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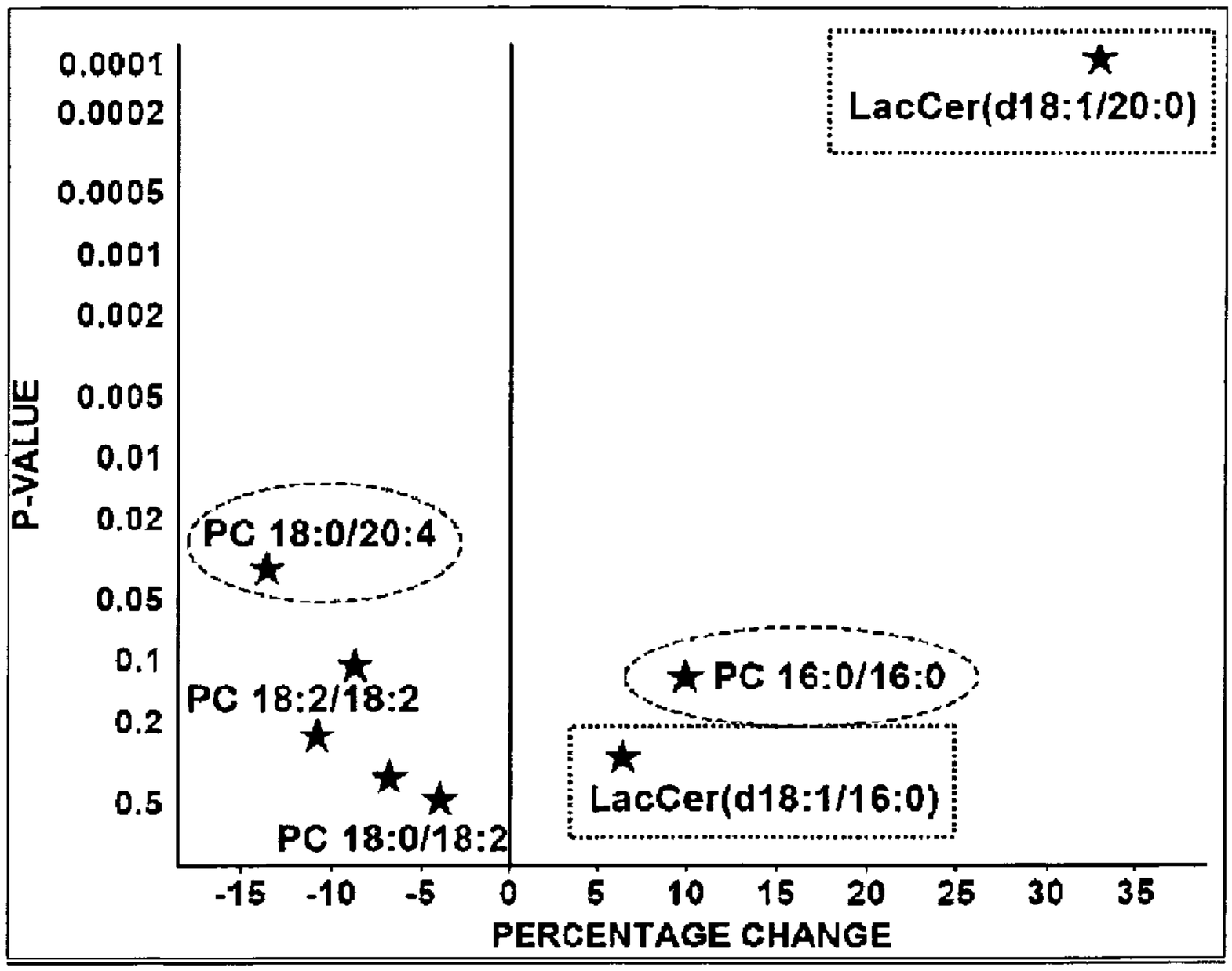
(71) Demandeur/Applicant:
ZORA BIOSCIENCES OY, FI

(72) Inventeurs/Inventors:
LAAKSONEN, REIJO, FI;
EKROOS, KIM, FI;
HURME, REINI, FI;
JANIS, MINNA, FI;
KATAINEN, RIIKKA, FI;
TARASOV, KIRILL, FI

(74) Agent: SMART & BIGGAR

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(54) Title: LIPIDOMIC BIOMARKERS FOR IDENTIFICATION OF HIGH-RISK CORONARY ARTERY DISEASE PATIENTS



(57) Abrégé/Abstract:
The present invention inter alia provides a method, and use thereof, of predicting severe CVD complications such as AMI or CVD death by detecting the lipid concentrations or lipid ratios of a biological sample and comparing it to a control and has identified specific lipid markers that are more specific and sensitive in predicting these CVD complications than currently utilized clinical markers. Also provided is an antibodies towards said lipids, and the use thereof for predicting, diagnosing, preventing and/or treating CVD complications. The invention additionally relates to kits comprising lipids and/or an antibody thereto, for use in the prediction and/or diagnosis of CVD complications.

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(71) Applicant *(for all designated States except US)*: **ZORA BIOSCIENCES OY** [FI/FI]; Biologinkuja 1, FI-02150 Espoo (FI).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **LAAKSONEN, Reijo** [FI/FI]; Himminpolku 11, FI-37500 Lempäälä (FI). **EKROOS, Kim** [FI/FI]; Kyyluodontie 1 B 1, FI-00200 Helsinki (FI). **HURME, Reini** [FI/FI]; Keltonkuja 4 B 4, FI-02180 Espoo (FI). **JÄNIS, Minna** [FI/FI]; Nöykkiönniitty 3 A 2, FI-02330 Espoo (FI). **KATAINEN, Riikka** [FI/FI]; Museokatu 34 B 35, FI-00100 Helsinki (FI). **TARASOV, Kirill** [FI/FI]; Leenankuja 2G 71, FI-02230 Espoo (FI).

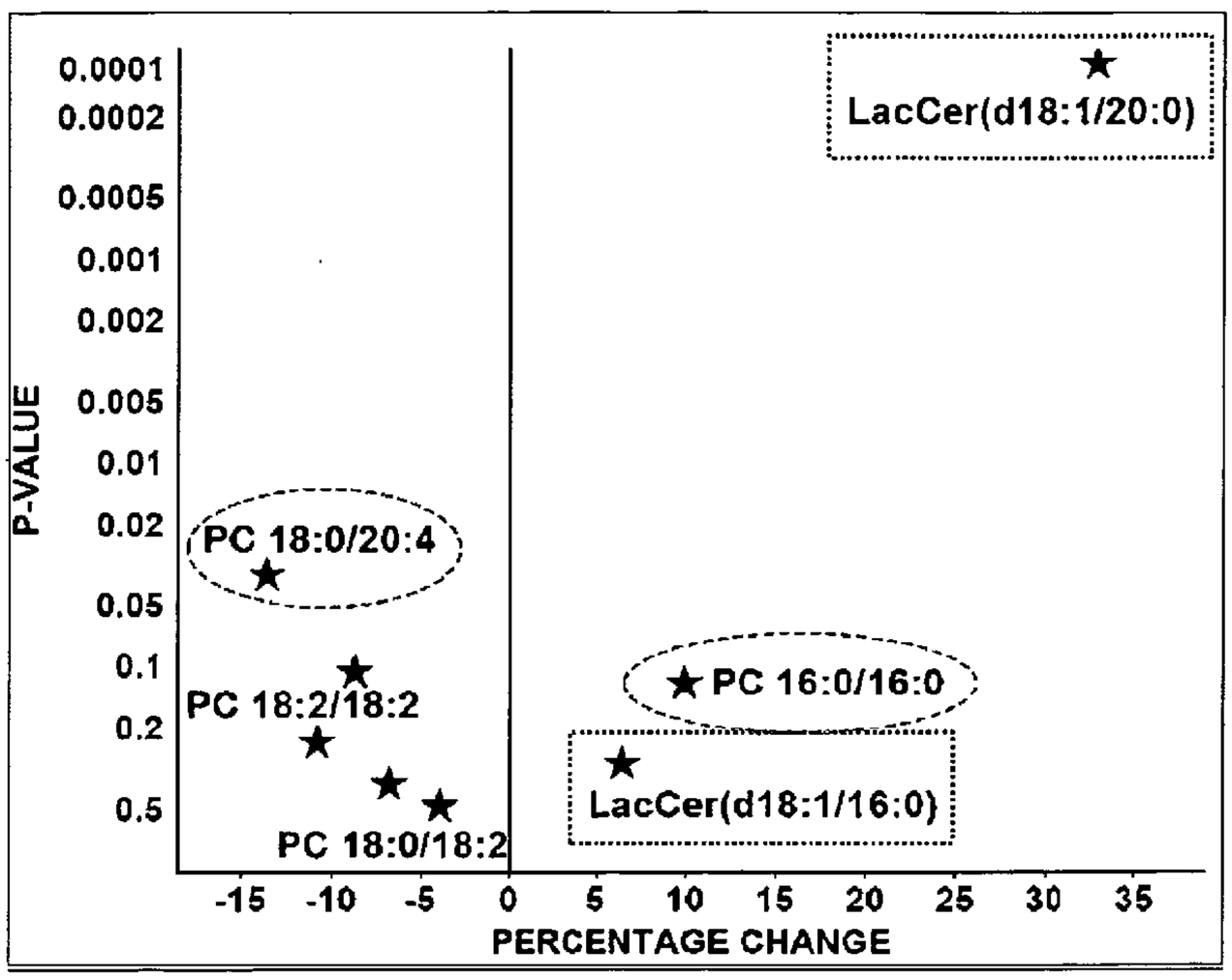
(74) Agent: **DÖRRIES, Hans-Ulrich**; df-mp, Fünf Höfe Theatinerstraße 16, 80333 München (DE).

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Lipidomic Biomarkers for Identification of High-Risk Coronary Artery Disease Patients

Description

Field of the Invention

This invention relates to methods and uses involving lipid levels to predict and prevent severe cardiovascular disease-associated fatal complications. The invention thus provides a means to identify and treat high-risk coronary artery disease patients. The methods include analyzing lipid levels of a biological sample, and comparing it to a control.

Background of the Invention

Worldwide, cardiovascular diseases (CVD) are among the leading causes of mortality and morbidity with ever-increasing prevalence. CVD is used to classify numerous conditions that affect the heart, heart valves, blood, and vasculature of the body. One of these conditions is coronary artery disease (CAD). Early targeted initiation of preventive measures of CVD-related fatal complications, such as acute myocardial infarction (AMI) and death, would be of great benefit and can provide a major opportunity in reducing mortality and morbidity in patients suffering from CVD. To this end, accurate identification of individuals who are at risk of developing CVD complications is essential. However, traditional risk assessment fails to recognize a substantial proportion of patients at high risk while a large proportion of individuals are classified as having intermediate risk, leaving patient management uncertain. Additional strategies to further refine risk assessment of high-risk CVD are therefore highly needed. To this end, the inventors have evaluated the role of novel lipidomic biomarkers as a prognostic tool for fatal cardiovascular events in CVD patients.

Plasma or serum total cholesterol, LDL-cholesterol or HDL-cholesterol concentrations have been used as gold standard biomarkers for CVD/CAD risk prediction. However, a number of coronary artery disease (CAD) or acute myocardial infarction (AMI) patients have LDL-C levels within the recommended range suggesting the need for additional diagnostic measures of the residual risk. It is evident from earlier large scale population studies that these measurements associate with the CAD risk and CAD endpoints such as AMI or cardiovascular death. Therefore, preventive treatment strategies have so far been addressed to lower LDL-C concentrations (mainly by statin treatment) and more recently also attempts to raise HDL-C have been made (e.g., by CETP-inhibitors). On the other hand, it has also been observed that one half of the AMI patients actually do have normal LDL cholesterol levels and that there is a substantial residual risk in statin treated patients despite a LDL-C lowering. Furthermore, recent publications have demonstrated that plasma levels of apolipoprotein B (apoB), the main surface protein on LDL particles, and LDL-C, the amount of cholesterol in those particles, are correlated and, considered separately, as positive risk factors. Plasma levels of apolipoprotein A_1, the main surface protein on HDL particles, and HDL-C, the amount of cholesterol in those particles, are also correlated with each other and, considered separately, as negative risk factors. Importantly, for a given usual apoB, lower LDL-C has been observed to associate with a higher risk of AMI supporting the view that, on average, LDL particles with low cholesterol content per particle (small, dense LDL particles) are particularly hazardous. Thus, it seems possible that LDL-C associates directly with the more dangerous molecules carried by LDL-particle and that LDL-C is only an indirect measurement of the risk. Therefore, it is of importance to search for molecules e.g., certain lipid species that are directly related with hazardous (i.e., fatal) cardiovascular events.

