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Pleiotropic beneficial cardiometabolic actions of a high-purity eicosapentaenoic acid product in high cardiovascular risk individuals

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Abstract

The ideal approach to the secondary dyslipidemia goal of lowering triglycerides (TG) is not well established. The available ω-3 fatty acid products differ from each other in composition and content. The purpose of the present study was to investigate the effect of a highly purified eicosapentaenoic acid (EPA) formulation on cardiometabolic biomarkers in high cardiovascular (CV) risk patients. The study included 226 subjects with high TG and ≥1 of the following CV risk factors: arterial hypertension, diabetes mellitus, ultrasound-documented atheromatosis, peripheral artery disease, previous myocardial infarction, or ischemic stroke. Participants received 2 g EPA twice daily for 3 months, along with typical nutritional counseling. Cardiometabolic hematological parameters (TG, low-density lipoprotein [LDL], high-density lipoprotein [HDL], non-HDL, total cholesterol [TChol], apolipoprotein A_1 [Apo A_1], apolipoprotein B [Apo B], glucose, glycated hemoglobin [HbA_1c], and C-reactive protein [CRP]) were measured at baseline and at 3 months. The mean patients' age was 61.1 ± 1.4 years and the mean baseline TG was 2.97 ± 0.15 mmol/L. Apart from Apo A_1, all other biomarkers significantly ($p < 0.05$) improved at 3 months, regardless of sex (except Apo B) and age: TG 1.75 ± 0.09 versus 2.97 ± 0.15 mmol/L, LDL 2.46 ± 0.08 versus 3.05 ± 0.13 mmol/L, HDL 1.22 ± 0.03 versus 1.11 ± 0.03 mmol/L, non-HDL 3.29 ± 0.10 versus 4.14 ± 0.16 mmol/L, TChol 4.55 ± 0.10 versus 5.15 ± 0.13 mmol/L, Apo A_1 26.8 ± 9.3 versus 22.5 ± 8.6 μmol/L, Apo B 1.25 ± 0.23 versus 1.29 ± 0.23 μmol/L, glucose 5.66 ± 0.11 versus 5.99 ± 0.17 mmol/L, HbA_1c 5.83 ± 0.1 versus 5.97 ± 0.1% and CRP 1.92 ± 0.2 versus 5.26 ± 2.8 mg/L. In conclusion, adding highly purified EPA product (4 g daily) on nutritional counseling leads to a significant TG reduction. In addition, this treatment appears to have pleiotropic beneficial cardiometabolic actions.

KEYWORDS
cardiometabolic biomarkers, dyslipidemia, high cardiovascular risk, high-purity eicosapentaenoic acid (EPA) product, hypertriglyceridemia

INTRODUCTION

Dyslipidemia is an established cardiovascular (CV) risk factor. The optimal management of dyslipidemia is essential especially for individuals with high CV risk and for the secondary prevention of CV events (Mach et al., 2019). The primary goal is lowering low-density lipoprotein (LDL)

Abbreviations: AH, arterial hypertension; Apo A_1, apolipoprotein A_1; Apo B, apolipoprotein B; BP, blood pressure; CRP, C-reactive protein; CV, cardiovascular; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ESH, European Society of Hypertension; HbA_1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAD, peripheral artery disease; T_2DM, type-2 diabetes mellitus; TChol, total cholesterol; TG, triglycerides.

(Mach et al., 2019). Nevertheless, there is always a residual CV risk that could be beneficially modified by lowering elevated triglycerides (TG) (Miller et al., 2008). This secondary goal is typically achieved with fibrates or/and ω-3 fatty acids (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]) (Mach et al., 2019).

Dietary supplements are a common source of ω-3 fatty acids, but they differ from each other in both composition and content. These products virtually all contain DHA in addition to EPA. However, lipid effects differ between DHA and EPA. In contrast to the increase in LDL levels with DHA-containing products (Harris et al., 1997), which is also a fact with fibrates (Komiya et al., 2021), high-purity EPA products do not raise LDL levels (Bays et al., 2011). Thus, after the REDUCE-IT (Reduction of Cardiovascular Events With EPA-Intervention Trial) study (Bhatt et al., 2019) that showed a 25% CV risk reduction with 4 g EPA, EPA-rich supplements at a high dose (2 g twice daily) have emerged as the treatment of choice for hypertriglyceridemia (ElSayed et al., 2023; Mach et al., 2019; Visseren et al., 2021).

