Clinical Biochemistry 44 (2011) 627–634

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Switching from statin monotherapy to ezetimibe/simvastatin or rosuvastatin modifies the relationships between apolipoprotein B, LDL cholesterol, and non-HDL cholesterol in patients at high risk of coronary disease☆,☆☆

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ARTICLE INFO

Article history:
Received 4 June 2010
Received in revised form 3 February 2011
Accepted 11 February 2011
Available online 22 February 2011

Keywords:
Ezetimibe/simvastatin
Rosuvastatin
Correlation
Apolipoprotein B
Low-density lipoprotein cholesterol
Non-high-density lipoprotein cholesterol

ABSTRACT

Objective: To evaluate relationships between apolipoprotein B (Apo B), LDL cholesterol (LDL-C), and non-HDL-C in high-risk patients treated with lipid-lowering therapy.

Design and methods: This post-hoc analysis calculated LDL-C and non-HDL-C levels corresponding to an Apo B of 0.9 g/L following treatment with 1) statin monotherapy (baseline) and 2) ezetimibe/simvastatin 10/20 mg or rosuvastatin 10 mg (study end). The percentages of patients reaching LDL-C, non-HDL-C, and Apo B targets were calculated at study end.

Results: After switching to ezetimibe/simvastatin or rosuvastatin, the LDL-C and non-HDL-C corresponding to Apo B = 0.9 g/L were closer to the more aggressive LDL-C and non-HDL-C goals (1.81 and 2.59 mmol/L, respectively). Only slightly >50% of the patients who reached minimum recommended LDL-C or non-HDL-C at study end also had an Apo B level <0.9 g/L with both treatments.

Conclusion: The use of Apo B for monitoring the efficacy of lipid-altering therapy would likely lead to more stringent criteria for lipid lowering.

Introduction

Both national and international guidelines identify low-density lipoprotein cholesterol (LDL-C) as the primary treatment target for reducing coronary heart disease (CHD) risk in patients with hypercholesterolemia [1,16,18,29]. Cholesterol management guidelines endorse a minimum LDL-C goal of <2.59 mmol/L in high risk patients with an optional target of <1.99 or <1.81 mmol/L in persons at very high risk of CHD [1,16,18,29]. Some patients with lipoprotein abnormalities, particularly those with increased triglyceride (TG) levels, may have excess levels of other apolipoprotein (Apo) B-containing lipoproteins (e.g., very low-density lipoprotein, intermediate-density lipoprotein, lipoprotein (a), and a preponderance of cholesterol-depleted, small, dense LDL particles), which confer additional atherogenic risk beyond that represented by LDL-C alone [8]. In such patients, non-high-density lipoprotein cholesterol (non-HDL-C; i.e., the sum of cholesterol carried by chylomicrons, very low-density lipoprotein, intermediate-density lipoprotein plus LDL) may be a more accurate predictor of CHD risk compared with LDL-C, especially among patients receiving statin therapy [2,15,19].

Apo B is another parameter with proven utility in assessing CHD risk [8]. Apo B is a reliable measure of the total number of atherogenic particles in the blood stream since each atherogenic lipoprotein contains a single molecule of Apo B [26,32]. Several studies have shown that Apo B is a more accurate parameter for assessing CHD risk compared with LDL-C [15,22,25,27,34,36]. LDL-C is inadequate at assessing the total

☆ Funding and author disclosure statements: the funding for this study was provided by Merck/Schering-Plough Pharmaceuticals, North Wales, PA, USA. The sponsor of this study was involved in the study design, data collection, data analysis, manuscript preparation, and publication decisions.

