDL-C goals in patients with PAD after endovascular treatment.**

Methods: **We reviewed 342 PAD patients treated with endovascular therapy from 2010 through 2012. We categorized patients into two groups based on the attained LDL-C levels at short-term follow-up (mean, 4.8 ± 2.8 months): group A (n = 160), with LDL-C <70 mg/dL; and group B (n = 182), with LDL-C ≥70 mg/dL. The primary end point was major adverse cardiovascular events (MACEs), a composite of all-cause death, nonfatal myocardial infarction, and stroke.**

Results: **Baseline characteristics were similar between group A and group B except for obstructive pulmonary disease (0% vs 7%; *P* = .001). More patients in group A received statin therapy than those in group B (93% vs 76%; *P* < .001). MACEs (4% vs 10%; *P* = .002) and all-cause mortality (2% vs 7%; *P* = .007) occurred less frequently in group A than in group B at 2 years. A Cox proportional hazards multivariate regression model identified attainment of LDL-C goal <70 mg/dL at short-term follow-up as an independent predictor of reduced MACEs (hazard ratio, 0.25; 95% confidence interval, 0.09-0.67; *P* = .006) along with age as a predictor of increased MACEs (hazard ratio, 1.04; 95% confidence interval, 1.00-1.08; *P* = .031).**

Conclusions: **Attainment of LDL-C goal <70 mg/dL at short-term follow-up is an independent predictor of reduced mortality and cardiovascular events after endovascular therapy in patients with PAD. (J Vasc Surg 2016;63:756-63.)**

The main cause of peripheral arterial disease (PAD) is atherosclerosis. Patients with PAD have an extensive atherosclerotic burden, often with coexisting coronary artery disease (CAD) and cerebrovascular disease.[1-5] Cardiovascular complications are the main cause of death among patients with PAD.[6-8]

Statins, which inhibit hydroxymethylglutaryl-coenzyme A reductase, have beneficial cardiovascular properties beyond their lipid-lowering effects, including stabilization of atherosclerotic plaques, reduction of oxidative stress and vascular inflammation, and enhancement of endothelial function.[9] In various clinical trials, statins have shown clinical benefits in primary and secondary prevention.[3,10-12] Recent guidelines for lipid management recommend high-intensity statin therapy for PAD patients.[13] However, in reality, there is generally less use of statins and thus less than optimal lipid control in patients with PAD.[6] To date, little information on the relationship between attained low-density lipoprotein cholesterol (LDL-C) levels and clinical outcomes in PAD patients has been reported in the literature. Accordingly, the purpose of this study was to investigate clinical outcomes in relation to early attainment of LDL-C goals in PAD patients.

METHODS

Study population. We retrospectively reviewed clinical data for 439 consecutive patients with symptomatic PAD who underwent endovascular treatment for lower extremity arterial disease at Severance Cardiovascular Hospital, Yonsei University Health System, from January 2010 to December 2012. After exclusion of patients with nonatherosclerotic causes of PAD such as thromboembolism or Buerger disease (n = 11), patients with previous bypass graft or endovascular treatment (n = 60), and patients whose LDL-C levels were not available at 3 to 6 months after intervention (n = 26), we included 342 patients for

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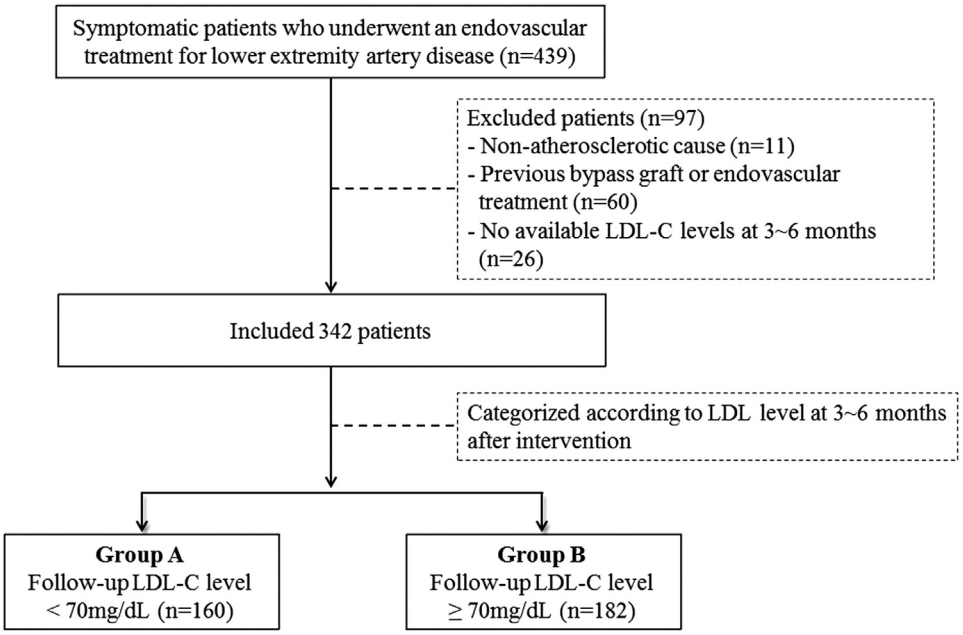

