Impact of A Two-Year Trial of Nutritional Ketosis on Indices of Cardiovascular Disease Risk in Patients With Type 2 Diabetes

Shaminie J. Athinarayanan
Virta Health https://orcid.org/0000-0001-5427-6748
Sarah J. Hallberg
Virta Health
Amy L. McKenzie
Virta Health
Katharina Lechner
German Heart Centre Munich: Deutsches Herzzentrum Munchen
Sarah King
University of California San Francisco
James P. McCarter
Abbott Diabetes Care Inc
Jeff S. Volek
The Ohio State University
Stephen D. Phinney
Virta Health
Ronald M. Krauss (Ronald.Krauss@ucsf.edu)
University of California San Francisco

Original investigation

Keywords: Type 2 diabetes, nutritional ketosis, cardiovascular risk, lipoprotein sub-fractionation, atherogenic lipoprotein phenotype

Posted Date: September 25th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-78136/v1

Version of Record: A version of this preprint was published on December 8th, 2020. See the published version at https://doi.org/10.1186/s12933-020-01178-2.

Abstract

Background: We have previously reported that in patients with type 2 diabetes (T2D) consumption of a very low carbohydrate diet capable of inducing nutritional ketosis over two years (continuous care intervention, CCI) resulted in improved body weight, glycemic control, and multiple risk factors for cardiovascular disease (CVD) with the exception of an increase in low density lipoprotein cholesterol (LDL-C). In the present study, we report the impact of this intervention on markers of risk for atherosclerotic cardiovascular disease (CVD), with a focus on lipoprotein subfraction particle concentrations as well as carotid-artery intima-media thickness (CIMT).

Methods: Analyses were performed in patients with T2D who completed 2 yrs of this study (CCI; n=194; usual care (UC): n=68). Lipoprotein subfraction particle concentrations were measured by ion mobility at baseline, 1, and 2 yrs and CIMT was measured at baseline and 2 yrs. Principal component analysis (PCA) was used to assess changes in independent clusters of lipoprotein particles.

Results: At two years, CCI resulted in a 23% decrease of small LDL IIIb and a 29% increase of large LDL I with no change in total LDL particle concentration or ApoB. The change in proportion of smaller and larger LDL was reflected by reversal of the small LDL subclass phenotype B in a high proportion of CCI participants (48.1%) and a shift in the PC representing the atherogenic lipoprotein phenotype characteristic of T2D from a major to a secondary component of the total variance. The increase in LDL-C in the CCI group was mainly attributed to larger cholesterol-enriched LDL particles. CIMT showed no change in either the CCI or UC group.

Conclusion: Consumption of a very low carbohydrate diet with nutritional ketosis for 2 yrs in patients with type 2 diabetes lowered levels of small LDL particles that are commonly increased in diabetic dyslipidemia and are a marker for heightened CVD risk. A corresponding increase in concentrations of larger LDL particles was responsible for higher levels of plasma LDL-C. The lack of increase in total LDL particles, ApoB, and in progression of CIMT, provide supporting evidence that this dietary intervention did not adversely affect risk of CVD.

Background

Global incidence of diabetes is rising substantially, with the expectation of a 50% increase between 2015 and 2040(1). The leading cause of death in patients with diabetes is cardiovascular disease (CVD) (2) and mitigating CVD risk has become a principal focus of current diabetes guidelines (3–4). Multiple studies have found that therapeutic carbohydrate restriction significantly improves a number of CVD risk factors (5–7), including elevated triglycerides and small dense LDL, low HDL-C, and markers of non-alcoholic fatty liver disease (8,9). These factors contribute to residual risk of CVD following statin treatment for lowering of LDL-cholesterol (LDL-C) (10).

Although LDL-C has been a mainstay for CVD risk prediction and management for decades, it is not characteristically elevated in patients with diabetes. Rather, the most common dyslipidemia in type 2 diabetes (T2D) consists of high triglycerides (TG), low HDL-cholesterol (HDL-C), and a preponderance of small dense LDL particles (11,12). This trait which is a central feature of metabolic syndrome, has been designated the atherogenic lipoprotein phenotype (ALP) or atherogenic dyslipidemia (11–14). Multiple studies have shown beneficial effects of carbohydrate restriction on this phenotype (15–17). Recently, very low carbohydrate diets that achieve nutritional ketosis have been shown to be of benefit in diabetes management, with effects including improvements in weight, HbA1c, triglycerides and HDL-C (5,18). However, such diets often result in increased concentrations of LDL-C (18,19), which has raised concerns regarding an adverse effect on CVD risk.

While LDL-C is taken to reflect the role of LDL particles in the development of CVD, it has been shown that measurement of LDL particles (20,21) and ApoB, which is a measure of the number of all atherogenic particles (LDL, IDL, VLDL) (20,22) can provide superior assessment of CVD risk, most notably when there is discordance between LDL-C and LDL particle concentrations (22). This discrepancy is commonly due to increased levels of small, dense, cholesterol-depleted particles, as is the case for the dyslipidemia of T2D. There is increasing evidence that levels of small, dense LDL are predictive of CVD incidence independent of LDL-C (23–27), whereas in general levels of large LDL show weak or absent associations with CVD risk (27). Properties of small LDL that may underlie this risk include increased circulation time due to decreased receptor-mediated uptake, increased vascular wall binding, and increased susceptibility to oxidation and glycation (28). Assessment of other lipoprotein particle subclasses, including those within VLDL and HDL, has provided the ability to further assess CVD risk (20).

We previously reported that two yrs of treatment with a continuous care intervention (CCI) produced significant improvements in weight, blood glucose, HbA1c, liver function, and inflammatory markers with no adverse effects on kidney markers (29). Participants in the CCI group had a 0.9% mean absolute reduction in HbA1c and a 10% average weight loss at two yrs (29). CCI is a personalized carbohydrate restriction (CR) intervention with guidance encouraging nutritional ketosis that is delivered and supported remotely using a telemedicine-approach, via one-to-one health coaching and physician-led treatment. At one yr, the intervention resulted in substantial improvements in multiple cardiometabolic risk markers including triglycerides, HDL-C, ApoA1, ApoB: ApoA1 ratio, and blood pressure (30,31). However, there

was an increase in LDL-C that was maintained through 2 yrs despite sustained improvements in TG and HDL-C (30). To further characterize changes in LDL and other lipoproteins at one and two yrs, we have here utilized the technique of ion mobility (IM) which directly measures concentrations of lipoprotein particle subclasses across the full diameter spectrum from HDL to VLDL. A novel feature of our statistical approach was to use both principal component analyses and assessment of LDL subclass phenotypes to obtain a more integrated assessment of the intervention on atherogenic dyslipidemia. Finally, we measured carotid intima-media thickness (CIMT) as a means of assessing the impact of the intervention on atherosclerosis and tested whether there were differences in changes in CIMT as well as lipoprotein subclasses between individuals in the highest and lowest quartiles of either LDL-C or ApoB responses.

Materials And Methods

Study Design and Intervention

The data analyzed for this study are measurements of CVD risk markers obtained at baseline and after one and two yrs of follow-up in participants in the clinical trial NCT02519309. This is an open-label, longitudinal trial of the effects of carbohydrate restriction including nutritional ketosis conducted in a cohort of patients with T2D. The study design, comprehensive details of the study intervention, and major exclusion criteria were previously published (29,31). Briefly, the trial recruited participants with an established diagnosis of T2D and a body mass index (BMI) >25kg/m^2, who self-selected to receive either the CCI or usual care (UC). All study participants were informed and consented to participate in the study, and the study was approved by the Franciscan Health Lafayette Institutional Review Board. Patients in the CCI group received nutritional advice on carbohydrate restriction to achieve and sustain nutritional ketosis. They were initially advised to consume <30grams of carbohydrates, approximately 1.5 g protein per kg reference body weight, and fat to satiety each day. Blood beta-hydroxybutyrate (BHB) was used as a marker of carbohydrate restriction, with BHB ≥ 0.5mM (32) indicating nutritional ketosis. Over time, BHB and dietary intake targets were modified according to patient health needs, goals, and values. The patients had access to a web-interfaced software application (app) that they used to communicate with their remote care team and receive telemedicine-based treatment. The app was used to upload selected biomarkers for monitoring adherence to nutritional intervention and health-related progress including body weight, blood glucose, and BHB. The frequency of reporting glucose and BHB was adjusted to each participant's preferences and current health needs. Participants with a confirmed history of hypertension additionally received an automatic sphygmomanometer, blood pressure readings were uploaded in the app for assessment by the care team. The reported blood glucose and blood pressure readings were evaluated routinely by the physician who adjusted diabetic and anti-hypertensive prescriptions as needed. Via the app, participants had access to online resources and the opportunity to participate in an online social support community.

Patients who chose UC comprised a reference group that was recruited from the same geographical and healthcare system. They continued with their existing care team without modification and received nutritional and lifestyle advice as recommended by the American Diabetes Association (ADA) between August 2015 and May 2018(3). No study-specific modification of treatment or care was made but the participants in the UC arm were required to obtain annual tests for measurement of clinical biomarkers.

Anthropometric Measures

Anthropometric measures were obtained for both CCI and UC participants in the clinic at baseline, 1 yr, and 2 yrs. Body weight and height were measured using a stadiometer and calibrated scale, respectively and the values were used to calculate body mass index (BMI). Manual blood pressure measurements were performed by trained staff. Dual-energy X-ray absorptiometry (DXA; Lunar GE Prodigy, Madison, WI) was utilized to measure total body composition and to estimate central abdominal fat (CAF), as previously described (29), in the CCI group only.

Lipid Analyses

An accredited Clinical Laboratory Improvement Amendment (CLIA) laboratory was used to analyze all the standard blood analytes. For the determination of total cholesterol, HDL-C, TG, ApoA1, and ApoB, an enzymatic, colorimetric method was employed using FDA approved Cobas c501 (Roche Diagnostics; Indianapolis, IN, USA) assays. LDL cholesterol (LDL-C) levels were calculated using the Friedewald equation, except if the TG level exceeded 400mg/dL, in which case LDL-C was not determined (n=15, 8, 8 in CCI and n=9, 10, 6 in UC at baseline, 1 year and 2 years, respectively). Both non-HDL and remnant cholesterol were calculated using simple formulas listed below. ApoB: ApoA1 ratios were computed.

Non-HDL = Total cholesterol – HDL-cholesterol

Remnant cholesterol = Total cholesterol – HDL-cholesterol – LDL-cholesterol

Lipoprotein Analyses

Particle concentrations of VLDL, IDL, LDL, and HDL subfractions were analyzed in specific particle-size intervals using ion mobility (IM), which uniquely allows for direct particle quantification as a function of particle diameter (21) following a procedure to remove other plasma proteins (24). The IM instrument utilizes an electrospray to create an aerosol of particles which then pass through a differential mobility analyzer coupled to a particle counter. Particle concentrations (nmol/L) were measured in 11 size intervals (Å): VLDL: large (424.0 to 547.0), medium (335.0 to 424.0), small (296.0 to 335.0); IDL: large (250.0 to 296.0) and small (233.3 to 250.0); LDL: large LDL I (224.6 to 233.3), medium LDL IIa (220.0 to 224.6), and LDL IIb (214.1 to 220.0), small LDL IIIa (208.2 to 214.1) and LDL IIIb (204.9 to 208.2), very small LDL IVa (199.0 to 204.9), LDL IVb (190.0 to 199.0) and LDL IVc (180.0 to 190.0); HDL: large HDL 2b (105.0 to 145.0) and smaller HDL 2a+3 (76.5 to 105.0). In addition, particles in the size range between LDL and HDL (145.0 to 180.0 Å) were measured (designated mid-zone). Peak LDL diameter was determined as described (22). Interassay variation was reduced by the inclusion of two in-house controls in each preparatory process and triplicate analysis. Inter- and intra-assay coefficients of variability were <15% for lipoprotein subclass concentrations and <0.8% for LDL peak diameter. In addition, LDL subclass phenotypes were determined as described previously (33): phenotype A (predominance of larger LDL particles with LDL peak diameter >21.88nm), phenotype B (predominance of small LDL particles with LDL peak diameter <21.55nm), or intermediate phenotype I (with LDL peak diameter between 21.55 and 21.88nm).

Carotid Intima-Media Thickness (CIMT) Measurement

Ultrasound assessment CIMT was performed in both CCI and UC participants. A high-resolution B mode carotid ultrasound was used (Philips EPIQ5 system; Amsterdam, Netherlands) and the scans were performed by trained and blinded technicians. The participants were placed in a supine position, and both right and left carotid arteries were evaluated with grayscale, spectral, and color Doppler images. The images were taken 1 cm distal to the carotid bulb, below its bifurcation limit. As previously published (30), three imaging planes, anterior, lateral, and posterior, were captured for each participant. These images were then analyzed using the edge detection software (Carotid Analyzer for Research, Medical Imaging Application, Coralville, IA) by a trained and blinded analyst. Any images that were classified “poor” and those with missing planes were removed from all the time points, before the right and left mean CIMT and diameter were calculated from the images. The right and left CIMT average measurements were then used to calculate the overall mean CIMT.