Lipid metabolite imbalance is a probable cause of dyslipidemia and the ensuing atherosclerosis manifested in its gravest form as the vulnerable atherosclerotic plaque. Atherosclerotic plaques are complex molecular formations that contain numerous

lipids. However, there are other factors than lipid rich plaques or LDL cholesterol that make lipids an attractive group of molecules for CVD studies. Lipids are tightly regulated which makes Lipidomic data robust and informative on the current state of the studied organism. Also, lipids are one of the culmination points of a biological system, more the true outcome than the predictor. Combining Lipidomic data with appropriate biobanked clinical material presents a good opportunity for biomarker discovery. Moreover, lipidomics can be used as a gauge of efficacy and safety in drug development and evolving theragnostics. Lipidomic biomarkers are prime candidates for true companion diagnostics in the CVD area and present many opportunities for improved translational medicine as well.

The plaque building blocks and lipoprotein components that are thought to traffic lipids to the site of lesion formation can now be resolved with Lipidomic studies correlating lipid structure and composition to function and thereby disease pathogenesis. While the number of lipid mediators in the human body is overwhelming, their identification and quantification is facilitated by the advances in mass spectrometry and lipid biochemistry, which today enable the simultaneous high throughput identification and quantification of hundreds of molecular lipid species in several lipid classes (Ejsing CS, *et al: Global analysis of the yeast lipidome by quantitative shotgun mass spectrometry. Proc Natl Acad Sci U S A* 2009, 106:2136-2141; Stahlman M, *et al: High-throughput shotgun lipidomics by quadrupole time-of-flight mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci* 2009 Hiukka A, *et al: ApoCIII-enriched LDL in type 2 diabetes displays altered lipid composition, increased susceptibility for sphingomyelinase, and increased binding to biglycan. Diabetes* 2009, 58:2018-2026; Linden D, *et al: Liver-directed overexpression of mitochondrial glycerol-3-phosphate acyltransferase results in hepatic steatosis, increased triacylglycerol secretion and reduced fatty acid oxidation. FASEB J* 2006, 20:434-443.) collectively referred to as the lipidome. Lipidomic studies identify lipid cellular distribution and describe their biochemical mechanisms, interactions and dynamics. Importantly, lipidomics quantifies the exact chemical composition of lipidomes (Han X, Gross RW: *Global analyses of*

cellular lipidomes directly from crude extracts of biological samples by ESI mass spectrometry: a bridge to lipidomics. *J Lipid Res* 2003, 44:1071-1079).

Due to both high sensitivity and selectivity of lipidomics, even the smallest sample amounts can be analyzed today. The bulk of the lipid data in the art today presents lipids in a sum composition format, *i.e.* phosphatidylcholine (PC) 34:1 (Brugger B, *et al: Quantitative analysis of biological membrane lipids at the low picomole level by nano-electrospray ionization tandem mass spectrometry. Proc Natl Acad Sci U S A* 1997, 94:2339-2344) where the molecular lipid and the attached fatty acid tails remain unidentified. The identification of molecular lipid species, e.g., PC 16:0/18:1 (Ekroos K, *et al: Charting molecular composition of phosphatidylcholines by fatty acid scanning and ion trap MS3 fragmentation*. *J Lipid Res* 2003, 44:2181-2192) is the main feature of advanced lipidomics, which delivers highly resolved molecular lipid species rather than summed fatty acid information. For example, the information of the type of fatty acids and their positions of attachment to the glycerol backbone making up the particular PC molecule is revealed. There are conventional techniques such as thin-layer chromatography combined with gas chromatography but they not only require considerably larger sample amounts and laborious sample preparation, but they do not deliver the molecular lipid species. Despite multiple mass spectrometry techniques capable of characterizing lipid entities, most of them are still unable to deliver reliable high-quality quantitative data in terms of absolute or close-to absolute concentrations. In the context of the present invention, electrospray ionization mass spectrometry-based lipidomics is the preferred technology and can utilize both shotgun and targeted lipidomics for exhaustive deciphering and precise quantification of molecular lipidomes. The superior quality and specificity of shotgun and targeted lipidomics will meet stringent regulatory standards, such as good laboratory practice guidelines (GLP) when set-up in the proper environment. Using these technologies quantification of up to two thousand molecular lipids is possible even in a high throughput format.

Lipidomics is a tool for differentiating patients based on their molecular lipid profiles. Personalized medicine and diagnostics enabled by lipidomics will facilitate the mission of the right individual receiving the right drug at the right time and dose. Several works employing analytes consisting of lipids, proteins and hydrophilic molecules among many others have been conducted to meet the needs of personalized medicine. Recently, non-hypothesis-driven metabolomic screenings have been used to identify novel CVD biomarkers.

For example, WO2004/038381 discloses a method for metabolomically facilitating the diagnosis of a disease state of a subject, or for predicting whether a subject is predisposed to having a disease state wherein the small molecule profile from a subject is obtained and compared to a standard small molecule profile.

WO2008/148857 discloses a method to assess the risk of cardiovascular disease in a patient (including atherosclerosis) by isolating the HDL fraction and sub-fraction from a blood sample of the patient. The components of the HDL fraction or sub-fraction to be measured were Sphingosine-1-Phosphate (S1P), sphingomyelin (SM) and Apolipoprotein A-I (apoA-l).

WO2008/11943 further discloses markers for detecting coronary artery disease that can indicate a patient at risk of having or developing coronary artery disease. These include 15 "first-choice" molecules which were: C18:3 Cholesterol ester, C32:1 Phosphatidylcholine, Alanine, Lipid (mainly VLDL), Lysine, Hexadecanoic acid, C36:2 Phosphatidylcholine, Formate, C32:2 Phosphatidylcholine, C18:2 (Linoleic Acid), Cholesterol, C 18:2 Lyso-phosphatidylcholine, C36:3 Phosphatidylcholine, C34:4 Phosphatidylcholine and C34:3 Phosphatidylcholine.

Furthermore, US2007/0099242 describes a method to determine if a subject is at risk to develop, or is suffering from cardiovascular disease. The method involves determining a change in the amount of a biomarker in the biological sample or HDL sub-fraction

thereof, compared to a control sample, wherein the biomarker is at least one of Apolipoprotein C-IV ("ApoC-IV"), Paraoxonase 1 ("PON-1"), Complement Factor 3 ("C3"), Apolipoprotein A-IV ("ApoA-IV"), Apolipoprotein E ("ApoE"), Apolipoprotein LI ("ApoL1"), Complement Factor C4 ("C4"), Complement Factor C4B1 ("C4B1"), Histone H2A, Apolipoprotein C-II ("ApoC-II"), Apolipoprotein M ("ApoM"), Vitronectin, Haptoglobin-related Protein and Clusterin. The document also discloses a method for detecting the presence of one or more atherosclerotic lesions wherein a change in the amount of a biomarker in the biological sample or HDL sub-fraction thereof is detected, compared to a control sample and wherein the biomarker is selected from PON-1, C3, C4, ApoE, ApoM and C4B1. All biomarkers mentioned in this document are protein or lipoprotein biomarkers.

From previous work it cannot be extrapolated that lipid analysis will yield by default a CVD biomarker predictive to the fatal outcomes associated with CVD/CAD. The present invention identifies biomarkers of high risk CVD by absolute, or close to absolute, quantification of defined molecular lipid species instead of profiling multiple analytes. Importantly, while many of the existing biomarker candidates are composite fingerprints of multiple factors, the lipidomics approach herein shows value already at a level of single species or ratios thereof.

In the present invention herein, lipid biomarker concentrations have been measured and quantified in patients with documented CAD who did not show fatal outcomes during the follow-up period (3 years) and in high-risk CAD patients who died due to cardiovascular events during the follow-up period. This invention thus enables accurate usage of the lipid-based biomarkers to identify high risk CVD/CAD patients. Another layer of accuracy was reached through a careful patient selection since it is important to control for factors which may affect the lipid concentration read-outs. Unlike the previous efforts described above, we used specific targeted platforms on a singular technology set-up to analyze lipid species in particular.

The technology and the way it was applied in the context of the inventive teaching presented herein is set apart from similar efforts in the field *inter alia* due to the following criteria. In sample preparation, samples are strictly controlled and treated identically to avoid potential artifacts that could arise from improper handling. In connection with the present invention, samples were carefully thawed slowly on ice and directly thereafter subjected to a custom-made automated lipid extraction which possesses currently the highest precision in liquid handling, therefore minimizing potential errors. Furthermore, sample freeze-thaw cycles were strictly controlled since this can dramatically affect the lipid stabilities. The automated lipid extraction is based on the method by Folch and colleagues (Folch J, *et al*: *A simple method for the isolation and purification of total lipids from animal tissues. J Biol Chem* 1957, 226(1):497-509) which uses chloroform and methanol. This method is preferred when a wide range, from polar to non-polar, of lipid classes are to be extracted with optimal recoveries thus preventing the loss of lipid species. Lipid class specific non-endogenous lipids, when applicable, were used as internal standards to gain highest precision in identification (minimizing false positives) and quantification of monitored molecular lipid species. In this way absolute or semi-absolute amounts of endogenous molecular lipids were determined with the highest precision that can be achieved with today's technologies. The endogenous lipids and respective standards were monitored at the molecular lipid level. In this way, not only false positive identifications were minimized, but molecular lipids could be precisely determined and quantified. Analysis quality was strictly controlled using a novel quality control system. This was mainly controlled by multiple internal standards (IS), external standards (ES), IS/ES ratios, and instrument control samples. By stringently controlling these components, technical and biological outliers were readily identified and rejected from further analysis. To obtain best precision in sensitivity, selectivity and quantification for each molecular lipid different targeted platforms were used. Some lipids are best analyzed using high performance liquid chromatography (HPLC) or ultra high performance liquid chromatography (UHPLC) combined with mass spectrometry based multiple reaction monitoring (MRM) whereas

others are best analyzed by direct infusion in combination with mass spectrometry-based precursor ion scanning and neutral loss scanning techniques.

Summary of the Invention

The present invention provides novel lipidomic markers for predicting and preventing severe CVD/CAD-associated complications, including AMI and death. These markers thus provide a means to identify and treat high-risk coronary artery disease patients. Specifically, it has been found that the lipid molecules, lipid-lipid ratios and lipid-clinical concentration ratios provided herein, when displaying an increased or decreased level -- as the case may be -- in samples from CAD patients, are useful lipidomic markers for the methods and uses in accordance with the present invention. These sensitive and specific markers were specifically tested to display superior diagnostic and prognostic value compared to the current clinically-used markers predictive for CVD/CAD outcomes. In fact, the currently available biomarkers such as LDL-C or HDL-C have only very limited or no value in predicting the CVD death risk in CAD patients. The present invention therefore represents a significant advantage to other markers which are currently used to diagnose and/or predict CVD and CVD complications, which include LDL-C, total plasma/serum cholesterol and Apolipoprotein B and A1. Thus, the lipidomic markers provided herein allow better diagnosis of or assessment of the risk to develop major CVD complications such as AMI or CVD death.

In accordance with the present invention, methods are *inter alia* disclosed herein for determining the risk of a patient to develop CVD complications, determining warning signs of CVD risks, (including death, myocardial infarction (MI), angina pectoris, transischemic attack (TIA) and stroke) in said patient.

Methods according to the invention typically comprise the steps of: a) providing a biological sample from a CAD subject; b) determining a lipid concentration, lipid-lipid

ratio, or lipid-clinical concentration ratio or (a) corresponding profile(s) from said sample (i.e., determining information on a lipidomic marker in accordance with the invention); and c) comparing said determined lipid concentration, lipid-lipid ratio, or lipid-clinical concentration ratio or said corresponding profile(s) to the corresponding lipid concentration, lipid-lipid ratio, or lipid-clinical concentration ratio or the corresponding profile(s) in a control.

The control may be a sample from (a) CAD patient(s) with no history of major CVD events. It may also be a sample that represents a combination of samples from a CAD patient population with no history of major CVD events. Alternatively, the control may be a set of data concerning a lipidomic marker in accordance with the present invention, e.g., information on the concentration of (a) lipid(s), lipid-lipid ratio(s), or lipid-clinical concentration ratio(s) in accordance with the present invention in a sample when taken from (a) CAD patient(s) with no history of major CVD events, or in a combination of samples taken from a CAD patient population with no history of major CVD events. Said information, and thus the corresponding set of data, may have been previously determined, calculated or extrapolated, or may have yet to be determined, calculated or extrapolated, or may also be taken from the literature.