☆☆ Disclosures: MF—research grant support, honoraria, and consultant and/or advisory board membership (AstraZeneca, Genzyme, Kowa, Merck, Merck/Schering-Plough Pharmaceuticals, Novartis, Pfizer, Sanofi-Aventis, SMB, Solvay, Takeda). HV—research grant support, honoraria, speakers' bureau and consultant and/or advisory board member (Pfizer, Solvay, Merck & Co., Inc., Merck/Schering-Plough Pharmaceuticals, AstraZeneca, Teva, Zentiva, Sanofi Aventis, KRKA). QD, AS, PB, AOJ-L—employees of Merck & Co., Inc. may own stock or hold stock options in the company.

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0009-9120/$ – see front matter
doi:10.1016/j.clinbiochem.2011.02.008

concentration of atherogenic particles particularly among high-risk patients who frequently have a preponderance of cholesterol-depleted, small, dense LDL particles [3,17,21,31].

To this end, the consensus statement issued by the American Diabetes Association (ADA) and the American College of Cardiology (ACC) Foundation identifies non-HDL-C and apo B as co-primary targets of therapy in high cardiometabolic risk patients [8]. Non-HDL-C goals of 3.37 and <2.59 mmol/L and apo B goals of<0.9 g/L and 0.8 g/L are recommended for high-risk and very high-risk individuals, respectively [8].

The use of Apo B in clinical practice to guide patient management is not widespread. The main reason is probably because Apo B is not currently recommended as a primary screening parameter by most international and national lipid treatment guidelines. Non-HDL-C and Apo B have been shown to correlate relatively strongly both in non-treated and statin-treated patients, although the strength of these associations varies depending on the population studied [4,6,24,28,33]. As a result, some have proposed using non-HDL-C as a surrogate measure of Apo B, thus obviating the need to introduce a new assay into the standard lipid panel [6].

Previous literature demonstrated that statins provide larger reductions in plasma LDL-C levels and result in a lowering of LDL-C to lower population percentile level than that seen for Apo B [4,6,9,10,30]. Thus, the use of LDL-C as the sole parameter in guiding the management of statin-treated patients may result in the underachievement of recommended non-HDL-C and most especially Apo B targets, thereby placing patients at unnecessary risk [7,8]. Although three recent studies evaluated the effects of statin therapy on the correlations between Apo B:LDL-C and Apo B:non-HDL-C [4,6,9], relatively little is known about the effects of other lipid-altering therapies on these correlations.

This post-hoc analysis of a previously published study [12] evaluated the relationship of Apo B with LDL-C and non-HDL-C values in a population of 618 high-risk hypercholesterolemic patients (i.e., defined by prior history of CHD; type 2 diabetes with high cardiovascular risk; or 10 year Framingham risk, >20%) who did not achieve their LDL-C goals while taking a stable dose of open-label statin monotherapy. Following 6 weeks of treatment with statin monotherapy, patients with LDL-C >2.59 mmol/L were switched to double-blind ezetimibe/simvastatin (EZE/SIMVA) 10/20 mg or rosuvastatin (ROSUVA) 10 mg for 6 weeks. Both EZE/SIMVA 10/20 mg and ROSUVA 10 mg were chosen for use in this study because they were expected to show greater LDL-C-lowering efficacy compared with the statins used at baseline. This analysis evaluated the correlations between Apo B and LDL-C or non-HDL-C following 1) 6 weeks of open-label treatment with statin monotherapy (i.e., baseline) and 2) 6 weeks of double-blind treatment with EZE/SIMVA 10/20 mg or ROSUVA 10 mg (i.e., study end). Simple linear regression (SLR) analyses were also performed at baseline and study end to evaluate the LDL-C and non-HDL-C values that are equivalent to the recommended Apo B targets of <0.9 and <0.8 g/L. Additional analyses were performed in patient subgroups defined by baseline TG values (i.e., TG, < and >2.26 mmol/L) and relative potency of the pre-randomization statin monotherapy (i.e., low and high). Analyses were performed to evaluate the proportions of patients reaching LDL-C, non-HDL-C, and Apo B targets.