Statistical analyses

Analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp, Armonk, N.Y., USA). All were first examined for normality and linearity using the skewness and kurtosis cut-offs suggested by Kline’s 2011 guidelines (34). Four outcomes were positively skewed (i.e., triglycerides, LDL IVa, LDL IVb, and LDL IVc), these variables were normalized by either removal of the top 1% of values or natural log transformations (as specified in the tables’ footnotes). Between-group and between completers versus dropouts' differences in baseline data were analyzed using independent sample t-tests.

All analyses were based on the per-protocol principle including only participants with available data at baseline and 2 yrs. We used linear mixed-effects models (LMMs) to analyze all the primary endpoints. The models included fixed effects of time, treatment group, and time-by-group interaction to estimate the adjusted means at each time point and to assess the time-effect of the treatments (baseline to 2 yrs) and between-treatment group differences (CCI versus UC). All models were adjusted for baseline age, sex, BMI, insulin use, statin use, HDL 2+3a, and mid-zone. BMI, insulin-use, HDL 2+3a and mid-zone were included as co-variates because they differed significantly between CCI and UC groups at baseline. A sensitivity analysis was conducted using data including all participants (262 CCI and 87 UC participants) based on the intent-to-treat principle. The estimation of the missing data in the LMMs was based on the maximum likelihood approach and an unstructured (UN) covariance structure was used to account for within-group correlation over time. The changes in the proportion of participants’ use of lipid-lowering and antihypertensive medications between baseline versus 2 yrs in both CCI and UC were analyzed using McNemar’s test with continuity correction when appropriate. Logistic generalized estimating equations (GEE) analysis with an unstructured covariance matrix were used to analyze the time-effect of each treatment group (CCI and UC) on the trichotomous categorical variable, LDL phenotype pattern (Pattern A, B and I). Covariates included baseline age, sex, BMI, insulin use, statin use, HDL 2+3a, and mid-zone.

Individual differences in the changes of LDL-C and ApoB between baseline and two years were assessed using hypo- and hyper-responder categories. For the classification of LDL-C and ApoB hypo- versus hyper-responders, we generated quartiles using the calculated delta LDL-C and delta ApoB from baseline to two years. The lowest (greatest decrease) and highest (greatest increase) quartiles were classified as hypo- and hyper-responders, respectively. A-one-way MANOVA was performed to assess the differences in the multivariate lipoprotein profiles at 2 yrs for the LDL-C and ApoB hypo- versus hyper-responders. Lipoprotein variables that failed the Shapiro-Wilk test of normality were log-transformed before inclusion in the MANOVA to meet the multivariate normality and outliers' assumptions. The 2-yr differences in mean CIMT between the LDL-C or ApoB hypo- and hyper-responder groups were assessed using independent T-tests.

Finally, measures of adiposity and BHB were tested as predictors of changes in lipids and lipoproteins. Linear and multiple linear regression analyses were used to assess the relationships between changes in BMI and CAF with lipids and lipoproteins. BHB values that were

uploaded in the app by the CCI participants were treated as count data, where the number of days participants reported a BHB value of ≥ 0.5 mM over the past 24 months was modeled using negative binomial regression for association with lipids, lipoproteins, and LDL phenotype shift.

A strict Bonferroni correction was applied to the LMM and MANOVA analyses, where P <0.0015 and P<0.003, respectively indicated statistical significance. For all other exploratory analyses, P<0.05 was used to determine statistical significance

Principal Component Analysis

There was a strong inter-correlation and dependency between the lipoprotein subclasses and lipid variables. To simplify analysis, principal component analysis (PCA) was performed on the 16 lipoproteins and 3 traditional lipids to reduce the variables by generating a new independent combination of the variables that explains the variance of the data. Separate PCAs were performed on baseline and two-year follow-up data in the CCI and UC treatment groups. Three steps were used: (1) Identification and extraction of major principal components, (2) Rotation of the principal components to identify relevant loading factors, and (3) Interpretation of the principal components and its associated variance. First, we assessed the data for sampling adequacy and its suitability for factor analysis using the Kaiser-Meyer-Olkin (KMO) statistic (cut-off>0.6) and the Barlett test of sphericity (p<0.001). Then, we performed PCA on the baseline CCI (n=223) and UC (n=70), and two-year follow-up CCI (n=140) and UC (n=46) data, separately. The major principal components represented in each dataset were extracted after assessing the scree plots, and an eigenvalue of 1 was used as a cut-off to select and retain the principal components. We used both varimax and promax rotation methods to identify loading factors for each principal component and a loading value cut-off > 0.40 was used to determine the individual lipoproteins and lipids represented in each component. The individual extracted principal components and their associated variance at baseline and two-years follow-up were qualitatively assessed. The variance of the individual PCs at baseline and two-years explains how much of the information in the data is captured by the respective PCs. A PC with the highest variance contribution represents the most information in the data, while a PC with less variance captures less information in the data. Changes in the rank of the PCs were assessed at baseline and two years.

Results

Participant Characteristics

A total of 262 CCI and 87 UC participants were enrolled in this study, with 194 CCI and 68 UC participants remaining enrolled for 2 yrs. As previously reported, baseline demographic characteristics of the two treatment groups were similar except for the proportion of African Americans (**Table 1**). All other baseline anthropometric measures, CVD risk markers, and average CIMT were similar between CCI and UC groups, except for weight and BMI (**Table 1**). Baseline levels of lipoprotein subclasses were well-matched between CCI and UC groups, except for mid-zone and small HDL 2a+3 which were significantly lower in the CCI group. At baseline, 50% of CCI and 59% of UC participants were on statin treatment (p=0.16). There were no significant differences in baseline characteristics of those who dropped out of the study versus those remaining, except for the baseline proportion of LDL phenotypes in UC (**Table 1**).

Lipids, Blood pressures, CIMT, Apoproteins, and Lipoproteins

The baseline versus 1- and 2-yr differences in lipids, blood pressures, apoproteins, lipoproteins, and CIMT in CCI and UC are shown in Table 1. As reported previously (30), in the CCI group, there were significant 1- and 2-yr increases in LDL-C (12.0% at 2 yrs, p= $2.0x10^{-3}$; **Supplementary Figure 1)** and HDL-C (18.2% at 2 yrs, p= $1.1x10^{-7}$; **SupplementaryFigure 1**) and decreases in TG (-21.0% at 2 yrs, p=$1.2x10^{-5}$; **Supplementary Figure 1)** and systolic (-4.6% at 2-yr, p=$8.9x10^{-5}$) and diastolic (-3.9% at 2-yr, p=$4.0x10^{-4}$) blood pressures (**Table 2**). No significant 1- or 2-yr differences from baseline in these measures were observed in the UC group. In addition, in the CCI but not the UC group, there were significant 1- and 2-yr reductions in other calculated lipid variables: remnant cholesterol (-22.4% at 2 yr, p=$3.1x10^{-7}$). There were no within-group and between-group differences in non-HDL-C in CCI and UC at 2 yrs (Table 2). There was a significant increase in ApoA1 (10.9% at 2 yr p=$1.4x10^{-7}$) and a marginally significant decrease in Apo B: ApoA1 ratio (-14.3% at 2 yr p=$2.0x10^{-3}$) in the CCI group, with no significant changes in UC (**Table 2**). Within-group significant changes at 1- and 2 yrs when compared to baseline values were observed for the following lipoprotein subfractions in CCI but not in UC: small LDL IIIa (-17.8% at 1 yr, p=$1.0x10^{-3}$; -15.8%, p=$3.0x10^{-3}$ [marginally significant]; **Supplementary Figure 1**), LDL IIIb (-23.1% at 2 yr, p=$1.0x10^{-3}$; **Supplementary Figure 1**), mid-zone (-6.8%, p=$7.4x10^{-7}$), IDL 2 (+28.0%, p=$2.0x10^{-10}$; **Supplementary Figure 1**), medium LDL IIa (+13.3% at 2yr, p=$5.0x10^{-3}$, marginally significant) and large LDL I (+29.1% at 2 yr, p=$2.4x10^{-8}$; **Supplementary Figure 1**). Among these fractions, the 2-yr changes in IDL-2 and LDL I and mid-zone were significantly different between the CCI and UC groups, while the difference in change of LDL IIIb was marginally significant. There were also non-significant reductions in very small LDLs (LDL IVa, LDL IVb, and LDL IVa; Figure 1A) and medium-sized LDL IIb (Figure 1A), in the CCI group at 2 yrs. Mean LDL peak diameter increased at 1 and 2 yrs in the CCI group (2.0% at 2 yr; p=$1.9x10^{-10}$) and the 2yr change was significantly

greater than in the UC group (1.5%, p= $1.0x10^{-3}$) (**Table 2**). No significant within- or between-group 2-year changes were observed for total VLDL and its respective VLDL subclasses, total IDL including IDL 1, total LDL, and total HDL including both HDL 2a+3 and HDL2b in either the CCI or UC groups. There were no within- or between-group differences in average CIMT in CCI and UC at 2 yrs (**Table 2**).

An intent-to-treat sensitivity analysis using all available data revealed results consistent with the per-protocol (completers) analysis (**Supplementary Table 1**).

Antihypertensive and lipid lowering medications

Reduced blood pressures in CCI were observed concurrent with reduced use of antihypertensive medication (p=$1.0x10^{-3}$) and diuretics (p=$7.0x10^{-3}$) at 2 yrs (**Supplementary Table 2**). In CCI, there were no significant changes in the use of statin medication at 2 yrs, but the use of other lipid-lowering medications (i.e., bile acid sequestrants, fibrates, niacin and omega-3 fatty acid ethyl esters) significantly decreased at 2 yrs (p=$8.0x10^{-3}$). In contrast, no significant changes in antihypertensive and lipid-lowering medications use were observed in the UC group (**Supplementary Table 2**).

Principal Component Analysis and LDL Phenotype Pattern

Principal component analysis was performed on the baseline and 2-yr data separately in the CCI and UC groups. In the baseline data of the CCI arm, three major principal components (PC1, PC2, PC3) were extracted that accounted for 77.3% of the overall variance. PC1, PC2, and PC3 represented 39.9%, 24.8%, and 12.7% of the total percentage variance of the data, respectively. PC1 consisted of contributions from small LDLs (LDL IIIa to LDL IVc), large VLDL, medium VLDL, and triglyceride in the positive direction and HDL-C in the negative direction (**Table 3**). Major contributors of PC2 were large and medium LDLs (LDL I to LDL IIb), IDLs, VLDL small, and LDL-C in the positive direction. Finally, contributors of PC3 were mainly HDL subclasses, both HDL 2b and HDL 2a+3, along with the mid-zone fraction and LDL IVc, all in the positive direction. In the 2-yr data from the CCI group, four principal components were extracted that explained 82.7% of the overall variance. The major component explained 39.9% of the total variance in the data and was consistent with the PC2 of baseline data (**Table 3**). The next two components were both consistent with PC1 of the baseline data and were therefore designated PC1a and PC1b, accounting for 22.9% and 13.9% of the variance, respectively. Small and very small LDLs contributed to both PC1a and PC1b with a greater contribution from small LDLs (LDL IIIa and IIIb) in PC1a and very small LDLs (LDL IVa to LDL IVb) in PC1b. PC1a was also represented by all VLDLs (mainly medium and large) and triglycerides in a positive and HDL-C in a negative direction. PC1b was strongly represented by the mid-zone fraction and was also moderately associated with TG, and intermediate and large VLDLs. The last extracted component explained 6.1% of the variance and corresponded closely to PC3 of the baseline data (**Table 3**). PCA on both the pre- and post-intervention UC data consistently extracted three components which corresponded closely to the PCs extracted from the baseline CCI data, except that HDL-C was not loaded in PC3 in the post-intervention data. The distribution of variance explained by each component was similar at baseline and 2 yrs.

The distribution of LDL peak diameter and its associated phenotypes among the CCI and UC participants at baseline, 1, and 2 yrs is shown in **Figure 1** (33). There was a significant shift in the proportion of LDL phenotypes from B to A at 1 and 2 yrs in the CCI group, while no changes in the proportion of LDL phenotypes were seen in the UC group (**Figure 1; Supplementary Table 3**).