As mentioned above, the lipidomic marker to be compared between the subject sample and the control (or control sample) may be one or more of the lipid concentration(s), lipid-lipid ratio(s), or lipid-clinical concentration ratio(s) or combinations thereof, i.e., the corresponding profile(s), as described and claimed herein. In this regard, the control or control sample allows establishment of the lipidomic marker baseline or starting point.

In connection with all aspects and embodiments of the invention described and claimed herein, the determination of the lipid concentration(s), the lipid-lipid ratio(s) or the lipid-clinical concentration ratio(s) is typically performed using an assay. Collecting information on a lipidomic marker (i.e., the concentration(s) of (a) lipid(s), lipid-lipid

ratio(s), or lipid-clinical concentration ratio(s) or combinations thereof, i.e., corresponding profile(s)) from the sample of a patient and, where appropriate, a corresponding control sample, can be performed with various chemical and high-resolution analytical techniques. Suitable analytical techniques include, but are not limited to, mass spectrometry and nuclear resonance spectroscopy. Any high-resolution technique capable of resolving individual lipids or lipid classes and providing structural information of the same can be used to collect the information on the lipidomic marker in question, e.g., lipid profile from the biological sample. Collecting the information on the lipidomic marker with mass spectrometry (MS) is one of the preferred embodiments of the current invention. The MS instrument can be coupled to a direct sample infusion method, such as a robotic nanoflow ion source device, or to a high performance separation method such as high performance liquid chromatography (HPLC) or ultra performance liquid chromatography (UPLC).

Again in accordance with all aspects and embodiments described and claimed herein, both the sample from the subject and the control sample is preferably a blood sample, more preferably a blood plasma sample, or also preferably a blood serum sample. It may also be a fraction of blood, blood plasma or blood serum, e.g., a lipoprotein fraction. A blood sample can be prepared and plasma or serum, or fractions thereof, can be separated therefrom with techniques well known to the person skilled in the art. Alternatively, both the sample from the subject and the control sample may also be a tissue sample, e.g., artery tissue, such as carotid artery tissue, or artery plaque material, such as carotid artery plaque material.

The lipidomic markers of the present invention allow for prediction and prevention of fatal CVD complications. This will facilitate earlier intervention, less symptom development and suffering and decreased morbidity/mortality associated with CVD. Thus, the lipidomic markers described and claimed herein allow for individual tailoring of drug intervention for patients being at risk to develop major CVD complications.

In other words, the present invention discloses diagnostic and/or predictive lipid markers and lipid-lipid or lipid-clinical concentration ratios for use in predicting CVD complications such as AMI or CVD death. The invention uses the measurement of lipid concentrations, lipid-lipid and/or lipid-clinical concentration ratios to determine the risk of said subject to develop CVD complications such as AMI and/or CVD death. The subject may have previously suffered from a cardiovascular disease event such as angina pectoris, myocardial infarction or stroke. The CVD may or may not be a result of atherosclerosis.

Claim 1 (note claims only have preferred embodiments) Accordingly, in one aspect of the invention, a method is provided for determining whether a subject is at risk to develop one or more CVD complications, such as AMI or CVD death, said method comprising determining in a sample from said subject the concentration(s) of one or more lipid(s), wherein (an) increased or decreased concentration(s) in said sample, when compared to a control sample, is (are) indicative of said subject having an increased risk of developing one or more CVD complications, such as AMI or CVD death, wherein the one or more lipid(s) whose increase(s) in concentration is (are) compared to the control is (are) selected from (Tables 4a and 7a):

Cer(d18:1/18:0), Cer(d18:1/20:0), Cer(d18:1/24:1), GlcCer(d18:1/18:0), LacCer(d18:1/18:0), LacCer(d18:1/20:0), LacCer(d18:1/22:0), LacCer(d18:1/24:0), PC O-32:0 (KDdiA-PC), PS O-16:0/18:2-alkenyl, PS O-16:1/18:2-alkyl, PS O-18:0/18:2-alkenyl (PS O-18:1/18:2-alkyl), PS O-18:2/16:0-alkenyl and Total LacCer;

and wherein the one or more lipid(s) whose decrease(s) in concentration is (are) compared to the control is (are) selected from (Tables 4a and 7a):

CE 14:0, CE 16:0, CE 17:1, CE 20:3, Cer(d18:0/22:0), Cer(d18:0/24:0), LPC 18:1, PC 16:0/18:2, PC 16:0/20:3, PC 16:0/20:4, PC 16:0/22:6, PC 18:0/18:1, PC 18:0/20:3, PC 18:0/20:4, PC 18:1/18:2, SM (d18:1/14:0) (d18:1/13:1-OH), SM (d18:1/23:0) (d18:1/22:1-OH), SM (d18:1/24:0) (d18:1/23:1-OH), Total CE, Total LPC and Total PC.

In a particular embodiment, a method is provided for determining whether a subject is at risk to develop one or more CVD complications, such as AMI or CVD death, wherein the subject is not undergoing statin treatment and wherein said method comprises determining in a sample from said subject the concentration(s) of one or more lipid(s), wherein (an) increased or decreased concentration(s) in said sample, when compared to a control sample, is (are) indicative of said subject having an increased risk of developing one or more CVD complications, such as AMI or CVD death, and wherein the one or more lipid(s) whose increase in concentration is (are) compared to the control is (are) selected from (Tables 4b and 7b):
Cer(d18:1/16:0), Cer(d18:1/18:0), Cer(d18:1/20:0), Cer(d18:1/22:0), Cer(d18:1/24:1), Cer(d18:1/26:1), GlcCer(d18:1/18:0), GlcCer(d18:1/20:0), GlcCer(d18:1/24:1), GlcCer(d18:1/26:1), LacCer(d18:1/18:0), LacCer(d18:1/20:0), LacCer(d18:1/22:0), LacCer(d18:1/24:0), LacCer(d18:1/24:1), PC O-32:0 (KDdiA-PC), PS O-16:0/18:2-alkenyl, PS O-16:1/18:2-alkyl, PS O-18:2/16:0-alkenyl, Total Cer, Total DAG and Total LacCer;

and wherein the one or more lipid(s) whose decrease(s) in concentration is (are) compared to the control is (are) selected from (Tables 4b and 7b):
CE 14:0, CE 17:1, CE 20:3, Cer(d18:0/24:0), LPC 18:1, PC 16:0/20:3, PC 16:0/20:4, PC 18:0/20:4, PC O-40:3, SM (d18:1/14:0) (d18:1/13:1-OH), Total LPC and Total PC.

In a preferred embodiment (for subjects that are either undergoing or not undergoing statin treatment), the one or more lipid(s) whose increase(s) in concentration is (are) compared to the control is (are) selected from (Table 10):
Cer(d18:1/20:0), LacCer(d18:1/20:0), Cer(d18:1/24:1), LacCer(d18:1/24:1), PS O-18:2/16:0-alkenyl, PS O-16:1/18:2-alkyl, Total Cer, Total LacCer, GlcCer(d18:1/24:1), LacCer(d18:1/22:0) and Cer(d18:1/18:0).

In another preferred embodiment, the one or more lipid(s) whose decrease(s) in concentration is (are) compared to the control is (are) selected from (Table 10):

Total PC, PC 16:0/20:4, Cer(d18:0/24:0), Total LPC, CE 14:0, CE 20:3, CE 17:1, PC 16:0/20:3, LPC 18:1, PC 18:0/20:3, PC 18:0/18:1 and Cer(d18:0/22:0).

In a particularly preferred embodiment, the one or more lipid(s) whose increase(s) in concentration is (are) compared to the control is (are) selected from (Table 13):
Cer(d18:1/20:0), LacCer(d18:1/20:0), Cer(d18:1/24:1), LacCer(d18:1/24:1), LacCer(d18:1/22:0) and Cer(d18:1/18:0).

In another particularly preferred embodiment, the one or more lipid(s) whose decrease(s) in concentration is (are) compared to the control is (are) selected from (Table 13):
PC 16:0/20:4 and Cer(d18:0/24:0).

In an alternative embodiment, the present invention relates to a method for determining whether a subject is at risk to develop one or more complications such as AMI or CVD death, comprising determining in a sample from said subject one or more lipid-lipid ratio(s), wherein (an) increased or decreased lipid-lipid ratio(s) in said sample, when compared to a control sample, is (are) indicative of said subject having an increased risk of developing one or more CVD complications, such as AMI or CVD death, wherein the one or more lipid-lipid ratio(s) whose increase(s) is (are) compared to the control is (are) selected from (Tables 5a and 8a):
CE 16:0/CE 18:3, CE 18:2/CE 18:3, CE 19:1/Cer(d18:0/22:0), Cer(d18:1/16:0)/LPC 18:1, Cer(d18:1/16:0)/Total PC, Cer(d18:1/18:0)/LPC 16:0, Cer(d18:1/18:0)/LPC 18:1, Cer(d18:1/18:0)/PC 16:0/18:1, Cer(d18:1/18:0)/PC 16:0/20:3, Cer(d18:1/18:0)/PC 16:0/20:4, Cer(d18:1/18:0)/PC 18:0/20:4, Cer(d18:1/18:0)/Total LPC, Cer(d18:1/18:0)/Total PC, Cer(d18:1/20:0)/PC 16:0/18:1, Cer(d18:1/20:0)/PC 16:0/20:3, Cer(d18:1/20:0)/PC 16:0/20:4, Cer(d18:1/20:0)/PC 18:0/20:4, Cer(d18:1/20:0)/PC 18:1/18:1, Cer(d18:1/20:0)/Total PC, Cer(d18:1/22:0)/LPC 18:2, Cer(d18:1/22:0)/PC 16:0/20:3, Cer(d18:1/22:0)/PC 16:0/20:4, Cer(d18:1/22:0)/Total PC, Cer(d18:1/24:1)/LPC 18:1, Cer(d18:1/24:1)/LPC 18:2, Cer(d18:1/24:1)/PC

16:0/18:1, Cer(d18:1/24:1)/PC 16:0/20:3, Cer(d18:1/24:1)/PC 16:0/20:4, Cer(d18:1/24:1)/PC 18:0/18:1, Cer(d18:1/24:1)/PC 18:0/20:3, Cer(d18:1/24:1)/PC 18:0/20:4, Cer(d18:1/24:1)/SM (d18:1/24:0) (d18:1/23:1-OH), Cer(d18:1/24:1)/Total CE, Cer(d18:1/24:1)/Total LPC, Cer(d18:1/24:1)/Total PC, Cer(d18:1/26:0)/PC O-40:0, GlcCer(d18:1/20:0)/PC 16:0/20:4, GlcCer(d18:1/20:0)/Total PC, GlcCer(d18:1/26:0)/Total CE, LacCer(d18:1/16:0)/Total LPC, LacCer(d18:1/18:0)/PC 16:0/18:1, LacCer(d18:1/18:0)/PC 16:0/20:3, LacCer(d18:1/18:0)/PC 18:0/18:1, LacCer(d18:1/18:0)/PC 18:0/20:3, LacCer(d18:1/18:0)/PC 18:1/18:1, LacCer(d18:1/18:0)/PC 18:1/18:2, LacCer(d18:1/18:0)/Total LPC, LacCer(d18:1/18:0)/Total PC, LacCer(d18:1/20:0)/PC 16:0/18:1, LacCer(d18:1/20:0)/PC 16:0/20:3, LacCer(d18:1/20:0)/PC 18:0/18:1, LacCer(d18:1/20:0)/PC 18:0/20:3 LacCer(d18:1/20:0)/PC 18:1/18:1, LacCer(d18:1/20:0)/PC 18:1/18:2, LacCer(d18:1/20:0)/PC 18:2/18:2, LacCer(d18:1/20:0)/SM (d18:1/17:1-OH), LacCer(d18:1/20:0)/SM (d18:1/18:0), LacCer(d18:1/20:0)/Total LPC, LacCer(d18:1/20:0)/Total PC, LacCer(d18:1/20:0)/Total SM, LacCer(d18:1/22:0)/PC 16:0/20:3, LacCer(d18:1/22:0)/PC 16:0/20:4, LacCer(d18:1/22:0)/PC 18:0/20:3, LacCer(d18:1/22:0)/SM (d18:1/14:0) (d18:1/13:1-OH), LacCer(d18:1/22:0)/Total LPC, LacCer(d18:1/22:0)/Total PC, LacCer(d18:1/24:0)/PC 16:0/20:3, LacCer(d18:1/24:0)/Total LPC, LacCer(d18:1/24:1)/Total LPC, LacCer(d18:1/24:1)/Total PC, LacCer(d18:1/24:1)/Total PC O, PC 16:0/16:0/PC 16:0/20:4, PC 16:0/16:0/Total PC, PC 16:0/18:2/Total PC, PC O-18:0/18:2-alkyl/PC O-36:5, PC O-32:0 (KDdiA-PC)/PC O-38:5, PS O-16:0/18:2-alkenyl/Total PS O, PS O-16:1/18:2-alkyl/Total PS O, PS O-18:0/18:2-alkenyl (PS O-18:1/18:2-alkyl)/Total PS O, PS O-18:2/16:0-alkenyl/Total PS O, Total Cer/Total PC, Total LacCer/Total PC and Total LacCer/Total PC O;

and wherein the one or more lipid-lipid ratio(s) whose decrease(s) is (are) compared to the control is (are) selected from (Tables 5a and 8a):