Such a pharmacological product has recently been available in Greece by Libytec Pharmaceuticals S.A. (Athens, Greece). It is a drinking oil in 2 g sachets, each containing 1875 mg EPA, 125 mg DHA, 150 IU Vitamin D3, and 12 mg Vitamin E (Table 1). The suggested product dose is 1–2 sachet(s) per day. A certification reporting the high purity of the supplement in EPA is in the possession of Libytec Pharmaceuticals S.A. The product has been notified to the National Medicines Agency(NMA)of Greece with the trade name "EPAVasc" (NMA notification No: 81089/03-09-2021).

The aim of the present study was to investigate the effect of the administration of this highly purified EPA formulation in a high dose (2 g twice daily, also called pharmacological dose) on CV and metabolic indices in subjects with increased CV risk.

METHODS

Study population and design

This open, noninterventional, observational study enrolled 226 subjects, aged >50 years, with high TG levels (1.53–5.65 mmol/L) and ≥1 of the following CV risk factors: arterial hypertension (AH), type-2 diabetes mellitus (T_2DM), ultrasound-documented atheromatosis, peripheral artery disease (PAD), previous myocardial infarction, or ischemic stroke. Patients with heart, hepatic, or renal failure and mental disorders were excluded from the study. Subjects already taking dietary supplements containing ω-3 fatty acids were also excluded. The enrollment and the follow-up of the participants were performed by 19 private practicing physicians (8 cardiologists, 8 internal medicine physicians, 2 diabetologists, and 1 general practitioner). Physicians and participants were dispersed in the entire Greek geographical territory representing, as far as possible, epidemiological patterns throughout the country. Each physician was planned to enroll 12 consecutive patients visiting him/her at his/her private office. No hospital patients were included. The first patient was enrolled on October 10, 2022, and the last one on March 31, 2023. The study was coordinated by two hospital centers: a European Society of Hypertension (ESH) center of excellence for hypertension, in Athens (the Greek capital), and an outpatient internal medicine unit in Lamia (a large provincial Greek city). It was conducted in accordance with the Declaration of Helsinki recommendations (World Medical Association, 2013), the International Society of Pharmacoepidemiology guidelines for good pharmacoepidemiology practices (ISPE, 2008), and the International Conference on Harmonization guidelines for good clinical practice (ICH, 2001). Approval was obtained from the human ethics committee of the two coordinating centers (Laiko General Hospital of Athens, Athens, Greece and General Hospital of Lamia, Lamia, Greece). Written informed consent was obtained from all patients prior to their inclusion in the study.

Participants included in the study were examined at two scheduled visits: at their inclusion in the study (baseline) and 3 months after inclusion. At baseline, a physical examination was performed and a comprehensive medical history was taken including demographic data (e.g., sex and age), CV risk factors, comorbidities, and previous medications (especially for AH, T_2DM, PAD, previous myocardial infarction, or ischemic stroke).

TABLE 1 Supplement composition.

	Per 1 sachet		Per 2 sachets	
Nutrient	Dose	Percentage of the recommended daily intake	Dose	Percentage of the recommended daily intake
EPA	1875 mg	-	3750 mg	-
DHA	125 mg	-	250 mg	-
Vitamin D3 (cholecalciferol)	3.75 mg (150 IU)	75%	7.5 mg (300 IU)	100%
Vitamin E (tocopherol)	12 mg	150%	24 mg	200%

Abbreviations: DHA, docosahexaenoic acid; EPA eicosapentaenoic acid.

Nutritional counseling regarding hypertriglyceridemia was typically provided to all participants at baseline. This included the following:

> Follow a diet low in fat, with less than 30% of daily calories from total fat. Choose polyunsaturated fats over saturated fats.
> Include oily fish two to three times per week within your fat allowance.
> Reduce consumption of high-sugar food and drinks, and choose unrefined carbohydrate sources such as higher fiber breads and cereals.
> Limit or abstain from alcohol.
> Lose weight if overweight.
> Participate in regular physical activity.
> If you have diabetes, aim for good blood glucose control.

In addition to dietary advice, patients commenced treatment at baseline with the highly purified EPA formulation "EPAVasc", at a dose of 4 g/24 h (2 g twice a day), according to current dyslipidemias guidelines. Any concomitant hypolipidemic medication (i.e., statin, ezetimibe, fibrate) remained unchanged during follow-up. Each patient received a total of 180 sachets of EPAVasc by his/her physician at baseline, which is the necessary amount for a 3-month treatment administration. At the end of follow-up, the empty sachets were returned to physicians in order to check the adherence to treatment.