LDL-C and Apo-B Hypo- versus Hyper-responders

Classification of CCI participants into hypo- and hyper-responders based on their LDL-C and Apo B responses from baseline to 2 yrs was used to assess possible differences in changes in lipoprotein profiles and mean CIMT. One-way MANOVA of the 17 lipoprotein subclasses and LDL peak diameter in LDL-C hypo- versus hyper-responders revealed a significant difference between the two categories in their overall lipoprotein profile (Pillai's Trace=0.66; F=5.09, p=$6.0x10^{-6}$). After correcting for multiple comparisons, LDL-C hyper-responders had significantly greater VLDL medium, VLDL small, IDL 1, IDL 2, LDL I, LDL IIa, and LDL IIb compared to LDL-C hypo-responders (**Table 4**). The MANOVA analyses of 17 lipoprotein variables in ApoB hypo- versus hyper-responders showed that the two ApoB categories were not significantly different in their lipoprotein profile (Pillai's Trace=0.37; F=1.75, p=0.37) **(Supplementary Table 4**). There were no statistically significant differences in mean CIMT at 2 yrs between the LDL-C (p=0.49) and ApoB (p=0.43) hypo- versus hyper-responders.

Relationships Between Changes in BMI and CAF with Lipids and Lipoprotein Subclasses

Univariate linear regression analyses revealed significant positive associations of 2-yr change in BMI with triglycerides, large VLDL, LDL IIIa, and LDL IIb, and inverse correlations with HDL-cholesterol, IDL-2, and HDL2b. The changes in CAF were positively associated with triglycerides, large VLDL, mid-zone, LDL IVa, LDL IIIa, LDL IIIb, and LDL IIb, and negatively associated with HDL-cholesterol, IDL 2, LDL I and HDL2b (**Supplementary Table 5**). Due to the high correlation between BMI and CAF, a multiple linear regression was performed including both changes in BMI and CAF as independent variables to confirm their associations with lipids and lipoproteins. In this model, only change

in BMI was significantly associated with triglycerides and LDL IIIa in a positive direction explaining 39.0% and 32.0% of its respective variance in the variables and BMI was also marginally correlated with large VLDL, LDL IIIb and LDL IIb, while the change in CAF was inversely associated with HDL-cholesterol, IDL 2, and HDL 2b, explaining 55.0%, 34.0% and 29.0% of the variance, respectively(**Supplementary Table 5**).

Relationships Between the Frequency of BHB values ≥0.5mM over Two Yrs and Lipids and Lipoprotein Subclasses

Supplementary Table 6 lists the significant results of generalized linear models using the negative binomial distribution for change in lipids and lipoproteins associated with the frequency of participants reporting BHB value ≥ 0.5mM from baseline to 2 yrs. The results show that higher log count of the number of times participants reported a BHB value ≥ 0.5mM was associated with greater increases in HDL-cholesterol, IDL-2, and LDL I, and greater decreases in triglycerides and the mid-zone particle fraction. Furthermore, there was a significant association of the BHB metric with LDL phenotype B to A conversion (**Supplementary Table 7**).

Discussion

Here, we present analyses of changes in CVD risk markers in patients with type 2 diabetes following a two-yr intervention with a very low carbohydrate diet aimed at achieving nutritional ketosis. We demonstrated that, compared with usual care, the very low carbohydrate diet reduced levels of very small LDL IIIb and increased concentrations of large LDL and the closely related IDL-2 species (35), with no significant change in total LDL particles and ApoB, a measure of all atherogenic lipoproteins. The results demonstrate a sustained improvement of the atherogenic lipoprotein phenotype characteristic of type 2 diabetes that comprises elevated plasma triglyceride and small, dense LDL particles, and reduced HDL-cholesterol (11,12). Therapies targeting this dyslipidemia have been reported to mitigate CVD residual risk and decreases CVD events among patients with diabetes (13,14).

Notably, the significant increase in LDL-C in the CCI group was primarily attributed to an increase in larger cholesterol enriched LDL particles. This is consistent with the finding that, among LDL subfractions, only larger LDL I and medium-sized LDL II, but not smaller particles, were significantly greater at 2 years in those in the upper versus lower quartile of dietary LDL-C response. The increase in larger LDL is likely due, at least in part, to high saturated fat intake, which has been shown to preferentially increase levels of these particles, particularly in the context of reduced carbohydrate intake (15,16,36). Since there is a growing consensus that concentrations of LDL particles and ApoB are superior to LDL-C as predictors of CVD, particularly when there is discordance between LDL-C and the particle measures (22,37), the present findings, including a lack of increase in total LDL particles and ApoB, provide reassurance that the increase in LDL-C with the dietary intervention does not signify an increase in CVD risk. This inference aligns with the observation in the PURE study, where higher dietary saturated fat consumption was associated with higher LDL-C, but not with higher all-cause or CVD mortality (38). Furthermore, this supposition is consistent with lack of progression of atherosclerosis in our study as assessed by CIMT. Given the stronger association of small versus large LDL particles with CVD risk (23–26), it remains possible that the reduction of very small LDL and other features of atherogenic dyslipidemia in the CCI group might lead to improvement in atherosclerosis measures with a longer-term intervention. A benefit of the dietary intervention on CVD risk might also be predicted by the observed reductions in remnant cholesterol (28), as well as the increases in HDL-C and the HDL protein ApoAI,(39,40), although recent studies have called into question whether reduced CVD risk can be reliably inferred by an increase in HDL-C (41,42).

Given the evidence for multiple metabolic relationships among the various lipoprotein classes, we turned to PCA to determine whether the effect of the very low carbohydrate diet could be defined by one or more independent clusters of inter-related changes in lipoprotein subfractions. From the baseline data of both the CCI and UC groups, we identified 3 independent PCs, all corresponding to PCs previously identified in healthy individuals (26). The major component in the present study (PC1) is consistent with PC2 in the earlier report, which in turn, closely reflects features of the atherogenic lipoprotein phenotype (26). Notably, this PC has been associated with increased CVD risk (26) and with chronic kidney disease (43). Moreover, it has been associated with a 22% increase in the odds of coronary artery calcification (CAC) in individuals with diabetes and metabolic syndrome (44) and with CAC in those with reduced kidney function (43). With dietary intervention in the CCI group, we found that PC1 shifted from the largest variance contributor at baseline to a secondary variance component. Furthermore, it could then be separated into two sub-components (PC1a and PC1b). Interestingly, small LDL IIIa and IIIb were relatively more strongly loaded onto PC1a, along with triglycerides and medium and large VLDL (positively) and HDL-C (negatively). In contrast, very small LDL IVa to LDL IVb were more strongly loaded onto PC1b, along with moderate loading of triglycerides and medium and large VLDL. These distinctions suggest that the very low carbohydrate intervention may have exposed effects on two independent components of the atherogenic lipoprotein phenotype, involving small and very small LDL particles, respectively. The diet-induced shift in PC1 from the primary to the secondary contributor to the overall variance is consistent with conversion from small LDL phenotype B to phenotype A in a high proportion of the CCI participants. This finding is in line with other studies reporting the reversal of phenotype B to A

through down-titration of carbohydrate intake relative to fat intake in healthy individuals (16) and in those with metabolic syndrome treated with an isocaloric low carbohydrate, high fat diet (17).

PC2 in the present study is consistent with the main PC (PC1) previously identified in healthy individuals (26) and is represented by LDL-C as well as large and medium LDL, IDL and small VLDL. Consistent with the increase in LDL-C in the CCI group, we showed that the associated variance in PC2 shifted from a secondary to the major contributor at 2 yrs. While the implications of this shift for CVD remain uncertain, it is notable that this PC was not found to be associated with CVD risk in healthy individuals (26) or with CAC in those with diabetes or metabolic syndrome (44).

Finally, the minor PC3, which was associated with reduced CVD risk in healthy individuals (26) and represents a spectrum of particles ranging from small HDL2a + 3 and large HDL2b to the smallest LDL species (LDL IVc), was not affected significantly by the dietary intervention. However, there was a trend toward increased HDL2b, which might have contributed to the observed increase in HDL-C and ApoAI.

The ion mobility analysis also identified a novel particle fraction in the size range between LDL and HDL, designated mid-zone, which was significantly reduced in the CCI group. The loading of this fraction onto PC1b suggests that it may represent a feature of this component of the atherogenic lipoprotein phenotype. However, it was also represented in PC3, raising the possibility that it may be heterogeneous, representing contributions from both LDL and HDL, and perhaps other particles in this size range. Further studies will be required to characterize this fraction and determine its metabolic significance and possible relation to CVD risk.

The findings from this study raise the question as to the extent to which reduced body weight and central adiposity may have contributed to the lipoprotein changes induced by the very low carbohydrate diet (15,45). Although the study design makes it difficult to disentangle these influences, we found that weight loss, abdominal fat reduction, and ketosis were differentially associated with specific lipoprotein particle changes. Both reduction in BMI and more frequent ketosis were correlated with improvement in TG, and reduced BMI was associated with lower levels of small LDLs. On the other hand, ketosis was related to increased large LDL I and conversion of LDL phenotype B to A, and, along with reduced central adiposity, to increased IDL 2 (closely related to large LDL [35]) and HDL-C. We speculate that carbohydrate restriction in conjunction with weight loss either through additive or synergistic actions may reduce the availability of the hepatic triglyceride pool for production of VLDL precursors of small LDLs (15). On the other hand, more frequent ketosis may reflect greater carbohydrate restriction and higher intake of fat, including saturated fat which, as noted above, preferentially increases level of larger LDL particles in conjunction with reduced carbohydrate intake (15,16, 36). One or both of these dietary effects may enhance the conversion of LDL phenotype B to A (16,46). Interestingly, a study performed in obese patients who underwent laparoscopic adjustable gastric banding failed to show significant changes in LDL levels and LDL subfractions despite a substantial weight loss of 13.4% at 13 months (47). Together, these observations, along with earlier studies (15,17) suggest that carbohydrate restriction and nutritional ketosis may contribute significantly to the observed lipoprotein changes independent of changes in adiposity.

A strength of this study is its 2-yr duration, the longest to evaluate lipoprotein changes in response to a very low carbohydrate diet including nutritional ketosis. While free-living ad libitum food consumption among participants who self-selected their intervention enhances the generalizability of the study by mimicking patient choice in lifestyle intervention for diabetes treatment, the lack of randomization and tight control over the food consumed by each group limits the strength of conclusions that can be drawn regarding differences between the CCI and UC groups who were provided different nutritional advice. However, within the CCI group, long term tracking of blood BHB as a marker of carbohydrate restriction provided the opportunity to explore the relationship between frequency of reported nutritional ketosis status and shift from LDL subclass phenotype B to A. Given that the study participants were mostly Caucasian, future research might assess lipoprotein changes observed in other races and ethnic groups.

Conclusion

In conclusion, these results demonstrate that in patients with type 2 diabetes, consumption of a very low carbohydrate diet with nutritional ketosis for 2 yrs was associated with sustained improvement in the atherogenic lipid and lipoprotein profile that is characteristic of this condition. This finding was reinforced by the use of an unbiased principal component analysis that identified this profile as one of three independent clusters of lipoprotein fractions, another of which accounted for the diet-induced increase in LDL-C. While the implications of these effects for CVD outcomes will require future long-term studies, both the lack of increase in total LDL particle number and carotid intima-media thickness point to the cardiovascular safety of a very low carbohydrate diet in the context of a substantial benefit for management of type 2 diabetes (18).

Abbreviations

CCI, continuous care intervention; UC, usual care; T2D, type 2 diabetes; CVD, cardiovascular disease; BMI, body mass index; BHB, beta-hydroxybutryrate; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; IDL, intermediate density lipoprotein; VLDL, very large density lipoprotein; ApoB, apolipoprotein B; ApoA1, apolipoprotein A1; ALP, atherogenic lipoprotein phenotype; CR, carbohydrate restriction; CAF, central abdominal fat; IM, ion mobility; CIMT, carotid-artery intima-media thickness; DXA, dual-energy X-ray absorptiometry; LMM, linear mixed-effect model; PCA, principal component analysis; MANOVA, multivariate analysis of variance; ADA, American Diabetes Association

Declarations

Ethics approval and consent to participate

All study participants were informed and consented to participate in the study, and the study was approved by the Franciscan Health Lafayette Institutional Review Board (Clinical trials.gov NCT02519309)

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Employees, consultants, founders and advisors of Virta Health Corp participated in the study design, data collection, analysis and interpretation of the data.

SJA, SJH, ALM, and SDP are employed by Virta Health Corp and were offered stock options. SDP and JSV are founders of Virta Health Corp. JPM is a shareholder and RMK is an advisor for Virta Health Corp. SMK and KL have no conflict of interests to declare.

Funding

This study was funded by Virta Health Corp

Author Contributions

S.J.H is the principal investigator of the study. R.M.K and S.J.H conceived the idea of performing lipoprotein analyses. S.J.A, A.L.M, S.M.K and S.J.H participated in data acquisition and compiling. S.J.A analyzed the data. S.J.A, R.M.K, A.L.M and S.J.H drafted the manuscript. R.M.K, A.L.M, S.J.A, S.J.H, S.D.P, J.S.V, K.L, and J.P.M edited the manuscript. All authors provided critical feedback and approved the final version of the manuscript.

Acknowledgements

The authors would like to acknowledge all investigators and study staff for their dedication to this study especially the clinical staff at Indiana University Health Arnett. We also thank the participants for their commitment to health and research.

