Journal of Clinical Lipidology (2017) ■, ■–■

Journal of Clinical Lipidology

Original Article

A comparison of the effects of low- and high-dose atorvastatin on lipoprotein metabolism and inflammatory cytokines in type 2 diabetes: Results from the Protection Against Nephropathy in Diabetes with Atorvastatin (PANDA) randomized trial

Handrean Soran, MSc, MD, FRCP*, Yifen Liu, PhD, Safwaan Adam, MRCP, Tarza Siahmansur, PhD, Jan H. Ho, MRCP, Jonathan D. Schofield, BSc, PhD, MRCP, See Kwok, MD, Matthew Gittins, PhD, Michael France, MRCPath, Naveed Younis, MD, FRCP, J. Martin Gibson, MD, PhD, FRCP, Paul N. Durrington, MD, FRCP, FRCPath, FAHA, FMedSci[1], Martin K. Rutter, MD, FRCP[1]

Cardiovascular Trials Unit, The Old St Mary's Hospital, Central Manchester University Hospitals, Manchester, United Kingdom (Drs Soran, Adam, Ho, Schofield, Kwok, France, Younis, and Durrington); Division of Cardiovascular Sciences, Cardiovascular Research Group, School of Medical Sciences, University of Manchester, Manchester, United Kingdom (Drs Soran, Liu, Adam, Siahmansur, Ho, Schofield, Kwok, and Durrington); Department of Diabetes, Manchester Diabetes Centre, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom (Drs Gittins and Rutter); Department of Clinical Biochemistry, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom (Dr France); Department of Diabetes and Endocrinology, University Hospital South Manchester NHS Foundation Trust, Wythenshawe Hospital, Manchester, United Kingdom (Dr Younis); and Department of Diabetes and Endocrinology, Salford Royal NHS Foundation Trust, University of Manchester, Manchester, United Kingdom (Dr Gibson)

KEYWORDS:
Apolipoprotein B;
Atorvastatin;
Glycated apolipoprotein B;
High-density lipoprotein;
Inflammatory cytokines;
Low-density lipoprotein;

BACKGROUND: Statin therapy is recommended in type 2 diabetes (T2DM) although views on treatment intensity and therapeutic targets remain divided.

OBJECTIVES: Our objectives were to compare the effects of high-intensity and moderate-intensity atorvastatin treatment on lipoprotein metabolism and inflammatory markers and how frequently treatment goals are met in high-risk T2DM patients.

METHODS: Patients with T2DM and albuminuria (urinary albumin:creatinine ratio >5 mg/mmol, total cholesterol <7 mmol/L, proteinuria <2 g/d, creatinine <200 μmol/L) were randomized to receive atorvastatin 10 mg (n = 59) or 80 mg (n = 60) daily. Baseline and 1-year follow-up data are reported.

[1] These authors contributed equally and are joint last authors.

* Corresponding author. Cardiovascular Trials Unit, The Old St Mary's Hospital, Central Manchester University Hospitals, Manchester M13 9WL, United Kingdom.

E-mail addresses: hsoran@aol.com; handrean.soran@mft.nhs.uk

Submitted May 10, 2017. Accepted for publication October 17, 2017.

https://doi.org/10.1016/j.jacl.2017.10.011

Therapeutic targets;
Type 2 diabetes mellitus;
Very-low-density lipoprotein

RESULTS: Patients were at high cardiovascular disease risk (observed combined mortality and nonfatal cardiovascular disease annual event rate 4.8%). The non-high-density lipoprotein cholesterol (HDL-C) goal of <2.6 mmol/L was achieved in 72% of participants receiving high-dose atorvastatin, but only in 40% on low-dose atorvastatin ($P < .005$). The proportion achieving apolipoprotein B (apoB) <0.8 g/L on high-dose and low-dose atorvastatin was 82% and 70%, respectively (NS). Total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, non-HDL-C, oxidized LDL, apoB, glyc-apoB, apolipoprotein E, and lipoprotein-associated phospholipase A2 decreased significantly, more so in participants on high-dose atorvastatin. Adiponectin increased and serum amyloid A decreased without dose dependency. Neither dose produced significant changes in HDL-C, cholesterol efflux, high-sensitivity C-reactive protein, glycated hemoglobin, serum paraoxonase-1, lecithin:-cholesterol acyltransferase, or cholesteryl ester transfer protein.