Biochemical and metabolic hematological parameters (TG, LDL, high-density lipoprotein [HDL], total cholesterol [TChol], apolipoprotein A_1 [Apo A_1], apolipoprotein B [Apo B], glucose, glycated hemoglobin [HbA_1c], and C-reactive protein [CRP]) were measured at baseline and at 3 months after dietary and pharmacological treatment initiation.

The primary endpoint of the study was to assess the effect of high-dose "EPAVasc" 3-month administration, along with nutritional advises, on these cardiometabolic indices in a prespecified cohort of increased CV risk subjects.

Inclusion criteria definitions

In line with the 2018 ESH guidelines (Williams et al., 2018), AH was defined as current treatment with blood pressure (BP)-lowering medication or as office systolic BP ≥140 mmHg or/and diastolic BP ≥90 mmHg or out-of-office BP ≥135/85, 120/70 or/and 130/80 mmHg for day-time, night-time and 24-h BP, respectively.

According to the 2019 World Health Organization guidelines (WHO, 2019), T_2DM was diagnosed in case of current antihyperglycemic treatment or if any of the following was present: fasting plasma glucose ≥7.00 mmol/L, plasma glucose 2 h after a 75 g oral glucose load ≥11.10 mmol/L, random plasma glucose ≥11.10 mmol/L or HbA_1c ≥ 6.5%.

Ultrasound-documented atheromatosis was defined as the presence of any arterial atheromatous plaque causing local stenosis <50%, whereas peripheral artery disease was defined as a ≥50% stenosis in any peripheral artery (carotid, upper arm, lower limb) (Aboyans et al., 2018).

The diagnosis of previous myocardial infarction or/and ischemic stroke was ascertained by the patient's documents and reports from previous hospitalization or/and previous invasive (coronary-brain angiography) or noninvasive (electrocardiogram, echocardiogram, myocardial perfusion study, transcranial Doppler ultrasonography, brain computed tomography/magnetic resonance imaging) examinations.

Statistical analysis

Continuous variables (such as TG) are presented as mean ± standard deviation, and categorical variables (such as sex) as observed number and percentage (*n*, %). Paired *t*-test was applied for the pairwise comparisons in biomarkers' levels between visits once normality was demonstrated (Kolmogorov–Smirnov test); otherwise, the nonparametric Wilcoxon test was used. Correlations were performed between biomarkers' changes at 3 months and potential confounders (such as age). Differences and correlations were considered significant for a two-sided p <0.05. The data analysis was performed using IBM SPSS 19 statistical software (2010, IBM, Route 100 Somers, NY, USA).

RESULTS

Baseline characteristics of the 226 patients enrolled in the study are presented in Table 2. Males were 141 (62.4%) and females 85 (37.6%). The mean age of the participants was 61.1 years, the mean TG level was 2.97 mmol/L, and the mean body mass index (BMI) was 29.1 kg/m^2. Ninety-one participants (40.3%) were on a dietary program concerning CV risk factors, whereas 16 (7.1%) were drinkers on a daily basis.

Treatment-related adverse reactions were only minor. Thus, there were no discontinuations of the treatment or/and withdrawals from the study due to adverse reactions/events.

With the exception of Apo A_1, all other measured biomarkers improved to a statistically significant degree ($p < 0.05$) at 3 months (Table 3, Figures 1 and 2): TG 1.75 ± 0.09 versus 2.97 ± 0.15 mmol/L (41.1% reduction), LDL 2.46 ± 0.08 versus 3.05 ± 0.13 mmol/L (19.5% reduction), HDL 1.22 ± 0.03 versus 1.11 ± 0.03 mmol/L (9.3% increase), non-HDL 3.29 ± 0.10

versus 4.14 ± 0.16 mmol/L (20.6% reduction), TChol 4.55 ± 0.10 versus 5.15 ± 0.13 mmol/L (11.6% reduction), Apo A_1 26.8 ± 9.3 versus 22.5 ± 8.6 μmol/L (19% increase), Apo B 1.25 ± 0.23 versus 1.29 ± 0.23 μmol/L (3.0% reduction), glucose 5.66 ± 0.11 versus 5.99 ± 0.17 mmol/L (5.6% reduction), HbA_1c 5.83 ± 0.1 versus 5.97 ± 0.1% (2.3% reduction), and CRP 1.92 ± 0.2 versus 5.26 ± 2.8 mg/L (63.5% reduction).

TABLE 2 Patients' baseline characteristics.