Authors' information

Not applicable

References

1. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040 **Diabetes** Clin. 2017;128: 40-50
2. Baena-Diaz JM, Penafiel J, Subirana I, Ramos R, Elosua R, Marin-Ibanez A, et al. Risk of cause-specific death in individuals with diabetes; A competing risks analysis. Diabetes Care 2016; 39: 1987-95
3. American Diabetes Association. Standards of Medical Care in Diabetes 2020. Diabetes Care 2020; 43 Suppl 1.
4. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. ESC Scientific Document Group, 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other

Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR), European Heart Journal 2016; 37: 2315–81.

5. Westman EC, Yancy WS, Mavropoulos JC, Marquart M, McDuffie JR. The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. Nutr Metab 2008; 5: org/10.1186/1743-7075-5-36.
6. Volek JS, Sharman MJ, Gomez AL, DiPasquale C, Roti M, Pumerantz A, et al. Comparison of a very low carbohydrate and low-fat diet on fasting lipids, LDL subclasses, insulin resistance and postprandial lipemic responses in overweight women. J Am Coll Nutr 2004; 23: 177-84.
7. Volek JS, Phinney SD, Forsythe CE, Quann EE, Wood RJ, Puglisi MJ, et al. Carbohydrate restriction has a more favorable impact on the metabolic syndrome than a low fat diet. Lipids 2009; 44: 297-309.
8. Tana C, Ballestri S, Ricci F, Di Vincenzo A, Ticinesi A, Gallina S, et al. Cardiovascular risk in non-alcoholic fatty liver disease: Mechanisms and therapeutic implications. Int J ENviron Res Public Health 2019; 16: doi.10.3390/ijerph16173104.
9. Duran EK, Aday AW, Cook NR, Burning JE, Ridker PM, Pradhan AD. Triglyceride-rich lipoprotein cholesterol, small dense LDL cholesterol and incident cardiovascular disease. J Am Coll Cardiol 2020; 75: 2122-35.
10. Reiner Z. Managing the residual cardiovascular disease risk associated with HDL-cholesterol and triglycerides in statin-treated patients: a clinical update. Nutr Metab Cardiovasc Dis 2013; 23: 799-807.
11. Feingold KR, Grunfeld C, Pang M, Doerrler W, Krauss RM. LDL subclass phenotypes and triglyceride metabolism in non-insulin-dependent diabetes. Arterioscler Thromb 1992; 12: 1496-502.
12. Krauss RM, Siri PW. Dyslipidemia in type 2 diabetes. Med Clin N Am 2004; 88: 897-909.
13. Bell DSH, Badarin FA, O'Keefe JH Jr. Therapies for diabetic dyslipidemia. Diabetes Obes Metab 2011; 13: 313-25.
14. Hamilton SJ, Watts GF. Atherogenic dyslipidemia and combination pharmacotherapy in diabetes: recent clinical trials. Rev Diabet Stud 2013; 10: 191-203.
15. Krauss RM, Blanche PJ, Rawlings RS, Fernstrom HS, Williams PT. Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia. Am J Clin Nutr 2006; 83: 1025-31.
16. Dreon DM, Fernstrom HA, Campos HA, Blanche P, Williams PT, Krauss RM. Changes in dietary saturated fat intake is correlated with change in mass of large low-density lipoprotein particles in men. Am J Clin Nutr 1998; 67: 828-36.
17. Hyde PN, Sapper TN, Crabtree CD, LaFountain RA, Bowling ML, Buga A, et al. Dietary carbohydrate restriction improves metabolic syndrome independent of weight loss. JCI Insight 2019; 4: doi.10.1172/jci.insight.128308.
18. Hallberg SJ, Dockter NE, Kushner JA, Athinarayanan SJ. Improving the scientific rigour of nutritional recommendations for adults with type 2 diabetes: A comprehensive review of the American Diabetes Association guideline-recommended eating patterns. Diabetes Obes Metab 2019; 21: 1769-79.
19. Retterstol K, Svendsen M, Narverud I, Holven KB. Effect of low carbohydrate, high fat diet on LDL cholesterol and gene expression in normal-weight; young adults: A randomized controlled study. Atherosclerosis 2018; 279: 52-61.
20. Moin D, Rohatgi A. Clinical applications of advanced lipoprotein testing in diabetes mellitus. Clin Lipidol 2011; 6: 371-87.
21. Caulfield MP, Li S, Lee G, Blanche PJ, Salameh WA, Benner WH, et al. Direct determination of lipoprotein particle sizes and concentrations by ion mobility analysis. Clin Chem 2008; 54: 1307-16.
22. Sniderman AD, St.Pierre AC, Cantin B, Dagenis GR, Despras JP, Lamarche B. Concordance/Discordance between plasma apolipoprotein B levels and the cholesterol indexes of atherosclerosis risk. Am J Cardiol 2003; 91: 1173-77.
23. Cromwell WC, Otvos JD, Keyes MJ, Pencina MJ, Sullivan L, Vasan RS, et al. LDL particle number and risk of future cardiovascular disease in the Framingham Offspring Study-Implications for LDL Management. J Clin Lipidol 2007; 1: 583-92.
24. Mora S, Caulfield MP, Wohlgemuth J, Chen Z, Superko HR, Rowland CM, et al. Atherogenic lipoprotein subfractions determined by ion mobility and first cardiovascular events after random allocation to high-intensity statin or placebo: The justification for the use of statins in prevention: An intervention trial evaluating rosuvastatin (JUPITER) trial. Circulation 2015; 132: 2220-29.
25. Lawler PR, Akinkuolie AO, Chu AY, Shah SH, Kraus WE, Craig D, et al. Atherogenic lipoprotein determinants of cardiovascular disease and residual risk among individuals with low low-density lipoprotein cholesterol. JAHA 2017; 6: doi.org/10.1161/JAHA.117.005549.
26. Musunuru K, Orho-Melander M, Caulfield MP, Li S, Salameh WA, Reitz RE, et al. Ion mobility analysis of lipoprotein subfractions identifies three independent axes of cardiovascular disease. Arterioscler Thromb Vasc Biol 2009; 29: 1975-80.
27. Krauss RM. All low-density lipoprotein particles are not created equal. Arterioscler Thromb Vasc Biol 2014; 34: 959-61.

28. Boren J, Chapman MJ, Krauss RM, Packard CJ, Bentzon JF, Binder CJ, et al. Low-density lipoprotein cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2020; 0: 1-28.doi:10.1093/eurheartj/ehz962.
29. Athinarayanan SJ, Adams RN, Hallberg SJ, McKenzie AL, Bhanpuri NH, Campbell WW., et al. Long-term effects of a novel continuous remote care intervention including nutritional ketosis for the management of Type 2 diabetes: A 2-yr non-randomized clinical trial. Front Endo 2019; 10, 348: org/10.3389/fendo.2019.00348.
30. Bhanpuri NH, Hallberg SJ, William PT, McKenzie AL, Ballard KD, Campbell WW, et al. Cardiovascular disease risk factor responses to a type 2 diabetes care model including nutritional ketosis induced by sustained carbohydrate restriction at 1 yr: an open label, non-randomized, controlled study. Cardiovasc Diabetol 2018; 17: 56.doi:10.1186/s12933-018-0698-8.
31. Hallberg SJ, McKenzie AL, William PT, Bhanpuri NH, Peters AL, Campbell WW, et al. Effectiveness and safety of a novel care model for the management of type 2 diabetes at 1 yr: an open-label, non-randomized, controlled study. Diabetes Ther 2018; 9: 583-612.
32. McKenzie AL, Hallberg SJ, Creighton BC, Volk BM, Link TM, Abner MK, et al. A novel intervention including individualized nutritional recommendations reduces hemoglobin A1c level, medication use, and weight in Type 2 Diabetes. JMIR Diabetes 2017; 2 :e5. doi:10.2196/diabetes.6981.
33. Choi YJ, Roberts BK, Wang X, Geaney JC, Naim S, Wojnoonski K, et al. Effects of PPAR- Ş agonist MBX-8025 on atherogenic dyslipidemia. Atherosclerosis 2012; 220: 470-76.
34. Kline RB. Principles and Practice of Structural Equation Modeling. 3rd New York: The Guilford Press 2011.
35. Musliner TA, Giotas C, Krauss RM. Presence of multiple subpopulations of lipoproteins of intermediate density in normal subjects. Arteriosclerosis 1986; 6: 79-87.
36. Bergeron N, Chiu S, Williams PT, King SM, Krauss RM. Effects of red meat, white meat, and nonmeat protein sources on atherogenic lipoprotein measures in the context of low compared with high saturated fat intake: a randomized controlled trial. Am J Clin Nutr 2019; 110: 24-33.
37. Sniderman AD, Lamarche B, Contois JH, de Graaf J. Discordance analysis and the Gordian Knot of LDL and non-HDL cholesterol versus apoB. Curr Opin Lipidol 2014; 25: 461-67.
38. Mente A, Dehghan M, Rangarajan S, McQueen M, Dagenais G, Wielgosz A, et al. Association of dietary nutrients with blood lipids and blood pressure in 18 countries: A cross-sectional analysis from the PURE study. Lancet Diabetes Endocrinol 2007; 5: 774-87
39. Davidson WS, Shah AS. High-density lipoprotein subspecies in health and human disease: Focus on Type 2 diabetes. Methodist Debakey Cardiovasc J 2019; 15: 55-61.
40. Duriez P, Fruchart JC. High-density lipoprotein subclasses and apolipoprotein A-I. Clinica Chimica 1999; 97: 97-114.
41. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt, Barbalic M, Jensen MK, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. Lancet 2012; 380: 572-80.
42. Hewing B, Moore KJ, Fisher EA. HDL and Cardiovascular Risk: Time to call the plmuber? Circulation Res 2012; 111: 1117-20.
43. Lamprea-Montealegre JA, McClelland RL, Astor BC, Matsushita K, Shlipak M, de Boer IH, et al. Chronic kidney disease, plasma lipoproteins, and coronoary artery calcium incidence: The Multi-Ethnic Study of Atherosclerosis. Arterioscler Thromb Vasc Biol 2013; 33: 652-58.
44. Aneni EC, Osondu CU, La Cruz JD, Martin SS, Blaha MJ, Younus A, et al. Lipoprotein sub-fractions by ion-mobility analysis and its association with subclinical coronary atherosclerosis in high-risk individuals. J Atheroscler Thromb 2019; 26: 50-63.
45. Siri-Tarino PW, Williams PT, Fernstrom HS, Rawlings RS, Krauss RM. Reversal of small, dense LDL subclass phenotype by normalization of adiposity. Obesity 2009; 17: 1768-75.
46. Krauss RM. Dietary and genetic probes of atherogenic dyslipidemia. Arterioscler Thromb Vasc Biol 2005; 25: 2265-72.
47. Coimbra S, Reis F, Ferreira C, Nunes S, Viana S, Catarino A, et al. Weight loss achieved by bariatric surgery modifies high-density lipoprotein subfractions and low-density lipoprotein oxidation towards atheroprotection. Clin Biochem 2019; 63: 46-53.

Tables

Table 1
Baseline characteristics

	All		Completers with data		Dropout or missing data		Completers-Dropouts
	N	Mean (SD) or ± SE	N	Mean (SD) or ± SE	N	Mean (SD) or ± SE	Mean ± SE
Age (years)	262	53.8(8.4)	194	54.4(8.2)	68	51.9(8.7)	2.5 ± 1.2
CCI	87	52.3(9.5)	68	51.4(9.4)	19	55.6(9.5)	-4.2 ± 2.4
Usual Care		1.4 ± 1.1		3.0 ± 1.2		-3.6 ± 2.4	
CCI vs. usual care							
African American (%)	262	6.9 ± 1.6	194	6.2 ± 1.7	68	8.8 ± 3.5	-2.6 ± 3.6
CCI	87	0.0 ± 0.0	68	0.0 ± 0.0	19	0.0 ± 0.0	—
Usual Care		6.9 ± 1.6*		6.2 ± 1.7*		8.8 ± 3.5	
CCI vs. usual care							
Body mass index (kg/m^2)	257	40.42(8.81)	190	40.41(8.42)	67	40.46(9.90)	-0.05 ± 1.25
CCI	83	36.72(7.26)	64	36.90(7.41)	19	36.11(6.89)	0.79 ± 1.91
Usual Care		3.70 ± 1.07*		3.51 ± 1.18		4.34 ± 2.43	
CCI vs. usual care							
Female (%)	262	66.79 ± 2.92	194	65.98 ± 3.41	68	69.12 ± 5.64	-3.14 ± 6.66
CCI	87	58.62 ± 5.31	68	60.29 ± 5.98	19	52.63 ± 11.77	7.66 ± 12.90
Usual Care		8.17 ± 6.06		5.69 ± 6.76		6.49 ± 12.35	
CCI vs. usual care							
Years since type 2 diabetes diagnosis	261	8.44(7.22)	193	8.15(7.02)	68	9.25(7.75)	-1.1 ± 1.02
CCI	71	7.85(7.32)	63	7.90(7.41)	8	7.38(7.05)	0.53 ± 2.77
Usual Care		0.59 ± 0.97		0.25 ± 1.03		1.88 ± 2.87	
CCI vs. usual care							
Cardiovascular Markers							
Systolic blood pressure (mmHg)	260	131.9(14.1)	192	132.2(14.2)	68	131.1(13.8)	1.2 ± 2.0
CCI	79	129.8(13.6)	61	129.0(13.6)	18	132.7(13.5)	-3.7 ± 3.7
Usual Care		2.1 ± 1.8		3.3 ± 2.1		-1.6 ± 3.6	
CCI vs. usual care							
Diastolic blood pressure (mmHg)	260	82.1(8.3)	192	81.7(8.0)	68	83.4(8.9)	-1.7 ± 1.2
CCI	79	82.0(8.9)	61	82.1(8.8)	18	81.8(9.6)	0.3 ± 2.4
Usual Care		0.1 ± 1.1		-0.4 ± 1.2		1.6 ± 2.4	
CCI vs. usual care							

Note. Abbreviations: SD, standard deviation; SE, standard error; CCI, continuous care intervention; UC, usual care; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IDL, intermediate density lipoprotein; VLDL, very low density lipoprotein; ACE, angiotensin converting enzyme inhibitors; ARB, angiotensin-receptor blockers.