Fig 1. Patient flow diagram. *LDL-C,* Low-density lipoprotein cholesterol.

the analysis. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The Institutional Review Board approved this study and waived the requirements for informed consent for this retrospective analysis. Fig 1 outlines the patient selection process.

Data collection and definitions. All patients were evaluated using an ankle-brachial index and at least one imaging study, either computed tomography or color duplex ultrasound, before endovascular treatment. Symptomatic PAD was defined as intermittent claudication or critical limb ischemia manifested as chronic ischemic rest pain, ulcers, or gangrene due to lower extremity arterial occlusive disease. Patients' baseline medical conditions, medical treatments, endovascular procedures, postprocedure follow-up management, and outcome were evaluated on the basis of electronic medical records.

All blood samples were obtained after 8 hours of fasting and were analyzed for lipid profile, consisting of total cholesterol, triglycerides, high-density lipoprotein cholesterol, and LDL-C. LDL-C concentrations were directly measured. However, if the measured LDL-C concentration was not available and triglyceride concentration was <400 mg/dL, LDL-C level was calculated by the Friedewald formula.[14] Baseline lipid levels were determined on admission before endovascular treatment. Follow-up LDL-C levels were measured between 3 and 6 months (mean, 4.8 ± 2.8 months) after the index procedure. Patients were classified into two groups based on the follow-up LDL-C level: group A (n = 160), with follow-up LDL-C <70 mg/dL; and group B (n = 182), with follow-up LDL-C ≥70 mg/dL.

Patients were treated with standard endovascular treatment methods for lower extremity arterial disease, as described previously.[15-19] Most patients received statin medication at discharge after the index procedure. The choice of statin was left to the physician's discretion. The intensity of statin therapy was categorized as high, moderate, or low on the basis of the 2013 American College of Cardiology/American Heart Association guidelines on the treatment of blood cholesterol. High-intensity statin therapy included atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg; moderate-intensity statin therapy included atorvastatin 10 to 20 mg, rosuvastatin 5 to 10 mg, simvastatin 20 to 40 mg, pravastatin 40 to 80 mg, fluvastatin XL 80 mg, or pitavastatin 2 to 4 mg; and low-intensity statin therapy included simvastatin 10 mg, pravastatin 10 to 20 mg, fluvastatin 20 to 40 mg, or pitavastatin 1 mg.[13] In addition, a combination of aspirin (100 mg/d) and either clopidogrel (75 mg/d) or cilostazol (200 mg/d) was generally prescribed for at least 1 year. After hospital discharge, patients were observed at 1 month and 3 to 6 months thereafter.

The primary end point was major adverse cardiovascular events (MACEs), a composite of all-cause death, nonfatal myocardial infarction, and stroke. Myocardial infarction was defined according to the third universal definition of myocardial infarction.[20] Stroke during follow-up was defined as ischemic or hemorrhagic stroke requiring hospitalization with symptoms lasting >24 hours. All clinical outcomes were examined by electronic medical record review or telephone contact.

Statistical analysis. Data are expressed as number (%), mean ± standard deviation (SD), or median (interquartile range). Continuous variables were compared using Student *t*-test, and comparisons of categorical data were made using χ^2 statistics or Fisher exact test. Event-free survival was