Clinical characteristics	
Age (years)	61.1 ± 1.4
Sex: male/female	141 (62.4)/85 (37.6)
Body mass index (kg/m^2)	29.1 ± 3.9
Normal weight (18.5–24.9 kg/m^2)	30 (13.3)
Overweight (25–29.9 kg/m^2)	109 (48.2)
Obese (≥ 30 kg/m^2)	87 (38.5)
On a dietary program	91 (40.3)
Triglycerides (mmol/L)	2.97 ± 0.15
Residence: urban/semiurban/rural	169 (74.8)/38 (16.8)/19 (8.4)
Cardiovascular risk factors and comorbidities	
Smoking	67 (29.6)
Drinking (on a daily basis)	16 (7.1)
Arterial hypertension	99 (43.8)
Diabetes mellitus	91 (40.3)
Ultrasound-documented atheromatosis	89 (39.4)
Peripheral artery disease	32 (14.2)
Previous myocardial infarction	38 (16.8)
Previous ischemic stroke	21 (9.3)
Concomitant medications	
Statin or/and ezetimibe	141 (62.4)
Fibrate	19 (8.4)
Anti-hypertensive agents	79 (35.0)
Anti-hyperglycemic agents	57 (25.2)
Antiplatelets	61 (27.0)

Note: Data are presented as mean ± standard deviation or *n* (%) patients.

TABLE 3 Treatment-induced changes in cardiometabolic biomarkers.

Biomarker	Baseline	3 Months	*p*-Value
Triglycerides (mmol/L)	2.97 ± 0.15	1.75 ± 0.09	<0.001
LDL cholesterol (mmol/L)	3.05 ± 0.13	2.46 ± 0.08	<0.001
HDL cholesterol (mmol/L)	1.11 ± 0.03	1.22 ± 0.03	<0.001
Non-HDL cholesterol (mmol/L)	4.14 ± 0.16	3.29 ± 0.10	<0.001
Total cholesterol (mmol/L)	5.15 ± 0.13	4.55 ± 0.10	<0.001
Apo A_1 (μmol/L)	22.5 ± 8.60	26.8 ± 9.30	0.315
Apo B (μmol/L)	1.29 ± 0.23	1.25 ± 0.23	0.015
Glucose (mmol/L)	5.99 ± 0.17	5.66 ± 0.11	<0.001
HbA_1c (%)	5.97 ± 0.12	5.83 ± 0.12	<0.001
CRP (mg/L)	5.26 ± 2.83	1.92 ± 0.23	<0.001

Note: Data are presented as mean ± standard deviation.
Abbreviations: Apo A_1, apolipoprotein A_1; Apo B, apolipoprotein B; CRP, C-reactive protein; HbA_1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Treatment with the studied high-purity EPA product, along with typical nutritional advises, led to a TG, LDL, HDL, TChol, Apo A_1, Apo B, glucose, HbA_1c, and CRP improvement in 97.3%, 77.0%, 72.6%, 81.0%, 40.5%, 40.5%, 65.5%, 64.1%, and 58.4% of patients, respectively.

Treatment-induced biomarkers' changes at 3 months were independent of age and pack-years of smoking (correlation coefficient $r < 0.3$, p = NS for all). Eicosapentaenoic acid-induced changes in biomarkers were also independent of sex, with the exception of Apo B (significant changes only in men) (Table 4). Moreover, biomarkers' changes were independent of BMI category (normal 18.5–24.9 kg/m^2, overweight: 25–29.9 kg/m^2, obesity: ≥30 kg/m^2) and the habit of daily drinking with the exception of glucose and HbA_1c, where significant ($p < 0.05$) reductions were observed only in overweight-obese patients and them not drinking daily. Furthermore, changes in biomarkers with EPA were independent of the adoption of a dietary program with the exception of Apo B and HbA1c where significant ($p < 0.05$) reductions were observed only in patients on a dietary program. Biomarkers' changes were also independent of residence, apart from HbA_1c (significant [$p < 0.05$] reduction only for urban and semiurban areas). Finally, EPA-induced changes in biomarkers' levels were significant regardless of the concomitant use of statin ± ezetimibe (except for HbA_1c [significant—$p < 0.05$—reduction only in those not taking drug(s)] and Apo B [significant—$p < 0.05$—reduction only in those taking drug(s)]) or fibrate (except for CRP: significant [$p < 0.05$] reduction only in those not taking fibrate).

DISCUSSION

This is probably the first study in Greece evaluating the effect of a high-purity EPA at a high dose on lipids, glycemic profile, and subclinical inflammation in high CV risk patients in daily clinical practice. The main findings of the study denote that this treatment seems highly and rapidly effective regarding the primary goal of lowering TG levels. Moreover, it seems to have beneficial effects on other atherogenic lipids (LDL and ApoB) and "protective" lipids (HDL, ApoA_1). Furthermore, other favorable pleiotropic effects regarding the glycemic and inflammatory profiles are apparent with high-purity EPA treatment.