*A significance level of $P < 0.0015$ ensures overall simultaneous significance of $P < 0.05$ over the 33 variables using Bonferroni correction.

	All		Completers with data		Dropout or missing data		Completers-Dropouts
Total cholesterol (mg/dL)	247	183.6(41.2)	184	181.9(40.3)	63	188.7(43.6)	-6.8 ± 6.0
CCI	79	183.8(45.8)	62	186.5(49.3)	17	174.0(28.7)	12.5 ± 12.5
Usual Care		-0.2 ± 5.5		-4.6 ± 6.3		14.7 ± 11.2	
CCI vs. usual care							
LDL-C(mg/dL)	232	102.5(32.9)	173	101.1(33.0)	59	106.6(32.6)	-5.5 ± 5.0
CCI	70	101.5(36.2)	56	103.8(38.3)	14	92.3(24.8)	11.5 ± 10.8
Usual Care		1.0 ± 4.6		-2.7 ± 5.3		14.3 ± 9.3	
CCI vs. usual care							
HDL-C(mg/dL)	247	42.2(13.4)	184	42.5(13.7)	63	41.3(12.7)	1.1 ± 2.0
CCI	79	37.6(11.2)	62	38.3(11.5)	17	35.2(10.1)	3.0 ± 3.1
Usual Care		4.6 ± 1.7		4.2 ± 1.9		6.1 ± 3.3	
CCI vs. usual care							
Triglycerides (mg/dL)	247	197.2(143.4)	184	200.7(153.5)	63	187.1(109.0)	13.5 ± 21.0
CCI	79	282.9(401.2)	62	283.7(443.6)	17	280.0(185.0)	3.7 ± 110.5
Usual Care		-85.7 ± 46.1		-83.0 ± 57.5		-92.9 ± 46.9	
CCI vs. usual care							
non-HDL (mg/dL)	247	141.4(41.1)	184	139.4(39.8)	63	147.4(44.4)	-8.0 ± 6.0
CCI	79	146.2(46.5)	62	148.2(50.7)	17	138.8(26.1)	9.4 ± 12.8
Usual Care		-4.7 ± 5.5		-8.8 ± 7.1		8.6 ± 11.3	
CCI vs. usual care							
Remnant cholesterol (mg/dL)	232	34.2(15.1)	173	34.5(15.6)	59	33.1(13.8)	1.5 ± 2.3
CCI	70	37.4(16.6)	56	36.3(16.6)	14	41.9(16.5)	-5.6 ± 5.0
Usual Care		-3.2 ± 2.1		-1.8 ± 2.4		-8.8 ± 4.3	
CCI vs. usual care							

Note. Abbreviations: SD, standard deviation; SE, standard error; CCI, continuous care intervention; UC, usual care; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IDL, intermediate density lipoprotein; VLDL, very low density lipoprotein; ACE, angiotensin converting enzyme inhibitors; ARB, angiotensin-receptor blockers.

*A significance level of P < 0.0015 ensures overall simultaneous significance of P < 0.05 over the 33 variables using Bonferroni correction.

	All		Completers with data		Dropout or missing data		Completers-Dropouts
Lipoproteins and Apoproteins							
VLDL Large (nmol/L)	240	23.3(13.8)	179	22.7(13.8)	61	24.8(13.6)	-2.1 ± 2.0
CCI	80	27.6(16.0)	62	26.4(16.1)	18	31.7(15.5)	-5.3 ± 4.3
Usual Care		-4.4 ± 1.9		-3.7 ± 2.1		-6.9 ± 3.8	
CCI vs. usual care							
VLDL Intermediate (nmol/L)	240	56.6(24.3)	179	55.3(24.5)	61	60.2(23.7)	-4.9 ± 3.6
CCI	80	64.7(28.2)	62	63.4(29.7)	18	69.1(22.5)	-5.8 ± 7.6
Usual Care		-8.1 ± 3.3		-8.0 ± 3.8		-8.9 ± 6.3	
CCI vs. usual care							
VLDL Small (nmol/L)	240	59.7(18.9)	179	58.2(18.7)	61	64.1(19.2)	-5.9 ± 2.8
CCI	80	62.5(21.9)	62	62.5(23.7)	18	62.7(14.7)	-0.2 ± 5.9
Usual Care		-2.9 ± 2.5		-4.3 ± 3.0		1.4 ± 4.2	
CCI vs. usual care							
IDL 1 (nmol/L)	240	137.7(42.1)	179	134.3(40.9)	61	147.9(44.1)	-13.6 ± 6.2
CCI	80	143.4(44.2)	62	143.6(48.2)	18	142.8(27.0)	0.8 ± 11.9
Usual Care		-5.7 ± 5.5		-9.3 ± 6.3		5.1 ± 11.0	
CCI vs. usual care							
IDL 2 (nmol/L)	240	125.2(41.3)	179	123.1(41.6)	61	131.5(40.1)	-8.4 ± 6.1
CCI	80	119.5(38.5)	62	122.9(42.1)	18	107.8(19.0)	15.1 ± 7.0
Usual Care		5.7 ± 5.2		0.2 ± 6.2		23.7 ± 6.8*	
CCI vs. usual care							
LDL I (nmol/L)	240	166.2(68.0)	179	164.4(69.2)	61	171.4(64.7)	-7.0 ± 10.1
CCI	80	156.9(69.6)	62	163.6(75.2)	18	133.8(39.1)	29.8 ± 18.5
Usual Care		9.3 ± 8.8		0.9 ± 10.4		37.6 ± 16.1	
CCI vs. usual care							
LDL IIa (nmol/L)	240	140.8(59.8)	179	138.0(59.0)	61	149.1(61.9)	-11.1 ± 8.9
CCI	80	139.3(63.8)	62	142.7(67.8)	18	127.6(47.4)	15.0 ± 14.1
Usual Care		1.5 ± 7.9		-4.7 ± 9.0		21.5 ± 15.8	
CCI vs. usual care							
LDL IIb (nmol/L)	240	179.6(70.2)	179	175.4(67.4)	61	191.8(77.0)	-16.4 ± 11.1
CCI	80	190.5(82.8)	62	188.9(86.3)	18	196.3(71.3)	-7.4 ± 22.3
Usual Care		-10.9±-9.5		-13.4 ± 10.7		-4.5 ± 20.3	
CCI vs. usual care							

Note. Abbreviations: SD, standard deviation; SE, standard error; CCI, continuous care intervention; UC, usual care; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IDL, intermediate density lipoprotein; VLDL, very low density lipoprotein; ACE, angiotensin converting enzyme inhibitors; ARB, angiotensin-receptor blockers.

*A significance level of P < 0.0015 ensures overall simultaneous significance of P < 0.05 over the 33 variables using Bonferroni correction.

	All		Completers with data		Dropout or missing data		Completers-Dropouts
LDL IIIa (nmol/L)	240	192.0(95.1)	179	189.7(91.4)	61	198.6(106.0)	-8.8 ± 14.1
CCI	80	207.6(92.0)	62	202.2(96.1)	18	226.4(75.5)	-24.3 ± 24.6
Usual Care		-15.7 ± 12.2		-12.5 ± 13.6		-27.9 ± 26.8	
CCI vs. usual care							
LDL IIIb (nmol/L)	240	87.0(57.2)	179	87.3(54.7)	61	86.1(64.5)	1.2 ± 8.5
CCI	80	100.1(58.1)	62	98.7(62.1)	18	105.1(42.4)	-6.5 ± 15.6
Usual Care		-13.1 ± 7.4		-11.3 ± 8.4		-19.0 ± 16.2	
CCI vs. usual care							
LDL IVa (nmol/L)	240	91.6(51.5)	179	92.3(51.4)	61	89.5(52.4)	2.8 ± 7.7
CCI	80	114.9(70.8)	62	114.5(76.8)	18	116.2(46.6)	-1.7 ± 19.1
Usual Care		-23.3 ± 8.6		-22.2 ± 10.5		-26.7 ± 13.7	
CCI vs. usual care							
LDL IVb (nmol/L)	240	79.6(28.6)	179	79.5(29.3)	61	79.7(26.6)	-0.2 ± 4.2
CCI	80	96.9(45.1)	62	94.1(44.2)	18	106.7(48.3)	-12.7 ± 12.1
Usual Care		-17.3 ± 5.4		-14.5 ± 6.0		-27.0 ± 8.8	
CCI vs. usual care							
LDL IVc (nmol/L)	240	89.5(21.7)	179	88.9(22.3)	61	91.2(19.8)	-2.3 ± 3.2
CCI	80	101.7(35.8)	62	99.3(33.3)	18	109.8(43.3)	-10.5 ± 9.6
Usual Care		-12.2 ± 4.2		-10.4 ± 3.8		-18.6 ± 10.5	
CCI vs. usual care							
Mid Zone (nmol/L)	240	878.1(161.5)	179	869.7(165.4)	61	902.5(148.0)	-32.8 ± 23.9
CCI	80	948.8(179.7)	62	930.6(180.9)	18	1011.3(165.3)	-80.7 ± 47.5
Usual Care		-70.7 ± 21.5*		-60.9 ± 25.0		-108.8(40.8)	
CCI vs. usual care							
HDL 2b (µmol/L)	240	5.9(1.2)	179	5.9(1.2)	61	6.1(1.3)	-0.3 ± 0.2
CCI	80	6.3(0.9)	62	6.3(1.0)	18	6.3(0.9)	-0.0 ± 0.3
Usual Care		-0.3 ± 0.1		-0.4 ± 0.2		-0.1 ± 0.3	
CCI vs. usual care							
HDL 2a + 3 (µmol/L)	240	16.8(2.6)	179	16.8(2.6)	61	16.9(2.5)	-0.0 ± 0.3
CCI	80	19.3(2.8)	62	19.3(2.8)	18	19.4(2.5)	-0.0 ± 0.7
Usual Care		-2.5 ± 0.3*		-2.5 ± 0.4*		-2.5 ± 0.7*	
CCI vs. usual care							

Note. Abbreviations: SD, standard deviation; SE, standard error; CCI, continuous care intervention; UC, usual care; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IDL, intermediate density lipoprotein; VLDL, very low density lipoprotein; ACE, angiotensin converting enzyme inhibitors; ARB, angiotensin-receptor blockers.

*A significance level of $P < 0.0015$ ensures overall simultaneous significance of $P < 0.05$ over the 33 variables using Bonferroni correction.