CE 14:0/Cer(d18:1/24:1), CE 16:0/Cer(d18:1/24:1), CE 16:1/CE 19:1, CE 16:1/Cer(d18:1/18:0), CE 16:1/Cer(d18:1/20:0), CE 16:1/Cer(d18:1/24:1), CE

16:1/GlcCer(d18:1/18:0), CE 16:1/GlcCer(d18:1/20:0), CE 16:1/LacCer(d18:1/16:0), CE 16:1/LacCer(d18:1/18:0), CE 16:1/LacCer(d18:1/20:0), CE 16:1/LacCer(d18:1/22:0), CE 16:1/LacCer(d18:1/24:0), CE 16:1/PC 16:0/16:0, CE 16:1/Total LacCer, CE 17:1/Cer(d18:1/24:1), CE 17:1/GlcCer(d18:1/24:1), CE 17:1/LacCer(d18:1/18:0), CE 18:1/Total LacCer, CE 18:3/Cer(d18:1/16:0), CE 18:3/Cer(d18:1/18:0), CE 18:3/Cer(d18:1/20:0), CE 18:3/Cer(d18:1/22:0), CE 18:3/Cer(d18:1/24:0), CE 18:3/Cer(d18:1/24:1), CE 18:3/GlcCer(d18:1/18:0), CE 18:3/GlcCer(d18:1/20:0), CE 18:3/LacCer(d18:1/18:0), CE 18:3/LacCer(d18:1/20:0), CE 18:3/LacCer(d18:1/22:0), CE 18:3/LacCer(d18:1/24:0), CE 18:3/PC 16:0/16:0, CE 18:3/PC O-34:1, CE 18:3/PS O-16:0/18:1-alkenyl (PS O-16:1/18:1-alkyl), CE 18:3/PS O-16:0/18:2-alkenyl, CE 18:3/PS O-16:1/18:2-alkyl, CE 18:3/Total CE, CE 18:3/Total Cer, CE 18:3/Total LacCer, CE 20:3/Cer(d18:1/24:1), CE 20:3/LacCer(d18:1/20:0), Cer(d18:0/22:0)/Cer(d18:1/18:0), Cer(d18:0/22:0)/Cer(d18:1/20:0), Cer(d18:0/22:0)/Cer(d18:1/22:0), Cer(d18:0/22:0)/Cer(d18:1/24:1), Cer(d18:0/22:0)/LacCer(d18:1/24:0), Cer(d18:0/22:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/22:0)/PS O-16:1/18:2-alkyl, Cer(d18:0/22:0)/Total CE, Cer(d18:0/24:0)/Cer(d18:1/16:0), Cer(d18:0/24:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/Cer(d18:1/20:0), Cer(d18:0/24:0)/Cer(d18:1/22:0), Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/24:0)/GlcCer(d18:1/20:0), Cer(d18:0/24:0)/LacCer(d18:1/24:0), Cer(d18:0/24:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/24:0)/PS O-16:1/18:2-alkyl, Cer(d18:0/24:0)/SM (d18:1/17:0) (d18:1/16:1-OH), Cer(d18:0/24:0)/Total CE, Cer(d18:0/24:0)/Total Cer, Cer(d18:0/24:1)/Total CE, GlcCer(d18:1/26:0)/LacCer(d18:1/20:0), GlcCer(d18:1/26:0)/LacCer(d18:1/22:0), LPC 16:0/LacCer(d18:1/20:0), LPC 16:0/LacCer(d18:1/22:0), LPC 16:0/LacCer(d18:1/24:1), LPC 16:0/Total LacCer, LPC 18:1/LacCer(d18:1/20:0), LPC 18:2/LacCer(d18:1/20:0), LPC 18:2/PS O-16:0/18:2-alkenyl, LPC 18:2/PS O-16:1/18:2-alkyl, PC 16:0/20:3/PS O-16:0/18:2-alkenyl, PC 16:0/20:3/PS O-16:1/18:2-alkyl, PC 18:1/18:2/PS O-16:0/18:2-alkenyl, PC 18:1/18:2/PS O-16:1/18:2-alkyl, SM (d18:1/24:0) (d18:1/23:1-OH)/Total Cer and Total LPC/Total LacCer.

In an alternative embodiment, the present invention relates to a method for determining whether a subject is at risk to develop one or more complications such as AMI or CVD death, wherein the subject is not undergoing statin treatment and wherein said method comprises determining in a sample from said subject one or more lipid-lipid ratio(s), wherein (an) increased or decreased lipid-lipid ratio(s) in said sample, when compared to a control sample, is (are) indicative of said subject having an increased risk of developing one or more CVD complications, such as AMI or CVD death, wherein the one or more lipid-lipid ratio(s) whose increase(s) is (are) compared to the control is (are) selected from (Tables 5b and 8b):

CE 16:0/CE 18:3, CE 18:0/CE 18:3, CE 18:2/CE 18:3, Cer(d18:1/16:0)/LPC 18:1, Cer(d18:1/16:0)/Total PC, Cer(d18:1/18:0)/LPC 18:1, Cer(d18:1/18:0)/PC 16:0/18:1, Cer(d18:1/18:0)/PC 16:0/20:3, Cer(d18:1/18:0)/PC 16:0/20:4, Cer(d18:1/18:0)/PC 18:0/18:1, Cer(d18:1/18:0)/PC 18:0/20:4, Cer(d18:1/18:0)/PC 18:1/18:1, Cer(d18:1/18:0)/SM (d18:1/14:0) (d18:1/13:1-OH), Cer(d18:1/18:0)/SM (d18:1/17:2-OH), Cer(d18:1/18:0)/SM (d18:1/18:1), Cer(d18:1/18:0)/Total CE, Cer(d18:1/18:0)/Total LPC, Cer(d18:1/18:0)/Total PC, Cer(d18:1/20:0)/PC 16:0/18:1, Cer(d18:1/20:0)/PC 16:0/20:3, Cer(d18:1/20:0)/PC 16:0/20:4, Cer(d18:1/20:0)/PC 18:0/18:1, Cer(d18:1/20:0)/PC 18:0/20:4, Cer(d18:1/20:0)/PC 18:1/18:1, Cer(d18:1/20:0)/SM (d18:1/14:0) (d18:1/13:1-OH), Cer(d18:1/20:0)/Total LPC, Cer(d18:1/20:0)/Total PC, Cer(d18:1/20:0)/Total PC O, Cer(d18:1/22:0)/LPC 18:2, Cer(d18:1/22:0)/PC 16:0/20:3, Cer(d18:1/22:0)/PC 16:0/20:4, Cer(d18:1/22:0)/PC 18:0/20:4, Cer(d18:1/22:0)/Total PC, Cer(d18:1/24:1)/LPC 18:1, Cer(d18:1/24:1)/LPC 18:2, Cer(d18:1/24:1)/PC 16:0/18:1, Cer(d18:1/24:1)/PC 16:0/18:2, Cer(d18:1/24:1)/PC 16:0/20:3, Cer(d18:1/24:1)/PC 16:0/20:4, Cer(d18:1/24:1)/PC 18:0/18:1, Cer(d18:1/24:1)/PC 18:0/18:2, Cer(d18:1/24:1)/PC 18:0/20:3, Cer(d18:1/24:1)/PC 18:0/20:4, Cer(d18:1/24:1)/PC 18:1/18:1, Cer(d18:1/24:1)/PC 18:1/18:2, Cer(d18:1/24:1)/PC O-40:3, Cer(d18:1/24:1)/SM (d18:1/17:1-OH), Cer(d18:1/24:1)/SM (d18:1/18:0), Cer(d18:1/24:1)/SM (d18:1/23:0) (d18:1/22:1-OH), Cer(d18:1/24:1)/SM (d18:1/24:0) (d18:1/23:1-OH), Cer(d18:1/24:1)/Total CE, Cer(d18:1/24:1)/Total LPC, Cer(d18:1/24:1)/Total PC, GlcCer(d18:1/26:0)/Total CE,

GlcCer(d18:1/26:1)/Total CE, LacCer(d18:1/18:0)/Total PC, LacCer(d18:1/20:0)/PC 16:0/20:3, LacCer(d18:1/20:0)/PC 16:0/20:4, LacCer(d18:1/20:0)/PC 18:0/18:1, LacCer(d18:1/20:0)/PC 18:0/20:3, LacCer(d18:1/20:0)/PC 18:0/20:4, LacCer(d18:1/20:0)/PC 18:1/18:2, LacCer(d18:1/20:0)/SM (d18:1/17:1-OH), LacCer(d18:1/20:0)/SM (d18:1/18:0), LacCer(d18:1/20:0)/Total CE, LacCer(d18:1/20:0)/Total LPC, LacCer(d18:1/20:0)/Total PC, LacCer(d18:1/20:0)/Total SM, LacCer(d18:1/24:0)/Total LPC, PC 16:0/16:0/PC 16:0/20:4, PC 16:0/16:0/Total PC, PC O-32:0 (KDdiA-PC)/Total PC O, PS O-16:0/18:2-alkenyl/Total PC, PS O-16:0/18:2-alkenyl/Total PC O, PS O-16:0/18:2-alkenyl/Total PS O, PS O-16:1/18:2-alkyl/Total PC, PS O-16:1/18:2-alkyl/Total PC O, PS O-16:1/18:2-alkyl/Total PS O, PS O-18:2/16:0-alkenyl/Total PC O, PS O-18:2/16:0-alkenyl/Total PS O, SM (d18:1/17:0) (d18:1/16:1-OH)/Total PC O, Total Cer/Total PC, Total DAG/Total LPC, Total DAG/Total PC, Total DAG/Total PC O and Total LacCer/Total PC;

and wherein the one or more lipid-lipid ratio(s) whose decrease(s) is (are) compared to the control is (are) selected from (Tables 5b and 8b):

CE 14:0/Cer(d18:1/18:0), CE 14:0/Cer(d18:1/24:1), CE 14:0/Total DAG, CE 15:0/Cer(d18:1/20:0), CE 16:0/Cer(d18:1/18:0), CE 16:0/Cer(d18:1/24:1), CE 16:1/CE 19:1, CE 16:1/Cer(d18:1/18:0), CE 16:1/Cer(d18:1/20:0), CE 16:1/Cer(d18:1/24:1), CE 16:1/GlcCer(d18:1/24:1), CE 16:1/LacCer(d18:1/18:0), CE 16:1/LacCer(d18:1/24:0), CE 16:1/Total LacCer, CE 17:1/Cer(d18:1/18:0), CE 17:1/Cer(d18:1/24:1), CE 18:2/Cer(d18:1/20:0), CE 18:2/Cer(d18:1/24:1), CE 18:3/Cer(d18:1/16:0), CE 18:3/Cer(d18:1/18:0), CE 18:3/Cer(d18:1/20:0), CE 18:3/Cer(d18:1/22:0), CE 18:3/Cer(d18:1/24:0), CE 18:3/Cer(d18:1/24:1), CE 18:3/GlcCer(d18:1/20:0), CE 18:3/LacCer(d18:1/20:0), CE 18:3/LacCer(d18:1/22:0), CE 18:3/LacCer(d18:1/24:0), CE 18:3/PC 16:0/16:0, CE 18:3/PC O-34:1, CE 18:3/PS O-16:0/18:2-alkenyl, CE 18:3/PS O-16:1/18:2-alkyl, CE 18:3/Total CE, CE 18:3/Total Cer, CE 18:3/Total DAG, CE 18:3/Total LacCer, CE 20:3/Cer(d18:1/24:1), CE 20:3/LacCer(d18:1/20:0), CE 20:4/Cer(d18:1/18:0), CE 20:4/Cer(d18:1/24:1), CE 20:4/GlcCer(d18:1/20:0), CE 20:4/GlcCer(d18:1/24:1), CE 20:4/LacCer(d18:1/20:0), CE 20:5/LacCer(d18:1/20:0),