Methods

Patients and study design

Full details of the methods of the INCROSS study are reported elsewhere [12]. In this multicenter, randomized, double-blind trial, active-controlled, parallel group study, 618 patients with documented hypercholesterolemia (LDL-C, 2.59–4.92 mmol/L at the screening visit and 2.59–4.14 mmol/L at the randomization visit) and high cardiovascular risk who were taking a stable daily dose of one of several statin medications for >6 weeks prior to the study randomization visit entered a 6 week open-label stabilization/screening period during which they continued to receive their pre-study statin dose. Patients were deemed to be of high cardiovascular risk if they met one or more of the following criteria: (i) history of CHD (i.e., stable and unstable angina, revascularization procedure, myocardial infarction, documented myocardial ischemia) or with established vascular atherosclerotic disease (i.e., peripheral vascular disease, ischemic stroke); (ii) type 2 diabetes without a history of vascular disease and with high cardiovascular risk (i.e., renal impairment [proteinuria, >300 mg/24 h, or creatinine clearance standardized for body surface area, <1.002 mL/s] and/or at least 2 CHD risk factors per Framingham risk calculation); (iii) CHD risk >20% over 10 years as determined by Framingham risk calculation. Fasting TG levels had to be <3.96 mmol/L 1 week prior to the randomization visit (i.e., week 0/baseline) to allow for the calculation of LDL-C by the Friedewald equation.

Patients who did not achieve their minimum recommended LDL-C goals (i.e., <2.59 mmol/L) after taking a stable dose (>6 weeks) of open-label statin monotherapy were stratified by study site and potency of their pre-randomization statin brand/dose (low [stratum 1: atorvastatin, 10 mg; fluvastatin, 80 mg; lovastatin, 20 mg; pravastatin, 40 mg; simvastatin, 20 mg] or high [stratum 2: atorvastatin, 20 mg; rosuvastatin, 5 mg; simvastatin, 40 mg]) and subsequently randomized in equal proportions to receive double-blind EZE/SIMVA 10/20 mg ($n = 314$) or ROSUVA 10 mg ($n = 304$) for 6 weeks. Both these treatments represent starting doses of more potent lipid-lowering therapies, and according to the product labels, should yield similar LDL-C reductions.

As previously described, the primary efficacy endpoint for this study was the percentage change from baseline (i.e., week 0) to study endpoint (i.e., last post baseline measurement during the 6 week active treatment period) in LDL-C. Secondary efficacy measurements included the proportion of patients achieving LDL-C goals (<2.59 and <1.81 mmol/L) as well as the mean percentage changes from baseline in total cholesterol, TG, HDL-C, non-HDL-C, and Apo B after 6 weeks of treatment.

The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies, and all patients provided written informed consent.

Laboratory methods

All analyses were conducted on fasting blood samples at a certified central laboratory (MRLI, Brussels, Belgium) according to standards specified by the National Heart Lung and Blood Institute and Centers for Disease Control and Prevention [23]. Plasma concentrations of TC, TG, and HDL-C were quantified enzymatically using the Hitachi 747 analyzer (Roche Diagnostics Corporation, Indianapolis, IN). LDL-C levels were calculated using the equation of Friedewald et al. [LDL-C = TC − HDL-C − (TG/2.2)] [14]. Ultracentrifugation was used to measure LDL-C values in patients with TG >4.5 mmol/L. HDL-C was quantified enzymatically after the removal of Apo B-containing lipoproteins by heparin and manganese chloride precipitation [20,37]. Non-HDL-C levels were calculated by subtracting HDL-C from TC values. Apo B concentrations in whole plasma were measured by immunonephelometry using a Dade Behring GmbH Nephelometer (Marburg, Germany) [13]. International Federation of Clinical Chemistry (IFCC) standards were used to calibrate the Apo B measurements.

Statistical analyses

The current report describes the results of a post-hoc exploratory analysis performed to evaluate the relationship between Apo B and LDL-C or non-HDL-C following (i) 6 weeks of open-label treatment with statin monotherapy (i.e., baseline/week 0) and (ii) 6 weeks of double-