	All		Completers with data		Dropout or missing data		Completers-Dropouts
LDL peak diameter (Å)	240	215.7(6.2)	179	215.6(6.3)	61	215.9(6.0)	-0.3 ± 0.9
CCI	80	213.3(6.5)	62	213.9(6.4)	18	211.3(6.4)	-2.6 ± 1.7
Usual Care		2.4 ± 0.8		1.7 ± 0.9		-4.6 ± 1.6	
CCI vs. usual care							
Total ApoB	248	105.1(28.8)	185	104.2(28.7)	63	107.7(29.4)	-3.5 ± 4.2
CCI	79	106.9(28.3)	62	108.3(31.0)	17	101.8(13.7)	6.5 ± 5.1
Usual Care		-1.9 ± 3.7		-4.2 ± 4.3		5.9 ± 7.4	
CCI vs. usual care							
Total ApoA1	248	145.7(27.6)	185	146.0(28.6)	63	145.0(24.8)	1.0 ± 4.0
CCI	79	148.7(21.5)	62	149.5(22.0)	17	145.9(19.9)	3.6 ± 5.9
Usual Care		-3.0 ± 3.4		-3.5 ± 4.0		-0.9 ± 6.5	
CCI vs. usual care							
ApoB:Apo A1 Ratio	248	0.7(0.2)	185	0.7(0.2)	63	0.8(0.2)	-0.0 ± 0.0
CCI	79	0.7(0.2)	62	0.7(0.3)	17	0.7(0.1)	-0.0 ± 0.0
Usual Care		0.0 ± 0.0		-0.0 ± 0.0		0.1 ± 0.1	
CCI vs. usual care							
LDL Phenotype Pattern A (%)	201	41.8 ± 3.5	151	43.0 ± 4.0	50	38.0 ± 6.9	-5.0 ± 8.1
CCI	62	25.8 ± 5.6	50	32.0 ± 6.7	12	0.0 ± 0.0	-32.0 ± 6.7 *
Usual Care		16.0 ± 6.6		11.0 ± 7.8		38.0 ± 6.9 *	
CCI vs. usual care							

Note. Abbreviations: SD, standard deviation; SE, standard error; CCI, continuous care intervention; UC, usual care; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IDL, intermediate density lipoprotein; VLDL, very low density lipoprotein; ACE, angiotensin converting enzyme inhibitors; ARB, angiotensin-receptor blockers.

*A significance level of P < 0.0015 ensures overall simultaneous significance of P < 0.05 over the 33 variables using Bonferroni correction.

	All		Completers with data		Dropout or missing data		Completers-Dropouts
LDL Phenotype Pattern B (%)	201	58.2 ± 3.5	151	57.0 ± 4.0	61	62.0 ± 6.9	-5.0 ± 8.1
CCI	62	74.2 ± 5.6	50	68.0 ± 6.7	18	100.0 ± 0.0	-32.0 ± 6.7 *
Usual Care		-16.0 ± 6.6		11.0 ± 7.8		38.0 ± 6.9 *	
CCI vs. usual care							
Medication							
Statin (%)	262	50.0 ± 5.3	194	53.0 ± 3.6	68	43.0 ± 6.0	-10.0 ± 7.0
CCI	87	59.0 ± 3.1	68	54.0 ± 6.1	19	74.0 ± 10.4	-19.3 ± 12.0
Usual Care		-8.6 ± 6.1		-1.8 ± 7.1		-31.0 ± 12.7	
CCI vs. usual care							
Any antihypertensive medication (%)	262	77.5 ± 2.6	194	76.8 ± 3.0	68	79.4 ± 4.9	-2.6 ± 5.9
CCI	87	65.5 ± 5.1	68	63.2 ± 5.9	19	73.7 ± 10.4	-10.4 ± 12.4
Usual Care		12.0 ± 5.4		13.6 ± 6.6		5.7 ± 10.8	
CCI vs. usual care							
ACE and ARB (%)	262	65.0 ± 3.0	194	62.0 ± 3.5	68	74.0 ± 5.4	-11.7 ± 6.7
CCI	87	55.0 ± 5.4	68	51.0 ± 6.1	19	68.0 ± 11.0	-17.0 ± 12.5
Usual Care		9.7 ± 6.0		10.4 ± 6.9		-5.1 ± 11.7	
CCI vs. usual care							
Diuretics (%)	262	41.0 ± 3.0	194	41.0 ± 3.5	68	41.0 ± 6.0	-0.5 ± 7.0
CCI	87	29.0 ± 4.9	68	24.0 ± 5.2	19	47.0 ± 11.8	-23.8 ± 12.9
Usual Care		12.1 ± 6.0		17.2 ± 6.3		-6.2 ± 13.0	
CCI vs. usual care							
Other Lipid Lowering Medication (%)	262	10.3 ± 1.9	194	9.3 ± 2.1	68	13.2 ± 4.1	-4.0 ± 4.3
CCI	87	19.5 ± 4.3	68	17.6 ± 4.7	19	26.3 ± 10.4	-8.7 ± 10.4
Usual Care		-9.2 ± 4.7		-8.4 ± 4.5		-13.1 ± 11.1	
CCI vs. usual care							

Note. Abbreviations: SD, standard deviation; SE, standard error; CCI, continuous care intervention; UC, usual care; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IDL, intermediate density lipoprotein; VLDL, very low density lipoprotein; ACE, angiotensin converting enzyme inhibitors; ARB, angiotensin-receptor blockers.

*A significance level of $P < 0.0015$ ensures overall simultaneous significance of $P < 0.05$ over the 33 variables using Bonferroni correction.

Table 2
Adjusted means and changes in lipids, lipoproteins, apoproteins, blood pressure, and CIMT over time by treatment group among completers

Variables	Visit	Continuous Care Intervention (n = 194)		Usual Care (n = 68)		Between Group Effect	
		Mean ± SE	Change from baseline (Mean, CI)	Mean ± SE	Change from baseline (Mean, CI)	Mean Difference	95% CI
Lipids, blood pressure, and CIMT							
Total Cholesterol (mg/dL)	**Baseline**	184.0 ± 3.4		174.2 ± 6.2		9.8	-4.3 to 24.0
	1 yr	194.8 ± 3.5	10.8, 1.3 to 20.2	168.5 ± 6.7	-5.8, -23.0 to 11,5	26.4 *	11.3 to 41.4 *
	2 yrs	195.6 ± 3.4	11.6, 2.3 to 20.8	171.9 ± 6.2	-2.3, -18.9 to 14.2	23.7 *	9.6 to 37.8 *
LDL-C(mg/dL)	**Baseline**	102.7 ± 2.8		99.2 ± 5.1		3.5	-8.0 to 15.0
	1 yr	114.0 ± 2.8	11.3, 3.6 to 19.0 *	87.6 ± 5.5	-11.6, -25.8 to 2.6	26.4 *	14.0 to 38.8 *
	2 yrs	115.0 ± 2.8	12.3,4.7 to 19.9 *	89.6 ± 5.1	-9.6, -23.1 to 4.0	25.4 *	13.8 to 36.9 *
HDL-C(mg/dL)	**Baseline**	43.3 ± 1.1		38.2 ± 1.9		5.2	0.8 to 9.6
	1 yr	51.7 ± 1.1	8.4, 5.5 to 11.3 *	35.1 ± 2.1	-3.1, -8.4 to 2.3	16.6 *	11.9 to 21.3 *
	2 yrs	51.2 ± 1.1	7.9, 5.0 to 10.8 *	40.9 ± 1.9	2.8, -2.4 to 7.9	10.3*	5.9 to 14.7
Triglycerides (mg/dL)[b]	**Baseline**	196.0 ± 12.1		226.5 ± 45.4		-30.5	-96.1 to 35.1
	1 yr	137.2 ± 9.2	-58.8, -36.2 to -82.3 *	239.5 ± 34.2	13.0, -95.3 to 96.6	-102.3 *	-173.5 to − 31.1 *
	2 yrs	154.8 ± 10.8	-41.2, -14.7 to -67.7 *	210.8 ± 19.9	-15.7, -99.3 to 41.6	-56.0	-99.8 to − 12.3
Systolic Blood Pressure (mmHg)	**Baseline**	131.9 ± 1.1		130.1 ± 2.0		1.7	-2.9 to 6.4
	1 yr	125.6 ± 1.2	-6.2, -9.3 to − 3.1 *	128.8 ± 2.0	-1.3, -6.7 to 4.0	-3.2	-7.9 to 1.6
	2 yrs	125.8 ± 1.1	-6.1, -9.1 to − 3.1 *	129.9 ± 2.0	-0.2, -5.5 to 5.2	-4.2	-8.8 to 0.5
Diastolic Blood Pressure (mmHg)	**Baseline**	81.7 ± 0.6		80.5 ± 1.2		1.2	-1.5 to 4.0
	1 yr	78.1 ± 0.7	-3.6, -5.4 to − 1.8 *	81.3 ± 1.2	0.8, -2.3 to 3.9	-3.2	-5.9 to − 0.4
	2 yrs	78.5 ± 0.6	-3.2, -4.9 to − 1.4 *	81.1 ± 1.2	0.7, -2.5 to 3.8	-2.6	-5.3 to 0.1

Abbreviations. SE, standard error; CI, 95% confidence interval; LDL, low density lipoprotein; HDL, high-density lipoprotein; IDL, intermediate density lipoprotein; VLDL, very low-density lipoprotein; CIMT, carotid intima-media thickness.

Note. Adjusted means and mean changes were obtained from an analysis using linear mixed-effects model (LMM) controlling for baseline age, sex, race, body mass index, HDL 2+3a, mid-zone, insulin use and statin use. a Variables normalized by removing the top 1% of values. Analyses were conducted excluding the top 1% values, although all cases were included using the maximum likelihood approach. b Variables normalized by natural log transformation. Non-transformed and unadjusted means, mean changes, CI and standard errors were provided in the table, but the significance level is calculated from the transformed analysis * P<0.0015 ensures overall simultaneous significance of P<0.05 over the 33 variables using Bonferroni correction Ï P<0.005

Variables	Visit	Continuous Care Intervention (n = 194)		Usual Care (n = 68)		Between Group Effect	
non-HDL (mg/dL)	**Baseline**	140.5 ± 3.4		136.1 ± 6.2		4.4	-9.7 to 18.6
	1 yr	143.1 ± 3.5	2.6, -6.9 to 12.0	133.4 ± 6.7	-2.7, -19.9 to 14.5	9.7	-5.3 to 24.8
	2 yrs	144.4 ± 3.4	3.9, -5.4 to 13.2	131.0-±6.2	-5.1, -21.6 to 11.5	13.4	-0.7 to 27.6
Remnant Cholesterol (mg/dL)	**Baseline**	33.5 ± 1.0		31.1 ± 1.9		2.5	-1.9 to 6.8
	1 yr	23.7 ± 1.1	-9.9, -12.8 to − 7.0 *	31.8 ± 2.1	0.7, -4.6 to 6.1	-8.1 *	-12.8 to − 3.5 *
	2 yrs	26.0 ± 1.0	-7.5, -10.4 to − 4.7 *	30.9 ± 1.9	-0.2, -5.3 to 4.9	-4.9	-9.2 to − 0.5
CIMT	**Baseline**	0.68 ± 0.01		0.69 ± 0.02		-0.01	-0.05 to 0.03
	1 yr	0.68 ± 0.01	0.00, -0.03 to 0.03	0.69 ± 0.02	0.00, -0.04 to 0.05	-0.01	-0.05 to 0.03
	2 yrs	0.67 ± 0.01	-0.01, -0.04 to 0.02	0.70 ± 0.02	0.01, -0.04 to 0.06	-0.03	-0.07 to 0.01
Apoproteins							
Total ApoB	**Baseline**	103.9 ± 2.2		101.1 ± 4.1		2.8	-6.5 to 12.2
	1 yr	104.5 ± 2.3	0.5, -5.7 to 6.8	102.3 ± 4.4	1.2, -10.2 to 12.7	2.1	-7.8 to 12.1
	2 yrs	101.3 ± 2.2	-2.6, -8.7 to 3.6	98.8 ± 4.1	-2.3, -13.2 to 8.7	2.5	-6.9 to 11.9
Total ApoA1	**Baseline**	148.1 ± 2.2		144.2 ± 4.0		2.8	-6.5 to 12.2
	1 yr	163.5 ± 2.2	15.3, 9.3 to 21.4 *	138.8 ± 4.3	1.2, -10.2 to 12.7	2.1	-7.8 to 12.1
	2 yrs	164.3 ± 2.2	16.2, 10.2 to 22.2 *	137.0 ± 4.0	-2.3, -13.2 to 8.7	2.5	-6.9 to 11.9
ApoB: ApoA1 ratio	**Baseline**	0.7 ± 0.0		0.7 ± 0.0		0.0	-0.1 to 0.1
	1 yr	0.7 ± 0.0	-0.1, -0.1 to − 0.0	0.8 ± 0.0	0.0, -0.1 to 0.1	-0.1	-0.2 to − 0.0
	2 yrs	0.6 ± 0.0	-0.1, -0.1 to − 0.0 Ï	0.7 ± 0.0	0.0, -0.1 to 0.1	-0.1	-0.2 to -0.0
Lipoproteins							
Total VLDL (nmol/L)	**Baseline**	138.6 ± 5.7		144.0 ± 8.4		-5.3	-25.4 to 14.8
	1 yr	128.7 ± 5.8	-9.9, -25.8 to 5.9	146.9 ± 8.7	3.0, -20.3 to 26.2	-18.2	-39.0 to 2.5

Abbreviations. SE, standard error; CI, 95% confidence interval; LDL, low density lipoprotein; HDL, high-density lipoprotein; IDL, intermediate density lipoprotein; VLDL, very low-density lipoprotein; CIMT, carotid intima-media thickness.