Cer(d18:0/22:0)/Cer(d18:1/18:0), Cer(d18:0/22:0)/Cer(d18:1/20:0), Cer(d18:0/22:0)/Cer(d18:1/24:1), Cer(d18:0/22:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/22:0)/PS O-16:1/18:2-alkyl, Cer(d18:0/22:0)/Total CE, Cer(d18:0/22:0)/Total DAG, Cer(d18:0/22:0)/Total GlcCer, Cer(d18:0/24:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/Cer(d18:1/20:0), Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/24:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/24:0)/PS O-16:1/18:2-alkyl, Cer(d18:0/24:0)/Total CE, Cer(d18:0/24:0)/Total Cer, DAG 16:0/18:1/Total DAG, GlcCer(d18:1/26:0)/LacCer(d18:1/20:0), LPC 16:0/LacCer(d18:1/24:0), LPC 18:1/LacCer(d18:1/20:0), LPC 18:2/LacCer(d18:1/20:0), PC 16:0/20:3/PS O-16:0/18:2-alkenyl, PC 16:0/20:3/PS O-16:1/18:2-alkyl, PC 16:0/20:4/PS O-16:0/18:2-alkenyl, PC 16:0/20:4/PS O-16:1/18:2-alkyl, PC 16:0/20:4/Total DAG, PC 18:0/20:3/PS O-16:0/18:2-alkenyl, PC 18:0/20:3/PS O-16:1/18:2-alkyl, PC 18:0/20:3/PS O-18:2/16:0-alkenyl, PC 18:0/20:4/PS O-16:0/18:2-alkenyl, PC 18:0/20:4/PS O-16:1/18:2-alkyl, PC 18:1/18:2/PS O-16:0/18:2-alkenyl, PC 18:1/18:2/PS O-16:1/18:2-alkyl, PC 18:1/18:2/Total Cer, PC O-40:3/PS O-18:2/16:0-alkenyl, SM (d18:1/23:0) (d18:1/22:1-OH)/Total DAG, SM (d18:1/24:0) (d18:1/23:1-OH)/Total Cer, Total CE/Total DAG and Total LPC/Total LacCer.

In a preferred embodiment (for subjects that are either undergoing or not undergoing statin treatment), the one or more lipid-lipid ratio(s) whose increase is (are) compared to the control is (are) selected from (Table 11):
GlcCer(d18:1/26:1)/Total CE, Cer(d18:1/24:1)/Total PC, Cer(d18:1/24:1)/PC 16:0/20:4, Cer(d18:1/20:0)/PC 16:0/20:4, LacCer(d18:1/20:0)/PC 16:0/20:3, Total Cer/Total PC, Total LacCer/Total PC, LacCer(d18:1/20:0)/PC 18:1/18:2, PS O-16:0/18:2-alkenyl/Total PS O, Cer(d18:1/18:0)/PC 16:0/20:4, LacCer(d18:1/20:0)/Total LPC and LacCer(d18:1/20:0)/PC 16:0/20:4;

In another preferred embodiment, the one or more lipid-lipid ratio(s) whose decrease is (are) compared to the control is (are) selected from (Table 11):

Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/22:0)/Cer(d18:1/24:1), DAG 16:0/18:1/Total DAG, Cer(d18:0/24:0)/Cer(d18:1/22:0), Cer(d18:0/24:0)/Total CE, Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/24:0)/Total Cer, Cer(d18:0/24:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/24:0)/LacCer(d18:1/24:0), Cer(d18:0/22:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/Cer(d18:1/22:0), Cer(d18:0/22:0)/Cer(d18:1/20:0), Cer(d18:0/22:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/22:0)/PS O-16:1/18:2-alkyl, GlcCer(d18:1/26:0)/LacCer(d18:1/20:0), Total LPC/Total LacCer and GlcCer(d18:1/26:0)/LacCer(d18:1/22:0).

In a particularly preferred embodiment, the one or more lipid-lipid ratio(s) whose increase is (are) compared to the control is (are) selected from (Table 13): Cer(d18:1/24:1)/PC 16:0/20:4, LacCer(d18:1/20:0)/PC 16:0/20:3, PS O-16:0/18:2-alkenyl/Total PS O and Cer(d18:1/18:0)/PC 16:0/20:4;

and the one or more lipid-lipid ratio(s) whose decrease is (are) compared to the control is (are) selected from (Table 13): GlcCer(d18:1/26:0)/LacCer(d18:1/20:0), DAG 16:0/18:1/Total DAG, Cer(d18:0/24:0)/Total Cer, Total LPC/Total LacCer, GlcCer(d18:1/26:0)/LacCer(d18:1/22:0), Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/24:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/24:0)/Cer(d18:1/22:0), Cer(d18:0/22:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/22:0)/PS O-16:1/18:2-alkyl and Cer(d18:0/24:0)/LacCer(d18:1/24:0);

In yet another alternative embodiment the present invention relates to a method for determining whether a subject is at risk to develop one or more CVD complications, such as AMI or CVD death, comprising determining in a sample from said subject one or more lipid-clinical concentration ratio(s), wherein (an) increased or decreased lipid-clinical concentration ratio(s) in said sample, when compared to a control sample, is (are) indicative of said subject having an increased risk of developing one or more CVD complications, such as AMI or CVD death, wherein the one or more lipid-clinical

concentration ratio(s) whose increase is (are) compared to the control is (are) selected from (Tables 6a and 9a):

Cer(d18:1/16:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/18:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/18:0)/apolipoprotein B (mg/dL), Cer(d18:1/18:0)/HDL cholesterol (EDTA) (mg/dL), Cer(d18:1/18:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/18:0)/total-c/HDL-c, Cer(d18:1/18:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/20:0)/apolipoprotein B (mg/dL), Cer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL), Cer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/20:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/22:0)/apolipoprotein B (mg/dL), Cer(d18:1/22:0)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:1/22:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL), Cer(d18:1/24:1)/apolipoprotein B (mg/dL), Cer(d18:1/24:1)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:1/24:1)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/24:1)/total-c/HDL-c, Cer(d18:1/24:1)/triglycerides (EDTA) (mg/dL), GlcCer(d18:1/24:0)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/16:0)/triglycerides (EDTA) (mg/dL), LacCer(d18:1/18:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/18:0)/apolipoprotein B (mg/dL), LacCer(d18:1/18:0)/HDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/18:0)/LDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/18:0)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/18:0)/total-c/HDL-c, LacCer(d18:1/18:0)/triglycerides (EDTA) (mg/dL), LacCer(d18:1/20:0)/apoA1/apoB, LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/apolipoprotein B (mg/dL), LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/20:0)/LDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/20:0)/LDL-c/HDL-c, LacCer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/20:0)/total-c/HDL-c, LacCer(d18:1/20:0)/triglycerides (EDTA) (mg/dL), LacCer(d18:1/22:0)/apoA1/apoB, LacCer(d18:1/22:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/22:0)/apolipoprotein B (mg/dL), LacCer(d18:1/22:0)/HDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/22:0)/LDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/22:0)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/22:0)/total-

c/HDL-c, LacCer(d18:1/22:0)/triglycerides (EDTA) (mg/dL), LacCer(d18:1/24:0)/apoA1/apoB, LacCer(d18:1/24:1)/apolipoprotein A-I (mg/dL), LacCer(d18:1/24:1)/apolipoprotein B (mg/dL), LacCer(d18:1/24:1)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/24:1)/triglycerides (EDTA) (mg/dL), PC O-32:0 (KDdiA-PC)/apolipoprotein A-I (mg/dL), PC O-32:0 (KDdiA-PC)/triglycerides (EDTA) (mg/dL), PC O-34:1/triglycerides (EDTA) (mg/dL), PS O-16:0/18:1-alkenyl (PS O-16:1/18:1-alkyl)/triglycerides (EDTA) (mg/dL), PS O-16:0/18:2-alkenyl/triglycerides (EDTA) (mg/dL), PS O-16:1/18:2-alkyl/triglycerides (EDTA) (mg/dL), PS O-18:2/16:0-alkenyl/HDL cholesterol (EDTA) (mg/dL), PS O-18:2/16:0-alkenyl/triglycerides (EDTA) (mg/dL), Total Cer/apolipoprotein A-I (mg/dL), Total Cer/total cholesterol (EDTA) (mg/dL), Total Cer/triglycerides (EDTA) (mg/dL), Total GlcCer/apolipoprotein B (mg/dL), Total GlcCer/total cholesterol (EDTA) (mg/dL), Total LacCer/apolipoprotein A-I (mg/dL), Total LacCer/apolipoprotein B (mg/dL), Total LacCer/total cholesterol (EDTA) (mg/dL) and Total LacCer/triglycerides (EDTA) (mg/dL);

and wherein the one or more lipid-clinical concentration ratio(s) whose decrease is (are) compared to the control is (are) selected from (Tables 6a and 9a):

CE 14:0/apolipoprotein B (mg/dL), CE 14:0/LDL cholesterol (EDTA) (mg/dL), CE 14:0/LDL-c/HDL-c, CE 14:0/total cholesterol (EDTA) (mg/dL), CE 14:0/total-c/HDL-c, CE 16:1/apolipoprotein B (mg/dL), CE 16:1/HDL cholesterol (EDTA) (mg/dL), CE 16:1/LDL cholesterol (EDTA) (mg/dL), CE 16:1/total cholesterol (EDTA) (mg/dL), CE 17:1/LDL-c/HDL-c, CE 18:3/apoA1/apoB, CE 18:3/apolipoprotein A-I (mg/dL), CE 18:3/apolipoprotein B (mg/dL), CE 18:3/HDL cholesterol (EDTA) (mg/dL), CE 18:3/LDL cholesterol (EDTA) (mg/dL), CE 18:3/LDL-c/HDL-c, CE 18:3/total cholesterol (EDTA) (mg/dL), CE 18:3/total-c/HDL-c, CE 20:3/apolipoprotein B (mg/dL), CE 20:3/LDL-c/HDL-c, CE 20:3/total-c/HDL-c, CE 20:5/apolipoprotein B (mg/dL), CE 20:5/HDL cholesterol (EDTA) (mg/dL), CE 20:5/LDL cholesterol (EDTA) (mg/dL), Cer(d18:0/22:0)/apolipoprotein B (mg/dL), Cer(d18:0/22:0)/LDL-c/HDL-c, Cer(d18:0/22:0)/total-c/HDL-c, Cer(d18:0/24:0)/apolipoprotein A-I (mg/dL), Cer(d18:0/24:0)/apolipoprotein B (mg/dL), Cer(d18:0/24:0)/HDL cholesterol (EDTA)

(mg/dL), Cer(d18:0/24:0)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:0/24:0)/LDL-c/HDL-c, Cer(d18:0/24:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:0/24:0)/total-c/HDL-c, LPC 18:2/apoA1/apoB, LPC 18:2/apolipoprotein B (mg/dL), LPC 18:2/HDL cholesterol (EDTA) (mg/dL), LPC 18:2/LDL cholesterol (EDTA) (mg/dL), LPC 18:2/LDL-c/HDL-c, LPC 18:2/total cholesterol (EDTA) (mg/dL), PC 16:0/20:3/apolipoprotein B (mg/dL), PC 16:0/20:3/HDL cholesterol (EDTA) (mg/dL), PC 16:0/20:3/LDL-c/HDL-c, PC 16:0/20:3/total-c/HDL-c, PC 16:0/20:4/apolipoprotein A-I (mg/dL), PC 16:0/20:4/apolipoprotein B (mg/dL), PC 16:0/20:4/LDL cholesterol (EDTA) (mg/dL), PC 16:0/20:4/LDL-c/HDL-c, PC 16:0/20:4/total cholesterol (EDTA) (mg/dL), PC 16:0/20:4/total-c/HDL-c, PC 18:0/18:1/LDL-c/HDL-c, PC 18:0/20:3/LDL-c/HDL-c, PC 18:0/20:3/total-c/HDL-c, PC 18:0/20:4/apoA1/apoB, Total LPC/LDL-c/HDL-c, Total LPC/total-c/HDL-c, Total PC/apolipoprotein B (mg/dL), Total PC/LDL-c/HDL-c, Total PC/total cholesterol (EDTA) (mg/dL) and Total PC/total-c/HDL-c.