The results of this study seem to be in agreement with large-scale published studies. In the MARINE (Multi-center, plAcebo-controlled, Randomized,

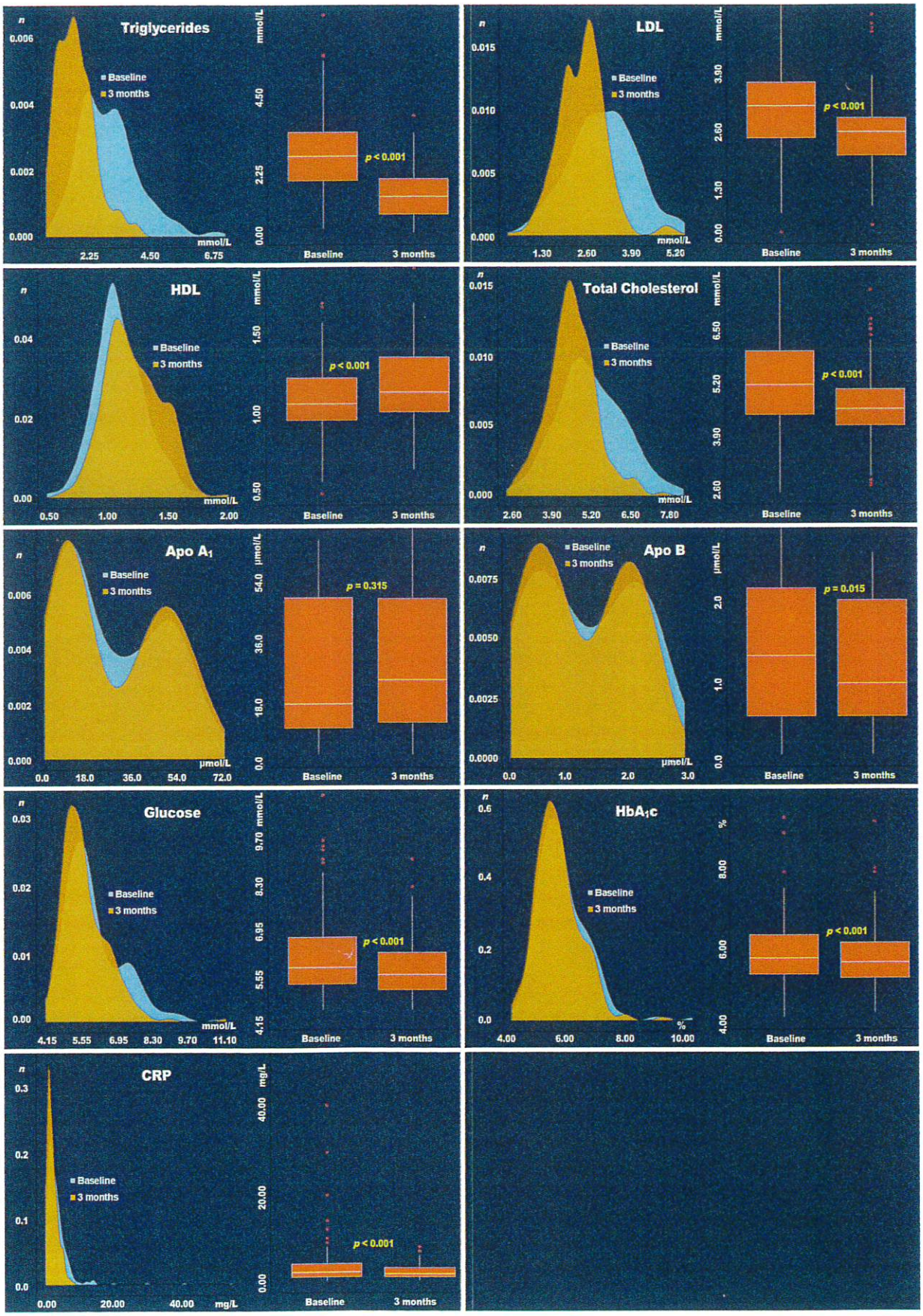

FIGURE 1 Treatment-induced changes in cardiometabolic biomarkers at 3 months. Apo A_1, apolipoprotein A_1; Apo B, apolipoprotein B; CRP, C-reactive protein; HbA_1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; *n*, percentage of patients.

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