Note. Adjusted means and mean changes were obtained from an analysis using linear mixed-effects model (LMM) controlling for baseline age, sex, race, body mass index, HDL 2+3a, mid-zone, insulin use and statin use. a Variables normalized by removing the top 1% of values. Analyses were conducted excluding the top 1% values, although all cases were included using the maximum likelihood approach. b Variables normalized by natural log transformation. Non-transformed and unadjusted means, mean changes, CI and standard errors were provided in the table, but the significance level is calculated from the transformed analysis * P<0.0015 ensures overall simultaneous significance of P<0.05 over the 33 variables using Bonferroni correction Ï P<0.005

Variables	Visit	Continuous Care Intervention (n = 194)		Usual Care (n = 68)		Between Group Effect	
	2 yrs	129.3 ± 5.9	-9.3, -25.3 to 6.6	144.1 ± 8.7	0.2, -23.0 to 23.4	-14.8	-35.7 to 6.0
VLDL Large (nmol/L)	**Baseline**	23.9 ± 1.0		22.2 ± 1.7		1.7	-2.3 to 5.7
	1 yr	19.1 ± 1.0	-4.8, -7.6 to − 2.0 *	22.7 ± 1.8	0.5, -4.3 to 5.2	-3.6	-7.7 to 0.6
	2 yrs	20.3 ± 1.0	-3.6, -6.4 to − 0.8	21.9 ± 1.7	-0.3, -5.0 to 4.4	-1.6	-5.7 to 2.4
VLDL Medium (nmol/L)	**Baseline**	57.3 ± 1.8		55.2 ± 3.1		2.1	-5.2 to 9.3
	1 yr	52.3 ± 1.8	-5.0, -10.0 to 0.0	54.6 ± 3.2	-0.5, -9.1 to 8.0	-2.4	-9.8 to 5.1
	2 yrs	52.5 ± 1.8	-4.7, -9.7 to 0.3	54.7 ± 3.1	-0.5, -8.9 to 7.9	-2.2	-9.4 to 5.1
VLDL Small (nmol/L)	**Baseline**	59.3 ± 1.5		55.8 ± 2.6		3.4	-2.6 to 9.5
	1 yr	63.2 ± 1.5	3.9, -0.3 to 8.1	55.0 ± 2.7	-0.8, -8.0 to 6.3	8.2	2.0 to 14.4
	2 yrs	59.2 ± 1.5	-0.1, -4.3 to 4.1	54.9 ± 2.6	-0.9, -8.0 to 6.1	4.3	-1.8 to 10.4
Total IDL (nmol/L)	**Baseline**	256.6 ± 8.0		255.1 ± 11.9		1.6	-27.0 to 30.1
	1 yr	285.1 ± 8.3	28.4, 5.9 to 50.9	256.1 ± 12.3	1.1, -32.0 to 34.1	28.9	-0.6 to 58.4
	2 yrs	288.9 ± 8.4	32.2, 9.6 to 54.9 Ï	261.5 ± 12.3	6.4, -26.5 to 39.4	27.3	-2.3 to 57.0
IDL 1 (nmol/L)	**Baseline**	136.2 ± 3.3		129.2 ± 5.7		7.0	-6.2 to 20.1
	1 yr	139.4 ± 3.3	3.2, -5.9 to 12.3	128.8 ± 5.9	-0.4, -15.9 to 15.0	10.6	-2.9 to 24.1
	2 yrs	136.4 ± 3.3	0.2, -8.9 to 9.2	128.3 ± 5.7	-0.9, -16.1 to 14.3	8.0	-5.1 to 21.1
IDL 2 (nmol/L)	**Baseline**	122.1 ± 3.8		113.3 ± 6.5		8.8	-6.3 to 23.8
	1 yr	152.1 ± 3.8	30.0, 19.6 to 40.4 *	112.0 ± 6.7	-1.3, -19.0 to 16.4	40.1 *	24.6 to 55.5 *
	2 yrs	156.3 ± 3.8	34.2, 23.9 to 44.6 *	114.0 ± 6.5	0.7, -16.7 to 18.1	42.3 *	27.2 to 57.3 *
Total LDL (nmol/L)	**Baseline**	991.8 ± 25.9		1028.7 ± 40.8		-36.9	-132.7 to 58.9
	1 yr	962.7 ± 26.8	-29.1, -101.9 to 43.7	1026.5 ± 43.1	-2.2, -117.2 to 112.8	-63.8	-164.4 to 36.8

Abbreviations. SE, standard error; CI, 95% confidence interval; LDL, low density lipoprotein; HDL, high-density lipoprotein; IDL, intermediate density lipoprotein; VLDL, very low-density lipoprotein; CIMT, carotid intima-media thickness.

Note. Adjusted means and mean changes were obtained from an analysis using linear mixed-effects model (LMM) controlling for baseline age, sex, race, body mass index, HDL 2+3a, mid-zone, insulin use and statin use. a Variables normalized by removing the top 1% of values. Analyses were conducted excluding the top 1% values, although all cases were included using the maximum likelihood approach. b Variables normalized by natural log transformation. Non-transformed and unadjusted means, mean changes, CI and standard errors were provided in the table, but the significance level is calculated from the transformed analysis * P<0.0015 ensures overall simultaneous significance of P<0.05 over the 33 variables using Bonferroni correction Ï P<0.005

Variables	Visit	Continuous Care Intervention (n = 194)		Usual Care (n = 68)		Between Group Effect	
	2 yrs	1002.0 ± 27.0	10.3, -62.8 to 83.4	1022.1 ± 42.3	-6.6, -120.2 to 107.0	-20.0	-119.6 to 79.6
LDL I (nmol/L)	**Baseline**	163.5 ± 6.0		155.6 ± 10.3		7.9	-16.0 to 31.8
	1 yr	207.7 ± 6.1	44.2, 27.6 to 60.7 *	146.1 ± 10.7	-9.6, -37.7 to 18.6	61.7 *	37.1 to 86.2 *
	2 yrs	211.1 ± 6.0	47.6, 31.1 to 64.0 *	152.9 ± 10.3	-2.8, -30.4 to 24.9	58.2 *	34.3 to 82.1 *
LDL IIa (nmol/L)	**Baseline**	137.8 ± 4.7		135.8 ± 8.0		2.0	-16.6 to 20.5
	1 yr	153.4 ± 4.7	15.6, 2.7 to 28.4	126.5 ± 8.3	-9.3, -31.1 to 12.5	26.9	7.8 to 45.9
	2 yrs	156.1 ± 4.7	18.3, 5.5 to 31.1 Ï	129.2 ± 8.0	-6.6, -28.0 to 14.8	26.9 Ï	8.4 to 45.4 Ï
LDL IIb (nmol/L)	**Baseline**	176.0 ± 5.6		170.1 ± 9.5		6.0	-16.1 to 28.0
	1 yr	169.7 ± 5.6	-6.3, -21.6 to 9.0	166.0 ± 9.9	-4.1, -30.0 to 21.9	3.7	-19.0 to 26.3
	2 yrs	174.9 ± 5.6	-1.1, -16.3 to 14.2	171.4 ± 9.5	1.3, -24.3 to 26.9	3.6	-18.5 to 25.7
LDL IIIa (nmol/L)	**Baseline**	191.5 ± 7.3		169.8 ± 12.6		21.7	-7.4 to 50.8
	1 yr	157.4 ± 7.4	-34.0, -54.2 to − 13.9 *	187.2 ± 13.0	17.4, -16.7 to 51.6	-29.8	-59.6 to 0.1
	2 yrs	161.1 ± 7.3	-30.3, -50.4 to − 10.3 Ï	193.5 ± 12.6	23.8, -9.9 to 57.4	-32.4	-61.5 to − 3.3
LDL IIIb (nmol/L)	**Baseline**	87.8 ± 4.4		84.7 ± 7.6		3.1	-14.6 to 20.7
	1 yr	66.5 ± 4.5	-21.2, -33.5 to − 9.0 *	98.0 ± 7.9	13.3, -7.5 to 34.1	-31.5 *	-49.6 to − 13.4*
	2 yrs	67.5 ± 4.4	-20.3, -32.5 to − 8.1 *	96.5 ± 7.6	11.8, -8.7 to 32.2	-29.0 *	-46.6 to − 11.3 *
LDL IVa (nmol/L)[a]	**Baseline**	89.1 ± 3.2		95.0 ± 5.6		-5.9	-18.7 to 6.9
	1 yr	76.4 ± 3.2	-12.7, -21.4 to − 4.0 Ï	93.1 ± 5.9	-1.9, -17.4 to 13.6	-16.7	-30.0 to − 3.4
	2 yrs	76.9 ± 3.2	-12.2, -20.9 to − 3.6	89.9 ± 5.6	-5.1, -20.2 to 10.1	-13.1	-25.9 to − 0.2
LDL IVb (nmol/L)[a]	**Baseline**	78.3 ± 1.8		82.8 ± 3.2		-4.5	-11.8 to 2.8
	1 yr	71.6 ± 1.8	-6.7, -11.7 to − 1.7	82.7 ± 3.3	-0.1, -8.8 to 8.6	-11.1 Ï	-18.6 to − 3.6 Ï

Abbreviations. SE, standard error; CI, 95% confidence interval; LDL, low density lipoprotein; HDL, high-density lipoprotein; IDL, intermediate density lipoprotein; VLDL, very low-density lipoprotein; CIMT, carotid intima-media thickness.

Note. Adjusted means and mean changes were obtained from an analysis using linear mixed-effects model (LMM) controlling for baseline age, sex, race, body mass index, HDL 2+3a, mid-zone, insulin use and statin use. a Variables normalized by removing the top 1% of values. Analyses were conducted excluding the top 1% values, although all cases were included using the maximum likelihood approach. b Variables normalized by natural log transformation. Non-transformed and unadjusted means, mean changes, CI and standard errors were provided in the table, but the significance level is calculated from the transformed analysis * P<0.0015 ensures overall simultaneous significance of P<0.05 over the 33 variables using Bonferroni correction Ï P<0.005

Variables	Visit	Continuous Care Intervention (n = 194)		Usual Care (n = 68)		Between Group Effect	
	2 yrs	73.2 ± 1.8	-5.1, -10.1 to − 0.2	81.5 ± 3.2	-1.3, -9.9 to 7.5	-8.3	-15.6 to − 1.0
LDL IVc (nmol/L)[a]	Baseline	88.9 ± 1.3		89.6 ± 2.2		-0.6	-5.8 to 4.5
	1 yr	83.6 ± 1.3	-5.3, -8.8 to − 1.7 Ï	88.6 ± 2.3	-0.9, -7.1 to 5.2	-5.0	-10.3 to 0.3
	2 yrs	84.0 ± 1.3	-5.0, -8.5 to − 1.4	85.7 ± 2.2	-3.8, -9.8 to 2.2	-1.8	-6.9 to 3.4
Mid-zone (nmol/L)	Baseline	875.3 ± 8.6		892.2 ± 14.7		-16.9	-50.9 to 17.1
	1 yr	828.6 ± 8.6	-46.6, -70.2 to − 23.1 *	890.5 ± 15.2	-1.7, -41.8 to 38.3	-61.8 *	-96.7 to − 26.9 *
	2 yrs	815.4 ± 8.6	-59.9, -83.4 to − 36.4 *	876.0 ± 14.7	-16.2, -55.6 to 23.2	-60.6 *	-94.6 to − 26.5 *
Total HDL	Baseline	22.9 ± 0.3		25.1 ± 0.5		-2.2	-3.4 to − 0.9
	1 yr	22.8 ± 0.4	-0.2, -1.1 to 0.8	24.8 ± 0.5	-0.3, -1.7 to 1.1	-2.0	-3.3 to − 0.7
	2 yrs	22.8 ± 0.4	-0.1, -1.1 to 0.9	25.3 ± 0.5	0.2, -1.2 to 1.6	-2.5	-3.8 to − 1.2
HDL 2b (µmol/L)	Baseline	6.0 ± 0.1		6.0 ± 0.1		0.0	-0.3 to 0.2
	1 yr	6.3 ± 0.1	0.4, 0.1 to 0.6 Ï	6.0 ± 0.1	-0.0, -0.4 to 0.4	0.3	0.0 to 0.7
	2 yrs	6.3 ± 0.1	0.3, 0.1 to 0.5	6.1 ± 0.1	0.1, -0.3 to 0.5	-0.1	-0.2 to 0.5
HDL 2a + 3 (µmol/L)	Baseline	17.3 ± 0.2		18.0 ± 0.3		-0.7	-1.3 to − 0.1
	1 yr	16.8 ± 0.2	-0.5, -0.9 to − 0.0	17.5 ± 0.3	-0.5, -1.2 to 0.3	-0.7	-1.4 to − 0.0
	2 yrs	17.0 ± 0.2	-0.3, -0.8 to 0.1	17.8 ± 0.3	-0.2, -0.9 to 0.6	-0.8	-1.5 to − 0.2
LDL Peak Diameters (Å)	Baseline	215.2 ± 0.5		215.0 ± 0.8		0.2	-1.7 to 2.1
	1 yr	219.6 ± 0.5	4.4, 3.1 to 5.7 *	215.1 ± 0.8	0.1, -2.1 to 2.3	4.5 *	2.6 to 6.5 *
	2 yrs	219.5 ± 0.5	4.3, 3.0 to 5.6 *	215.8 ± 0.8	0.8, -1.4 to 3.0	3.7 *	1.8 to 5.6 *

Abbreviations. SE, standard error; CI, 95% confidence interval; LDL, low density lipoprotein; HDL, high-density lipoprotein; IDL, intermediate density lipoprotein; VLDL, very low-density lipoprotein; CIMT, carotid intima-media thickness.