In yet another alternative embodiment the present invention relates to a method for determining whether a subject is at risk to develop one or more CVD complications, such as AMI or CVD death, wherein the subject is not undergoing statin treatment and wherein said method comprises determining in a sample from said subject one or more lipid-clinical concentration ratio(s), wherein (an) increased or decreased lipid-clinical concentration ratio(s) in said sample, when compared to a control sample, is (are) indicative of said subject having an increased risk of developing one or more of CVD complications, such as AMI or CVD death, wherein the one or more lipid-clinical concentration ratio(s) whose increase is (are) compared to the control is (are) selected from (Tables 6b and 9b):

Cer(d18:1/16:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/16:0)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:1/16:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/18:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/18:0)/apolipoprotein B (mg/dL), Cer(d18:1/18:0)/HDL cholesterol (EDTA) (mg/dL), Cer(d18:1/18:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/18:0)/total-c/HDL-c,

Cer(d18:1/18:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/20:0)/apolipoprotein B (mg/dL), Cer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL), Cer(d18:1/20:0)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/20:0)/total-c/HDL-c, Cer(d18:1/20:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/22:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/22:0)/apolipoprotein B (mg/dL), Cer(d18:1/22:0)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:1/22:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/22:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/24:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/24:0)/apolipoprotein B (mg/dL), Cer(d18:1/24:0)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:1/24:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL), Cer(d18:1/24:1)/apolipoprotein B (mg/dL), Cer(d18:1/24:1)/HDL cholesterol (EDTA) (mg/dL), Cer(d18:1/24:1)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:1/24:1)/LDL-c/HDL-c, Cer(d18:1/24:1)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/24:1)/total-c/HDL-c, Cer(d18:1/24:1)/triglycerides (EDTA) (mg/dL), GlcCer(d18:1/20:0)/apolipoprotein B (mg/dL), GlcCer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL), GlcCer(d18:1/24:1)/apolipoprotein B (mg/dL), GlcCer(d18:1/26:1)/apolipoprotein A-I (mg/dL), LacCer(d18:1/16:0)/triglycerides (EDTA) (mg/dL), LacCer(d18:1/18:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/18:0)/apolipoprotein B (mg/dL), LacCer(d18:1/18:0)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/20:0)/apoA1/apoB, LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/apolipoprotein B (mg/dL), LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/20:0)/LDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/20:0)/LDL-c/HDL-c, LacCer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/20:0)/total-c/HDL-c, LacCer(d18:1/20:0)/triglycerides (EDTA) (mg/dL), LacCer(d18:1/22:0)/apoA1/apoB, LacCer(d18:1/22:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/22:0)/apolipoprotein B (mg/dL), LacCer(d18:1/22:0)/HDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/22:0)/LDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/22:0)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/24:1)/apolipoprotein A-I (mg/dL), LacCer(d18:1/24:1)/apolipoprotein B

(mg/dL), LacCer(d18:1/24:1)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/24:1)/triglycerides (EDTA) (mg/dL), PC O-34:1/apolipoprotein B (mg/dL), PS O-16:0/18:2-alkenyl/triglycerides (EDTA) (mg/dL), PS O-16:1/18:2-alkyl/triglycerides (EDTA) (mg/dL), Total Cer/apolipoprotein A-I (mg/dL), Total Cer/apolipoprotein B (mg/dL), Total Cer/LDL cholesterol (EDTA) (mg/dL), Total Cer/total cholesterol (EDTA) (mg/dL), Total DAG/apolipoprotein A-I (mg/dL), Total DAG/triglycerides (EDTA) (mg/dL), Total GlcCer/apolipoprotein B (mg/dL), Total LacCer/apolipoprotein A-I (mg/dL), Total LacCer/apolipoprotein B (mg/dL) and Total LacCer/total cholesterol (EDTA) (mg/dL).

and wherein the one or more lipid-clinical concentration ratio(s) whose decrease is (are) compared to the control is (are) selected from (Tables 6b and 9b):

CE 14:0/apoA1/apoB, CE 14:0/apolipoprotein B (mg/dL), CE 14:0/LDL-c/HDL-c, CE 14:0/total-c/HDL-c, CE 16:1/apoA1/apoB, CE 18:3/apoA1/apoB, CE 18:3/apolipoprotein A-I (mg/dL), CE 18:3/apolipoprotein B (mg/dL), CE 18:3/HDL cholesterol (EDTA) (mg/dL), CE 18:3/LDL cholesterol (EDTA) (mg/dL), CE 18:3/LDL-c/HDL-c, CE 18:3/total cholesterol (EDTA) (mg/dL), CE 18:3/total-c/HDL-c, CE 20:5/triglycerides (EDTA) (mg/dL), Cer(d18:0/24:0)/apolipoprotein B (mg/dL), Cer(d18:0/24:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:0/24:0)/total-c/HDL-c, PC 18:0/20:4/apoA1/apoB, PC O-38:6/apolipoprotein A-I (mg/dL), Total LPC/apoA1/apoB and Total PC/apolipoprotein A-I (mg/dL).

In a preferred embodiment (for subjects that are either undergoing or not undergoing statin treatment), the one or more lipid-clinical concentration ratio(s) whose increase is (are) compared to the control is (are) selected from (Table 12):

Cer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Total Cer/apolipoprotein A-I (mg/dL), Total LacCer/apolipoprotein A-I (mg/dL), Cer(d18:1/18:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/22:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL) and Cer(d18:1/24:1)/apolipoprotein B (mg/dL).

In another preferred embodiment, the one or more lipid-clinical concentration ratio(s) whose decrease is (are) compared to the control is (are) selected from (Table 12): Cer(d18:0/24:0)/apolipoprotein B (mg/dL), Cer(d18:0/24:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:0/24:0)/apolipoprotein B (mg/dL), PC 16:0/20:4/apolipoprotein B (mg/dL) and Cer(d18:0/24:0)/apolipoprotein A-I (mg/dL).

In a particularly preferred embodiment, the lipid-clinical concentration ratio whose increase is compared to the control is (are) selected from (Table 13): Cer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Total LacCer/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL) and Cer(d18:1/18:0)/apolipoprotein A-I (mg/dL).

For the purposes of the invention, and particularly for lipid-clinical concentration ratios, an Apolipoprotein A-I measurement may alternatively be an Apolipoprotein A-II measurement.

claim 2 (note claims only have preferred embodiments) In another aspect the present invention relates to a method for evaluating the effectiveness of a treatment of CVD and/or one or more of its complications, such as AMI or CVD death, in a subject, comprising determining in a sample from said subject the concentration(s) of one or more lipid(s), wherein (an) increased or decreased concentration(s) in said sample, when compared to a control sample, is (are) indicative of effectiveness of said treatment, wherein the one or more lipid(s) whose increase(s) in concentration is (are) compared to the control is (are) selected from (Table 4a and 7a): Cer(d18:1/18:0), Cer(d18:1/20:0), Cer(d18:1/24:1), GlcCer(d18:1/18:0), LacCer(d18:1/18:0), LacCer(d18:1/20:0), LacCer(d18:1/22:0), LacCer(d18:1/24:0), PC O-32:0 (KDdiA-PC), PS O-16:0/18:2-alkenyl, PS O-16:1/18:2-alkyl, PS O-18:0/18:2-alkenyl (PS O-18:1/18:2-alkyl), PS O-18:2/16:0-alkenyl and Total LacCer;

and wherein the one or more lipid(s) whose decrease(s) in concentration is (are) compared to the control is (are) selected from (Table 4a and 7a):
CE 14:0, CE 16:0, CE 17:1, CE 20:3, Cer(d18:0/22:0), Cer(d18:0/24:0), LPC 18:1, PC 16:0/18:2, PC 16:0/20:3, PC 16:0/20:4, PC 16:0/22:6, PC 18:0/18:1, PC 18:0/20:3, PC 18:0/20:4, PC 18:1/18:2, SM (d18:1/14:0) (d18:1/13:1-OH), SM (d18:1/23:0) (d18:1/22:1-OH), SM (d18:1/24:0) (d18:1/23:1-OH), Total CE, Total LPC and Total PC.

In a particular embodiment, the present invention relates to a method for evaluating the effectiveness of a treatment of CVD and/or one or more of its complications, such as AMI or CVD death, in a subject, wherein the subject is not undergoing statin treatment and wherein said method comprises, determining in a sample from said subject the concentration(s) of one or more lipid(s), wherein (an) increased or decreased concentration(s) in said sample, when compared to a control sample, is (are) indicative of effectiveness of said treatment, wherein the one or more lipid(s) whose increase(s) in concentration is (are) compared to the control is (are) selected from (Table 4b and 7b):
Cer(d18:1/16:0), Cer(d18:1/18:0), Cer(d18:1/20:0), Cer(d18:1/22:0), Cer(d18:1/24:1), Cer(d18:1/26:1), GlcCer(d18:1/18:0), GlcCer(d18:1/20:0), GlcCer(d18:1/24:1), GlcCer(d18:1/26:1), LacCer(d18:1/18:0), LacCer(d18:1/20:0), LacCer(d18:1/22:0), LacCer(d18:1/24:0), LacCer(d18:1/24:1), PC O-32:0 (KDdiA-PC), PS O-16:0/18:2-alkenyl, PS O-16:1/18:2-alkyl, PS O-18:2/16:0-alkenyl, Total Cer, Total DAG and Total LacCer;
and wherein the one or more lipid(s) whose decrease(s) in concentration is (are) compared to the control is (are) selected from (Table 4b and 7b):
CE 14:0, CE 17:1, CE 20:3, Cer(d18:0/24:0), LPC 18:1, PC 16:0/20:3, PC 16:0/20:4, PC 18:0/20:4, PC O-40:3, SM (d18:1/14:0) (d18:1/13:1-OH), Total LPC and Total PC.

In a preferred embodiment (for subjects that are either undergoing or not undergoing statin treatment), the one or more lipid(s) whose increase in concentration is (are) compared to the control is (are) selected from (Table 10):

Cer(d18:1/20:0), LacCer(d18:1/20:0), Cer(d18:1/24:1), LacCer(d18:1/24:1), PS O-18:2/16:0-alkenyl, PS O-16:1/18:2-alkyl, Total Cer, Total LacCer, GlcCer(d18:1/24:1), LacCer(d18:1/22:0) and Cer(d18:1/18:0).

In another preferred embodiment, the one or more lipid(s) whose decrease in concentration is (are) compared to the control is (are) selected from (Table 10): Total PC, PC 16:0/20:4, Cer(d18:0/24:0), Total LPC, CE 14:0, CE 20:3, CE 17:1, PC 16:0/20:3, LPC 18:1, PC 18:0/20:3, PC 18:0/18:1 and Cer(d18:0/22:0).

In a particularly preferred embodiment, the one or more lipid(s) whose increase in concentration is (are) compared to the control is (are) selected from (Table 13): Cer(d18:1/20:0), LacCer(d18:1/20:0), Cer(d18:1/24:1), LacCer(d18:1/24:1), LacCer(d18:1/22:0) and Cer(d18:1/18:0);

and the one or more lipid(s) whose decrease in concentration is (are) compared to the control is (are) selected from (Table 13): PC 16:0/20:4 and Cer(d18:0/24:0).