CONCLUSIONS: High-dose atorvastatin is more effective in achieving non-HDL-C therapeutic goals and in modifying LDL-related parameters. Recommended apoB treatment targets may require revision. Despite the increase in adiponectin and the decrease in serum amyloid A, HDL showed no change in functionality.

Introduction

Statin treatment was recommended in type 2 diabetes mellitus (T2DM) after publication of the Collaborative Atorvastatin Diabetes Study (CARDS),[1] the first trial of a statin in primary prevention of atherosclerotic cardiovascular disease (CVD) in T2DM, and the Cholesterol Treatment Trialists' (CTT) collaboration meta-analysis combining CARDS results with those of T2DM participants, who had been included in earlier primary and secondary prevention trials not designed specifically to test that a statin could decrease CVD incidence in T2DM.[2] Initially there was concern expressed about whether this recommendation should apply universally to T2DM without clinical evidence of CVD.[3] However, recently even in people without diabetes, the threshold for 10-year absolute CVD risk required for the introduction of statin treatment has been decreased to 10% in the United Kingdom.[4] and 7.5% in the United States.[5] There must be few T2DM patients whose CVD risk does not exceed these thresholds, and thus, the debate has moved on to when moderate-intensity statin therapy, such as atorvastatin 10 mg daily, and when intensive statin treatment, such as atorvastatin 80 mg daily, is warranted. Certainly, the more intensive approach is justified in secondary prevention and may also be in a proportion of patients who have yet to experience a vascular event, but are assessed as being at particularly high risk on other grounds, such as duration of diabetes, nephropathy, and hypertension.[6] There is a dichotomy of views about the extent to which treatment should be targeted at achieving specific goals in terms of either low-density lipoprotein cholesterol (LDL-C) or non-high-density lipoprotein cholesterol (non-HDL-C). The National Lipid Association[7] and the European Society of Cardiology and allied societies[8] have retained the goals of LDL-C <2.6 and <1.8 mmol/L depending on the degree of CVD risk, whereas the American College of Cardiology/American Heart Association[5] and the National Institute of Health and Clinical Excellence[4] have less emphasis on goals, although National Institute of Health and Clinical Excellence recently revised its guidance by advising at least a 40% decrease in non-HDL-C on follow-up.[4] This is frequently impractical because the pretreatment value is unknown when, for example, patients have already commenced statin treatment by the time they are referred to a hospital diabetes clinic or when they present with an acute coronary syndrome. Surprisingly too, in diabetes, with the exception of their effect on LDL-C, there is a dearth of information about the effects of intensive statin treatment as opposed to moderate statin treatment on other potentially atherogenic aspects of lipoprotein metabolism. Even for LDL-C, the proportion of patients in whom therapeutic targets are achieved is largely unreported in diabetes. Furthermore, the effects of intensifying statin treatment on inflammatory cytokines implicated in atherosclerosis are unknown. We have compared the effects of atorvastatin 10 mg with those of 80 mg daily in participants in the first year of the Protection Against Nephropathy in Diabetes with Atorvastatin (PANDA) trial.[9]

An atherogenic lipoprotein profile consisting of low HDL-C, raised triglycerides (TGs), and increased small dense LDL (SD-LDL) particles is common in T2DM.[10,11] SD-LDL particles are more susceptible to oxidation and glycation, possibly because their plasma half-life is increased compared with more buoyant LDL particles and more apolipoprotein B100 (apoB) lysine groups are exposed on their surface.[12] Glycoxidation increases LDL atherogenicity, and in T2DM, there may be accelerated LDL glycoxidation.[13] Phospholipase A2 (PLA2; also known as platelet-activating factor) largely located on LDL is associated with predisposition to atherosclerosis.[13] Apolipoprotein E (apoE) may also be involved in atherogenesis in diabetes, which, like familial dysbetalipoproteinemia in which apoE is clearly raised, is associated with peripheral atherosclerosis. ApoE is cleared through hepatic LDL receptors