Note. Adjusted means and mean changes were obtained from an analysis using linear mixed-effects model (LMM) controlling for baseline age, sex, race, body mass index, HDL 2+3a, mid-zone, insulin use and statin use. a Variables normalized by removing the top 1% of values. Analyses were conducted excluding the top 1% values, although all cases were included using the maximum likelihood approach. b Variables normalized by natural log transformation. Non-transformed and unadjusted means, mean changes, CI and standard errors were provided in the table, but the significance level is calculated from the transformed analysis * P<0.0015 ensures overall simultaneous significance of P<0.05 over the 33 variables using Bonferroni correction Ï P<0.005

Table 3
Principal Components and Respective Loading of Each Lipoprotein/Lipid from Baseline and Two-year Follow-up Data

Variables	Continuous Care Intervention							Usual Care					
	Baseline			Two-year Follow-up				Baseline			Two-year Follow-up		
	PC1	PC2	PC3	PC2	PC1a	PC1b	PC3	PC1	PC2	PC3	PC1	PC2	PC3
HDL 2a + 3	0.322	0.402	**0.804**	0.404	**0.47**	0.348	**0.634**	0.442	0.367	**0.697**	0.05	0.448	**0.668**
HDL 2b	-0.04	0.275	**0.870**	0.171	-0.079	0.104	**0.918**	0.302	0.374	**0.888**	-0.336	0.432	**0.682**
Mid-zone	0.367	0.262	**0.821**	0.319	**0.463**	**0.698**	**0.476**	**0.707**	0.324	**0.552**	0.297	0.205	**0.837**
LDL IVc	**0.606**	0.180	**0.791**	0.3	**0.523**	**0.798**	**0.443**	**0.812**	0.182	**0.477**	**0.467**	0.155	**0.851**
LDL IVb	**0.710**	0.027	**0.540**	0.091	0.342	**0.874**	0.057	**0.771**	0.02	0.288	**0.64**	-0.153	**0.511**
LDL IVa	**0.829**	-0.071	0.318	-0.035	**0.481**	**0.862**	-0.109	**0.837**	0.012	0.053	**0.847**	-0.201	0.154
LDL IIIb	**0.904**	0.038	0.214	0.099	**0.738**	**0.76**	-0.22	**0.865**	0.189	-0.062	**0.884**	-0.084	0.013
LDL IIIa	**0.828**	0.344	0.184	0.32	**0.814**	**0.651**	-0.28	**0.761**	**0.551**	-0.062	**0.85**	0.332	0.069
LDL IIb	0.362	**0.821**	0.172	**0.675**	**0.682**	0.396	-0.235	0.253	**0.885**	0.091	0.41	**0.781**	0.212
LDL IIa	-0.051	**0.895**	0.215	**0.906**	0.328	0.068	0.084	-0.053	**0.891**	0.333	-0.084	**0.89**	0.283
LDL I	-0.259	**0.842**	0.364	**0.856**	0.02	-0.087	**0.512**	-0.116	**0.806**	**0.602**	-0.359	**0.81**	0.295
IDL 2	-0.119	**0.784**	**0.601**	**0.734**	0.056	-0.057	**0.731**	0.179	**0.833**	**0.623**	-0.187	**0.874**	0.288
IDL 1	**0.600**	**0.79**	**0.525**	**0.852**	**0.736**	0.353	0.266	**0.629**	**0.878**	0.332	**0.575**	**0.782**	0.179
VLDL Small	**0.571**	**0.749**	**0.540**	**0.828**	**0.629**	0.211	0.409	**0.615**	**0.853**	0.386	**0.579**	**0.735**	0.253
VLDL Medium	**0.870**	0.405	0.350	**0.547**	**0.939**	**0.414**	0.053	**0.826**	**0.64**	0.223	**0.842**	0.393	0.269
VLDL Large	**0.897**	0.168	0.250	0.339	**0.948**	**0.448**	-0.102	**0.866**	0.424	0.162	**0.843**	0.261	0.332
Triglycerides	**0.788**	-0.093	0.067	0.003	**0.804**	**0.533**	-0.150	**0.853**	0.172	0.101	**0.741**	0.17	0.364
LDL-C	0.051	**0.769**	0.157	**0.932**	0.321	0.109	0.242	0.218	**0.892**	0.273	0.146	**0.883**	0.217
HDL-C	**-0.574**	0.172	**0.432**	0.08	-0.451	-0.294	**0.783**	**-0.437**	0.137	**0.617**	**-0.719**	0.433	0.182
% Variance Explained	39.9	24.8	12.7	39.9	22.9	13.9	6.1	46.6	23.8	10.3	38.2	28.0	11.2

Abbreviations. PC, principal component; LDL, low density lipoprotein; HDL, high-density lipoprotein; IDL, intermediate density lipoprotein; VLDL, very low-density lipoprotein; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; CCI, continuous care intervention

Extraction Method: Principal Component Analysis, Rotation Method: Promax with Kaiser Normalization

Used a loading cut-off > 0.4 for selecting individual lipoproteins/lipids represented in each PC (Bolded)

Note: PC are listed by % variance explained by greatest to least. CCI 2-year components PC2, PC1a and PC1b are named based on similarity in the loading lipoproteins/lipids to baseline PC2 and PC1.

Table 4
Multivariate analysis of variance (MANOVA) of lipoprotein subclasses in LDL-C hypo- versus hyper-responders

One-way MANOVA analysis result				
Statistics	**Value**	**F**	**Significance**	ω^2
Pillai's Trace	0.658	5.092	**6.0×10^{-6}**	0.658
Univariate analysis results				
Variables	**Hypo-responder (n = 29) Mean (SD)**	**Hyper-responder (n = 34) Mean (SD)**	**F, p-value**	ω^2
VLDL Large (nmol/L)	15.7 (8.5)	19.7 (9.0)	3.4, 0.07	0.052
VLDL Medium (nmol/L)	42.2 (16.8)	56.2 (17.0)	**10.7, 2.0×10^{-3}**	0.149
VLDL Small (nmol/L) [a]	48.2 (14.4)	71.4 (16.1)	**38.1, 6.1×10^{-8}**	0.384
IDL 1 (nmol/L) [a]	111.9 (25.7)	159.9 (31.2)	**45.0, 7.3×10^{-9}**	0.425
IDL 2 (nmol/L) [a]	139.2 (58.0)	198.2 (61.9)	**20.5, 2.9×10^{-5}**	0.251
LDL I (nmol/L) [a]	184.9 (79.2)	275.8 (92.8)	**22.9, 1.1×10^{-5}**	0.273
LDL IIa (nmol/L) [a]	127.3 (39.1)	202.4 (62.0)	**38.8, 4.9×10^{-8}**	0.388
LDL IIb (nmol/L) [a]	141.8 (47.3)	210.6 (67.8)	**22.3, 1.4×10^{-5}**	0.267
LDL IIIa (nmol/L) [a]	128.2 (51.8)	173.8 (89.1)	5.5, 0.02	0.083
LDL IIIb (nmol/L) [a]	52.4 (15.5)	61.8 (28.2)	1.9, 0.18	0.030
LDL IVa(nmol/L)	70.5 (17.5)	69.2 (15.2)	0.1, 0.75	0.002
LDL IVb(nmol/L) [a]	75.0 (20.9)	70.7 (14.9)	0.7, 0.40	0.012
LDL IVc (nmol/L)	84.7 (15.2)	83.4 (12.7)	0.1, 0.71	0.002
Mid-zone (nmol/L)	823.0 (148.9)	814.6 (119.2)	0.1, 0.80	0.001
HDL 2b (μmol/L) [a]	6.5 (1.4)	6.2 (1.1)	1.1, 0.29	0.018
HDL 2a + 3 (μmol/L)	15.9 (2.0)	17.0 (2.0)	4.7, 0.03	0.072
LDL Peak Diameter (Å)	221.0 (5.7)	221.3 (6.0)	0.0, 0.84	0.001

Abbreviations. M, mean; SD, standard deviation; LDL, low density lipoprotein; HDL, high-density lipoprotein; IDL, intermediate density lipoprotein; VLDL, very low-density lipoprotein.

[a] Variables normalized by natural log transformation. Non-transformed and unadjusted means, and standard deviations were provided in the table, but the significance level is calculated from the transformed analysis

$P < 0.003$ Bonferroni corrected significance value over 17 variables with an overall simultaneous significance of $P < 0.05$

Figures

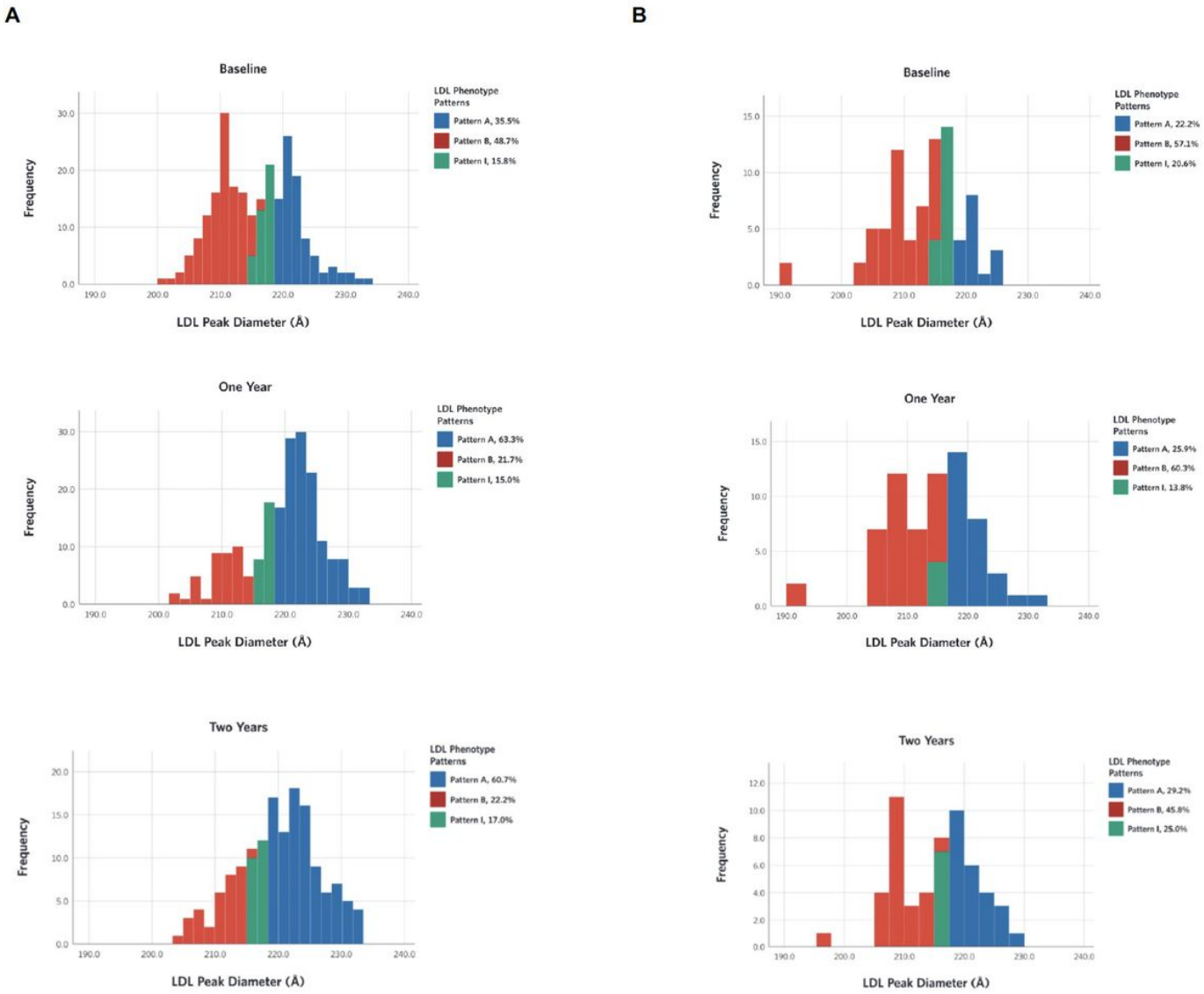

Figure 1

Distribution of LDL Phenotype Pattern and LDL Peak Diameters (Å) at baseline, one and two years A. Continuous Care Intervention B. Usual Care

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplement5.docx