In another alternative embodiment the invention relates to a method for evaluating the effectiveness of a treatment of CVD and/or one or more of its complications, such as AMI or CVD death, in a subject, comprising determining in a sample from said subject one or more lipid-lipid ratio(s), wherein (an) increased or decreased lipid-lipid ratio(s) in said sample, when compared to a control sample, is (are) indicative of effectiveness of said treatment, wherein the one or more lipid-lipid ratio(s) whose increase(s) is (are) compared to the control is (are) selected from (Tables 5a and 8a):

CE 16:0/CE 18:3, CE 18:2/CE 18:3, CE 19:1/Cer(d18:0/22:0), Cer(d18:1/16:0)/LPC 18:1, Cer(d18:1/16:0)/Total PC, Cer(d18:1/18:0)/LPC 16:0, Cer(d18:1/18:0)/LPC 18:1, Cer(d18:1/18:0)/PC 16:0/18:1, Cer(d18:1/18:0)/PC 16:0/20:3, Cer(d18:1/18:0)/PC 16:0/20:4, Cer(d18:1/18:0)/PC 18:0/20:4, Cer(d18:1/18:0)/Total LPC, Cer(d18:1/18:0)/Total PC, Cer(d18:1/20:0)/PC 16:0/18:1, Cer(d18:1/20:0)/PC 16:0/20:3, Cer(d18:1/20:0)/PC 16:0/20:4, Cer(d18:1/20:0)/PC 18:0/20:4,

Cer(d18:1/20:0)/PC 18:1/18:1, Cer(d18:1/20:0)/Total PC, Cer(d18:1/22:0)/LPC 18:2, Cer(d18:1/22:0)/PC 16:0/20:3, Cer(d18:1/22:0)/PC 16:0/20:4, Cer(d18:1/22:0)/Total PC, Cer(d18:1/24:1)/LPC 18:1, Cer(d18:1/24:1)/LPC 18:2, Cer(d18:1/24:1)/PC 16:0/18:1, Cer(d18:1/24:1)/PC 16:0/20:3, Cer(d18:1/24:1)/PC 16:0/20:4, Cer(d18:1/24:1)/PC 18:0/18:1, Cer(d18:1/24:1)/PC 18:0/20:3, Cer(d18:1/24:1)/PC 18:0/20:4, Cer(d18:1/24:1)/SM (d18:1/24:0) (d18:1/23:1-OH), Cer(d18:1/24:1)/Total CE, Cer(d18:1/24:1)/Total LPC, Cer(d18:1/24:1)/Total PC, Cer(d18:1/26:0)/PC O-40:0, GlcCer(d18:1/20:0)/PC 16:0/20:4, GlcCer(d18:1/20:0)/Total PC, GlcCer(d18:1/26:0)/Total CE, LacCer(d18:1/16:0)/Total LPC, LacCer(d18:1/18:0)/PC 16:0/18:1, LacCer(d18:1/18:0)/PC 16:0/20:3, LacCer(d18:1/18:0)/PC 18:0/18:1, LacCer(d18:1/18:0)/PC 18:0/20:3, LacCer(d18:1/18:0)/PC 18:1/18:1, LacCer(d18:1/18:0)/PC 18:1/18:2, LacCer(d18:1/18:0)/Total LPC, LacCer(d18:1/18:0)/Total PC, LacCer(d18:1/20:0)/PC 16:0/18:1, LacCer(d18:1/20:0)/PC 16:0/20:3, LacCer(d18:1/20:0)/PC 18:0/18:1, LacCer(d18:1/20:0)/PC 18:0/20:3 LacCer(d18:1/20:0)/PC 18:1/18:1, LacCer(d18:1/20:0)/PC 18:1/18:2, LacCer(d18:1/20:0)/PC 18:2/18:2, LacCer(d18:1/20:0)/SM (d18:1/17:1-OH), LacCer(d18:1/20:0)/SM (d18:1/18:0), LacCer(d18:1/20:0)/Total LPC, LacCer(d18:1/20:0)/Total PC, LacCer(d18:1/20:0)/Total SM, LacCer(d18:1/22:0)/PC 16:0/20:3, LacCer(d18:1/22:0)/PC 16:0/20:4, LacCer(d18:1/22:0)/PC 18:0/20:3, LacCer(d18:1/22:0)/SM (d18:1/14:0) (d18:1/13:1-OH), LacCer(d18:1/22:0)/Total LPC, LacCer(d18:1/22:0)/Total PC, LacCer(d18:1/24:0)/PC 16:0/20:3, LacCer(d18:1/24:0)/Total LPC, LacCer(d18:1/24:1)/Total LPC, LacCer(d18:1/24:1)/Total PC, LacCer(d18:1/24:1)/Total PC O, PC 16:0/16:0/PC 16:0/20:4, PC 16:0/16:0/Total PC, PC 16:0/18:2/Total PC, PC O-18:0/18:2-alkyl/PC O-36:5, PC O-32:0 (KDdiA-PC)/PC O-38:5, PS O-16:0/18:2-alkenyl/Total PS O, PS O-16:1/18:2-alkyl/Total PS O, PS O-18:0/18:2-alkenyl (PS O-18:1/18:2-alkyl)/Total PS O, PS O-18:2/16:0-alkenyl/Total PS O, Total Cer/Total PC, Total LacCer/Total PC and Total LacCer/Total PC O;

and wherein one or more lipid-lipid ratio(s) whose decrease is (are) compared to the control is (are) selected from (Tables 5a and 8a):

CE 14:0/Cer(d18:1/24:1), CE 16:0/Cer(d18:1/24:1), CE 16:1/CE 19:1, CE 16:1/Cer(d18:1/18:0), CE 16:1/Cer(d18:1/20:0), CE 16:1/Cer(d18:1/24:1), CE 16:1/GlcCer(d18:1/18:0), CE 16:1/GlcCer(d18:1/20:0), CE 16:1/LacCer(d18:1/16:0), CE 16:1/LacCer(d18:1/18:0), CE 16:1/LacCer(d18:1/20:0), CE 16:1/LacCer(d18:1/22:0), CE 16:1/LacCer(d18:1/24:0), CE 16:1/PC 16:0/16:0, CE 16:1/Total LacCer, CE 17:1/Cer(d18:1/24:1), CE 17:1/GlcCer(d18:1/24:1), CE 17:1/LacCer(d18:1/18:0), CE 18:1/Total LacCer, CE 18:3/Cer(d18:1/16:0), CE 18:3/Cer(d18:1/18:0), CE 18:3/Cer(d18:1/20:0), CE 18:3/Cer(d18:1/22:0), CE 18:3/Cer(d18:1/24:0), CE 18:3/Cer(d18:1/24:1), CE 18:3/GlcCer(d18:1/18:0), CE 18:3/GlcCer(d18:1/20:0), CE 18:3/LacCer(d18:1/18:0), CE 18:3/LacCer(d18:1/20:0), CE 18:3/LacCer(d18:1/22:0), CE 18:3/LacCer(d18:1/24:0), CE 18:3/PC 16:0/16:0, CE 18:3/PC O-34:1, CE 18:3/PS O-16:0/18:1-alkenyl (PS O-16:1/18:1-alkyl), CE 18:3/PS O-16:0/18:2-alkenyl, CE 18:3/PS O-16:1/18:2-alkyl, CE 18:3/Total CE, CE 18:3/Total Cer, CE 18:3/Total LacCer, CE 20:3/Cer(d18:1/24:1), CE 20:3/LacCer(d18:1/20:0), Cer(d18:0/22:0)/Cer(d18:1/18:0), Cer(d18:0/22:0)/Cer(d18:1/20:0), Cer(d18:0/22:0)/Cer(d18:1/22:0), Cer(d18:0/22:0)/Cer(d18:1/24:1), Cer(d18:0/22:0)/LacCer(d18:1/24:0), Cer(d18:0/22:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/22:0)/PS O-16:1/18:2-alkyl, Cer(d18:0/22:0)/Total CE, Cer(d18:0/24:0)/Cer(d18:1/16:0), Cer(d18:0/24:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/Cer(d18:1/20:0), Cer(d18:0/24:0)/Cer(d18:1/22:0), Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/24:0)/GlcCer(d18:1/20:0), Cer(d18:0/24:0)/LacCer(d18:1/24:0), Cer(d18:0/24:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/24:0)/PS O-16:1/18:2-alkyl, Cer(d18:0/24:0)/SM (d18:1/17:0) (d18:1/16:1-OH), Cer(d18:0/24:0)/Total CE, Cer(d18:0/24:0)/Total Cer, Cer(d18:0/24:1)/Total CE, GlcCer(d18:1/26:0)/LacCer(d18:1/20:0), GlcCer(d18:1/26:0)/LacCer(d18:1/22:0), LPC 16:0/LacCer(d18:1/20:0), LPC 16:0/LacCer(d18:1/22:0), LPC 16:0/LacCer(d18:1/24:1), LPC 16:0/Total LacCer, LPC 18:1/LacCer(d18:1/20:0), LPC 18:2/LacCer(d18:1/20:0), LPC 18:2/PS O-16:0/18:2-alkenyl, LPC 18:2/PS O-

16:1/18:2-alkyl, PC 16:0/20:3/PS O-16:0/18:2-alkenyl, PC 16:0/20:3/PS O-16:1/18:2-alkyl, PC 18:1/18:2/PS O-16:0/18:2-alkenyl, PC 18:1/18:2/PS O-16:1/18:2-alkyl, SM (d18:1/24:0) (d18:1/23:1-OH)/Total Cer and Total LPC/Total LacCer.

In another alternative embodiment the invention relates to a method for evaluating the effectiveness of a treatment of CVD and/or one or more of its complications, such as AMI or CVD death, in a subject, wherein the subject is not undergoing statin treatment and wherein said method comprises comprising determining in a sample from said subject one or more lipid-lipid ratio(s), wherein (an) increased or decreased lipid-lipid ratio(s) in said sample, when compared to a control sample, is (are) indicative of effectiveness of said treatment, wherein the one or more lipid-lipid ratio(s) whose increase(s) is (are) compared to the control is (are) selected from (Tables 5b and 8b):
CE 16:0/CE 18:3, CE 18:0/CE 18:3, CE 18:2/CE 18:3, Cer(d18:1/16:0)/LPC 18:1, Cer(d18:1/16:0)/Total PC, Cer(d18:1/18:0)/LPC 18:1, Cer(d18:1/18:0)/PC 16:0/18:1, Cer(d18:1/18:0)/PC 16:0/20:3, Cer(d18:1/18:0)/PC 16:0/20:4, Cer(d18:1/18:0)/PC 18:0/18:1, Cer(d18:1/18:0)/PC 18:0/20:4, Cer(d18:1/18:0)/PC 18:1/18:1, Cer(d18:1/18:0)/SM (d18:1/14:0) (d18:1/13:1-OH), Cer(d18:1/18:0)/SM (d18:1/17:2-OH), Cer(d18:1/18:0)/SM (d18:1/18:1), Cer(d18:1/18:0)/Total CE, Cer(d18:1/18:0)/Total LPC, Cer(d18:1/18:0)/Total PC, Cer(d18:1/20:0)/PC 16:0/18:1, Cer(d18:1/20:0)/PC 16:0/20:3, Cer(d18:1/20:0)/PC 16:0/20:4, Cer(d18:1/20:0)/PC 18:0/18:1, Cer(d18:1/20:0)/PC 18:0/20:4, Cer(d18:1/20:0)/PC 18:1/18:1, Cer(d18:1/20:0)/SM (d18:1/14:0) (d18:1/13:1-OH), Cer(d18:1/20:0)/Total LPC, Cer(d18:1/20:0)/Total PC, Cer(d18:1/20:0)/Total PC O, Cer(d18:1/22:0)/LPC 18:2, Cer(d18:1/22:0)/PC 16:0/20:3, Cer(d18:1/22:0)/PC 16:0/20:4, Cer(d18:1/22:0)/PC 18:0/20:4, Cer(d18:1/22:0)/Total PC, Cer(d18:1/24:1)/LPC 18:1, Cer(d18:1/24:1)/LPC 18:2, Cer(d18:1/24:1)/PC 16:0/18:1, Cer(d18:1/24:1)/PC 16:0/18:2, Cer(d18:1/24:1)/PC 16:0/20:3, Cer(d18:1/24:1)/PC 16:0/20:4, Cer(d18:1/24:1)/PC 18:0/18:1, Cer(d18:1/24:1)/PC 18:0/18:2, Cer(d18:1/24:1)/PC 18:0/20:3, Cer(d18:1/24:1)/PC 18:0/20:4, Cer(d18:1/24:1)/PC 18:1/18:1, Cer(d18:1/24:1)/PC 18:1/18:2, Cer(d18:1/24:1)/PC O-40:3, Cer(d18:1/24:1)/SM (d18:1/17:1-OH),

Cer(d18:1/24:1)/SM (d18:1/18:0), Cer(d18:1/24:1)/SM (d18:1/23:0) (d18:1/22:1-OH), Cer(d18:1/24:1)/SM (d18:1/24:0) (d18:1/23:1-OH), Cer(d18:1/24:1)/Total CE, Cer(d18:1/24:1)/Total LPC, Cer(d18:1/24:1)/Total PC, GlcCer(d18:1/26:0)/Total CE, GlcCer(d18:1/26:1)/Total CE, LacCer(d18:1/18:0)/Total PC, LacCer(d18:1/20:0)/PC 16:0/20:3, LacCer(d18:1/20:0)/PC 16:0/20:4, LacCer(d18:1/20:0)/PC 18:0/18:1, LacCer(d18:1/20:0)/PC 18:0/20:3, LacCer(d18:1/20:0)/PC 18:0/20:4, LacCer(d18:1/20:0)/PC 18:1/18:2, LacCer(d18:1/20:0)/SM (d18:1/17:1-OH), LacCer(d18:1/20:0)/SM (d18:1/18:0), LacCer(d18:1/20:0)/Total CE, LacCer(d18:1/20:0)/Total LPC, LacCer(d18:1/20:0)/Total PC, LacCer(d18:1/20:0)/Total SM, LacCer(d18:1/24:0)/Total LPC, PC 16:0/16:0/PC 16:0/20:4, PC 16:0/16:0/Total PC, PC O-32:0 (KDdiA-PC)/Total PC O, PS O-16:0/18:2-alkenyl/Total PC, PS O-16:0/18:2-alkenyl/Total PC O, PS O-16:0/18:2-alkenyl/Total PS O, PS O-16:1/18:2-alkyl/Total PC, PS O-16:1/18:2-alkyl/Total PC O, PS O-16:1/18:2-alkyl/Total PS O, PS O-18:2/16:0-alkenyl/Total PC O, PS O-18:2/16:0-alkenyl/Total PS O, SM (d18:1/17:0) (d18:1/16:1-OH)/Total PC O, Total Cer/Total PC, Total DAG/Total LPC, Total DAG/Total PC, Total DAG/Total PC O and Total LacCer/Total PC;

and wherein the one or more lipid-lipid ratio(s) whose decrease(s) is (are) compared to the control is (are) selected from (Tables 5b and 8b):

