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Oxidized Phospholipids on Apolipoprotein B-100 and Recurrent Ischemic Events Following Stroke or Transient Ischemic Attack

Young Sup Byun, MD,[a,b] Xiaohong Yang, BS,[a] Weihang Bao, PhD,[c] David DeMicco, PharmD,[c] Rachel Laskey, PhD,[c] Joseph L. Witztum, MD,[d] Sotirios Tsimikas, MD,[a] for the SPARCL Trial Investigators

ABSTRACT

BACKGROUND Biomarkers to predict recurrent stroke and targets of therapy to prevent stroke are lacking.

OBJECTIVES This study evaluated whether patients with prior cerebrovascular events and elevated levels of oxidized phospholipids on apolipoprotein B-100 (OxPL-apoB), but without prior coronary artery disease (CAD), are at risk for recurrent stroke and CAD events following high-dose statin therapy.

METHODS In the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial, OxPL-apoB levels were measured in 4,385 patients with stroke or transient ischemic attack at baseline and in 3,106 patients at 5 years following randomization to placebo or 80 mg atorvastatin. The primary endpoint was the time from randomization to a second nonfatal or fatal stroke. Secondary endpoints included first major coronary events and any cardiovascular event.

RESULTS Patients with recurrent stroke had higher baseline median OxPL-apoB levels than patients without (15.5 nmol/l vs. 11.6 nmol/l; $p < 0.0001$). After multivariable adjustment, elevated baseline OxPL-apoB predicted recurrent stroke (hazard ratio [HR]: 4.3; $p < 0.0001$), first major coronary events (HR: 4.0; $p < 0.0001$), and any cardiovascular event (HR: 4.4; $p < 0.0001$). These comparisons for any endpoint did not differ by treatment, shown as a nonsignificant interaction test. The net reclassification improvement, integrated discrimination improvement, and area under the receiver-operating characteristic curve (AUC) were all significantly improved by adding OxPL-apoB to the models, with ΔAUC +0.0505 ($p < 0.0001$) for recurrent stroke, ΔAUC +0.0409 ($p < 0.0001$) for first major coronary event, and ΔAUC +0.0791 ($p < 0.0001$) for any cardiovascular event.

CONCLUSIONS Elevated OxPL-apoB levels predicted recurrent stroke and first major coronary events in patients with prior stroke or transient ischemic attack. The lack of statin–OxPL-apoB treatment interaction suggested that OxPLs might be statin-independent therapeutic targets to reduce risk of cardiovascular events. (Lipitor in the Prevention of Stroke, for Patients Who Have Had a Previous Stroke [SPARCL]; NCT00147602) (J Am Coll Cardiol 2017;69:147–58) © 2017 by the American College of Cardiology Foundation.

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From the [a]Division of Cardiovascular Diseases, University of California, San Diego, La Jolla, California; [b]Division of Cardiology, Department of Internal Medicine, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Republic of South Korea; [c]Pfizer, Inc., New York, New York; and the [d]Division of Endocrinology/Metabolism, University of California, San Diego, La Jolla, California. Pfizer, Inc. sponsored the SPARCL clinical trial. The cost of the OxPL-apoB assays was funded by a laboratory service agreement from Pfizer, Inc. to the University of California San Diego. Dr. Byun was supported by the Inje Research and Scholarship Foundation. Drs. Bao, DeMicco, and Laskey are employees of Pfizer, Inc., with ownership of stock in Pfizer Inc. Drs. Witztum and Tsimikas are supported by National Institutes of Health grants R01-HL119828, P01-HL088093, P01 HL055798, R01-HL106579, R01-HL078610, and R01-HL124174; and are coinventors and receive royalties from patents owned by the University of California-San

ABBREVIATIONS AND ACRONYMS

apoB = apolipoprotein B-100

AUC = area under the receiver-operating characteristic curves

CVD = cardiovascular disease

LDL-C = low-density lipoprotein cholesterol

OSE = oxidation-specific epitope

OxPL = oxidized phospholipid

OxPL-apoB = oxidized phospholipids on apolipoprotein B-100

TIA = transient ischemic attack

Cerebrovascular disease is a major contributor to morbidity and mortality across the globe (1,2). In the United States, although the relative risk of dying from stroke is declining, approximately 800,000 people continue to experience new or recurrent strokes every year. As the population ages, cerebrovascular events have the potential to reach a higher incidence than myocardial infarction (MI). In fact, stroke burden is disproportionately higher in China, Africa, and South America compared with ischemic heart disease and with stroke rates in other counties (2). Although ischemic heart disease and ischemic stroke have commonalities in risk factors and underlying disease mechanisms, the strength of the association varies according to individual risk factors. Novel biomarkers and therapeutic targets would be useful to predict new or recurrent stroke and identify high-risk individuals for preventive measures.

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Oxidation-specific epitopes (OSE) are a major class of atherosclerosis-relevant antigens that define oxidative modifications on lipoproteins, apoptotic cells, and proteins (3). Present on apolipoproteins in the lipid phase as well as oxidized lipids covalently bound to amino acids on the protein moiety, OSEs share molecular identity with danger-associated molecular patterns on apoptotic cells as well as with pathogen-associated molecular patterns on microbial pathogens. OSEs are recognized by a common set of innate pattern recognition receptors, which have been evolutionarily selected to protect against the proinflammatory properties of OSEs (4,5). When OSEs activate arcs of immunity, the general response is to generate inflammation, which in turn mediates proatherogenic potential.

Phosphocholine-containing oxidized phospholipids (OxPLs) are well-studied OSEs that are highly immunogenic, proinflammatory, and present in atherosclerotic lesions of animals and humans, particularly in pathologically defined vulnerable and disrupted plaques (6,7). OxPLs are important contributors to early and late events in atherogenesis by activating proinflammatory genes in endothelial cells and macrophages (8), leading to inflammatory cascades in the vessel wall (9). Additionally, OxPLs on oxidized low-density lipoprotein cholesterol (LDL-C) lead to uptake of this even more damaging form of LDL-C by macrophages, promoting foam cell formation (10). OxPL can be measured on apolipoprotein B-100 (apoB) lipoproteins (OxPL-apoB) in plasma using the E06 natural antibody that recognizes the phosphocholine head group of OxPL. Elevated OxPL-apoB levels correlate with the presence of anatomical cardiovascular disease (CVD), and predict new CVD events in community-based settings in people with and without prior CVD (11–16).

The relationship of these biomarkers to cardiovascular outcomes in patients with prior cerebrovascular events is not defined. The SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial demonstrated that 80 mg atorvastatin reduced the overall incidence of recurrent stroke and cardiovascular events in patients with recent stroke or transient ischemic attack (TIA) but without known coronary heart disease (17). The aim of this current study was to assess the predictive value of OxPL-apoB levels, the effect of atorvastatin therapy, and their relationship to recurrent stroke or first major coronary event.

METHODS

OxPL-apoB levels were obtained from patients enrolled in SPARCL (17), a randomized trial comparing placebo versus 80 mg atorvastatin for secondary prevention of recurrent cerebrovascular events. Participants had experienced a stroke or TIA 1 to 6 months before study entry, had LDL-C levels of 100 to 190 mg/dl (2.6 to 4.9 mmol/l), and had no known coronary heart disease, and they were randomized to double-blind treatment with 80 mg of atorvastatin/day or placebo. The SPARCL trial's primary outcome was time from randomization to a first nonfatal or fatal stroke, the same endpoint that was used in the current substudy. Secondary endpoints were major coronary events (death from cardiac causes, nonfatal MI, or resuscitation after cardiac arrest) and any cardiovascular event. The latter covered the major coronary events plus stroke or TIA, unstable angina, any coronary event (acute coronary event plus a coronary

Diego on oxidation-specific antibodies and biomarkers related to oxidized lipoproteins. Dr. Witztum is a consultant to Ionis Pharmaceuticals, Cymabay Pharmaceuticals, Intercept Pharmaceuticals, and Prometheus; and has public stock in Ionis Pharmaceuticals. Dr. Tsimikas currently holds a dual appointment at the University of California-San Diego and Ionis Pharmaceuticals. Dr. Yang has reported that she has no relationships relevant to the contents of this paper to disclose.

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