CE 14:0/Cer(d18:1/18:0), CE 14:0/Cer(d18:1/24:1), CE 14:0/Total DAG, CE 15:0/Cer(d18:1/20:0), CE 16:0/Cer(d18:1/18:0), CE 16:0/Cer(d18:1/24:1), CE 16:1/CE 19:1, CE 16:1/Cer(d18:1/18:0), CE 16:1/Cer(d18:1/20:0), CE 16:1/Cer(d18:1/24:1), CE 16:1/GlcCer(d18:1/24:1), CE 16:1/LacCer(d18:1/18:0), CE 16:1/LacCer(d18:1/24:0), CE 16:1/Total LacCer, CE 17:1/Cer(d18:1/18:0), CE 17:1/Cer(d18:1/24:1), CE 18:2/Cer(d18:1/20:0), CE 18:2/Cer(d18:1/24:1), CE 18:3/Cer(d18:1/16:0), CE 18:3/Cer(d18:1/18:0), CE 18:3/Cer(d18:1/20:0), CE 18:3/Cer(d18:1/22:0), CE 18:3/Cer(d18:1/24:0), CE 18:3/Cer(d18:1/24:1), CE 18:3/GlcCer(d18:1/20:0), CE 18:3/LacCer(d18:1/20:0), CE 18:3/LacCer(d18:1/22:0), CE 18:3/LacCer(d18:1/24:0), CE 18:3/PC 16:0/16:0, CE 18:3/PC O-34:1, CE 18:3/PS O-16:0/18:2-alkenyl, CE 18:3/PS O-16:1/18:2-alkyl, CE 18:3/Total CE, CE 18:3/Total Cer, CE 18:3/Total DAG,

CE 18:3/Total LacCer, CE 20:3/Cer(d18:1/24:1), CE 20:3/LacCer(d18:1/20:0), CE 20:4/Cer(d18:1/18:0), CE 20:4/Cer(d18:1/24:1), CE 20:4/GlcCer(d18:1/20:0), CE 20:4/GlcCer(d18:1/24:1), CE 20:4/LacCer(d18:1/20:0), CE 20:5/LacCer(d18:1/20:0), Cer(d18:0/22:0)/Cer(d18:1/18:0), Cer(d18:0/22:0)/Cer(d18:1/20:0), Cer(d18:0/22:0)/Cer(d18:1/24:1), Cer(d18:0/22:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/22:0)/PS O-16:1/18:2-alkyl, Cer(d18:0/22:0)/Total CE, Cer(d18:0/22:0)/Total DAG, Cer(d18:0/22:0)/Total GlcCer, Cer(d18:0/24:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/Cer(d18:1/20:0), Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/24:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/24:0)/PS O-16:1/18:2-alkyl, Cer(d18:0/24:0)/Total CE, Cer(d18:0/24:0)/Total Cer, DAG 16:0/18:1/Total DAG, GlcCer(d18:1/26:0)/LacCer(d18:1/20:0), LPC 16:0/LacCer(d18:1/24:0), LPC 18:1/LacCer(d18:1/20:0), LPC 18:2/LacCer(d18:1/20:0), PC 16:0/20:3/PS O-16:0/18:2-alkenyl, PC 16:0/20:3/PS O-16:1/18:2-alkyl, PC 16:0/20:4/PS O-16:0/18:2-alkenyl, PC 16:0/20:4/PS O-16:1/18:2-alkyl, PC 16:0/20:4/Total DAG, PC 18:0/20:3/PS O-16:0/18:2-alkenyl, PC 18:0/20:3/PS O-16:1/18:2-alkyl, PC 18:0/20:3/PS O-18:2/16:0-alkenyl, PC 18:0/20:4/PS O-16:0/18:2-alkenyl, PC 18:0/20:4/PS O-16:1/18:2-alkyl, PC 18:1/18:2/PS O-16:0/18:2-alkenyl, PC 18:1/18:2/PS O-16:1/18:2-alkyl, PC 18:1/18:2/Total Cer, PC O-40:3/PS O-18:2/16:0-alkenyl, SM (d18:1/23:0) (d18:1/22:1-OH)/Total DAG, SM (d18:1/24:0) (d18:1/23:1-OH)/Total Cer, Total CE/Total DAG and Total LPC/Total LacCer.

In a preferred embodiment (for subjects that are either undergoing or not undergoing statin treatment), the one or more lipid-lipid ratio(s) whose increase is (are) compared to the control is (are) selected from (Table 11):

GlcCer(d18:1/26:1)/Total CE, Cer(d18:1/24:1)/Total PC, Cer(d18:1/24:1)/PC 16:0/20:4, Cer(d18:1/20:0)/PC 16:0/20:4, LacCer(d18:1/20:0)/PC 16:0/20:3, Total Cer/Total PC, Total LacCer/Total PC, LacCer(d18:1/20:0)/PC 18:1/18:2, PS O-16:0/18:2-alkenyl/Total PS O, Cer(d18:1/18:0)/PC 16:0/20:4, LacCer(d18:1/20:0)/Total LPC and LacCer(d18:1/20:0)/PC 16:0/20:4.

In another preferred embodiment, the one or more lipid-lipid ratio(s) whose decrease is (are) compared to the control is (are) selected from (Table 11): Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/22:0)/Cer(d18:1/24:1), DAG 16:0/18:1/Total DAG, Cer(d18:0/24:0)/Cer(d18:1/22:0), Cer(d18:0/24:0)/Total CE, Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/24:0)/Total Cer, Cer(d18:0/24:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/24:0)/LacCer(d18:1/24:0), Cer(d18:0/22:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/Cer(d18:1/22:0), Cer(d18:0/22:0)/Cer(d18:1/20:0), Cer(d18:0/22:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/22:0)/PS O-16:1/18:2-alkyl, GlcCer(d18:1/26:0)/LacCer(d18:1/20:0), Total LPC/Total LacCer and GlcCer(d18:1/26:0)/LacCer(d18:1/22:0).

In a particularly preferred embodiment, the one or more lipid-lipid ratio(s) whose increase is (are) compared to the control is (are) selected from (Table 13): Cer(d18:1/24:1)/PC 16:0/20:4, LacCer(d18:1/20:0)/PC 16:0/20:3, PS O-16:0/18:2-alkenyl/Total PS O and Cer(d18:1/18:0)/PC 16:0/20:4;
and the one or more lipid-lipid ratio(s) whose decrease is (are) compared to the control is (are) selected from (Table 13): GlcCer(d18:1/26:0)/LacCer(d18:1/20:0), DAG 16:0/18:1/Total DAG, Cer(d18:0/24:0)/Total Cer, Total LPC/Total LacCer, GlcCer(d18:1/26:0)/LacCer(d18:1/22:0), Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/24:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/24:0)/Cer(d18:1/22:0), Cer(d18:0/22:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/22:0)/PS O-16:1/18:2-alkyl and Cer(d18:0/24:0)/LacCer(d18:1/24:0).

In yet another alternative embodiment the invention relates to a method for evaluating the effectiveness of a treatment of CVD and/or one or more of its complications, such as AMI or CVD death, in a subject, comprising determining in a sample from said subject one or more lipid-clinical concentration ratio(s), wherein (an) increased or

decreased lipid-clinical concentration ratio(s) in said sample, when compared to a control sample, is (are) indicative of effectiveness of said treatment, wherein the one or more lipid-clinical concentration ratio(s) whose increase(s) is (are) compared to the control is (are) selected from (Tables 6a and 9a):

Cer(d18:1/16:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/18:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/18:0)/apolipoprotein B (mg/dL), Cer(d18:1/18:0)/HDL cholesterol (EDTA) (mg/dL), Cer(d18:1/18:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/18:0)/total-c/HDL-c, Cer(d18:1/18:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/20:0)/apolipoprotein B (mg/dL), Cer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL), Cer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/20:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/22:0)/apolipoprotein B (mg/dL), Cer(d18:1/22:0)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:1/22:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL), Cer(d18:1/24:1)/apolipoprotein B (mg/dL), Cer(d18:1/24:1)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:1/24:1)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/24:1)/total-c/HDL-c, Cer(d18:1/24:1)/triglycerides (EDTA) (mg/dL), GlcCer(d18:1/24:0)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/16:0)/triglycerides (EDTA) (mg/dL), LacCer(d18:1/18:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/18:0)/apolipoprotein B (mg/dL), LacCer(d18:1/18:0)/HDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/18:0)/LDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/18:0)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/18:0)/total-c/HDL-c, LacCer(d18:1/18:0)/triglycerides (EDTA) (mg/dL), LacCer(d18:1/20:0)/apoA1/apoB, LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/apolipoprotein B (mg/dL), LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/20:0)/LDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/20:0)/LDL-c/HDL-c, LacCer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/20:0)/total-c/HDL-c, LacCer(d18:1/20:0)/triglycerides (EDTA) (mg/dL), LacCer(d18:1/22:0)/apoA1/apoB, LacCer(d18:1/22:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/22:0)/apolipoprotein B (mg/dL), LacCer(d18:1/22:0)/HDL cholesterol

(EDTA) (mg/dL), LacCer(d18:1/22:0)/LDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/22:0)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/22:0)/total-c/HDL-c, LacCer(d18:1/22:0)/triglycerides (EDTA) (mg/dL), LacCer(d18:1/24:0)/apoA1/apoB, LacCer(d18:1/24:1)/apolipoprotein A-I (mg/dL), LacCer(d18:1/24:1)/apolipoprotein B (mg/dL), LacCer(d18:1/24:1)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/24:1)/triglycerides (EDTA) (mg/dL), PC O-32:0 (KDdiA-PC)/apolipoprotein A-I (mg/dL), PC O-32:0 (KDdiA-PC)/triglycerides (EDTA) (mg/dL), PC O-34:1/triglycerides (EDTA) (mg/dL), PS O-16:0/18:1-alkenyl (PS O-16:1/18:1-alkyl)/triglycerides (EDTA) (mg/dL), PS O-16:0/18:2-alkenyl/triglycerides (EDTA) (mg/dL), PS O-16:1/18:2-alkyl/triglycerides (EDTA) (mg/dL), PS O-18:2/16:0-alkenyl/HDL cholesterol (EDTA) (mg/dL), PS O-18:2/16:0-alkenyl/triglycerides (EDTA) (mg/dL), Total Cer/apolipoprotein A-I (mg/dL), Total Cer/total cholesterol (EDTA) (mg/dL), Total Cer/triglycerides (EDTA) (mg/dL), Total GlcCer/apolipoprotein B (mg/dL), Total GlcCer/total cholesterol (EDTA) (mg/dL), Total LacCer/apolipoprotein A-I (mg/dL), Total LacCer/apolipoprotein B (mg/dL), Total LacCer/total cholesterol (EDTA) (mg/dL) and Total LacCer/triglycerides (EDTA) (mg/dL);

and wherein the one or more lipid-clinical concentration ratio(s) whose decrease is (are) compared to the control is (are) selected from Tables 6a and 9a:

CE 14:0/apolipoprotein B (mg/dL), CE 14:0/LDL cholesterol (EDTA) (mg/dL), CE 14:0/LDL-c/HDL-c, CE 14:0/total cholesterol (EDTA) (mg/dL), CE 14:0/total-c/HDL-c, CE 16:1/apolipoprotein B (mg/dL), CE 16:1/HDL cholesterol (EDTA) (mg/dL), CE 16:1/LDL cholesterol (EDTA) (mg/dL), CE 16:1/total cholesterol (EDTA) (mg/dL), CE 17:1/LDL-c/HDL-c, CE 18:3/apoA1/apoB, CE 18:3/apolipoprotein A-I (mg/dL), CE 18:3/apolipoprotein B (mg/dL), CE 18:3/HDL cholesterol (EDTA) (mg/dL), CE 18:3/LDL cholesterol (EDTA) (mg/dL), CE 18:3/LDL-c/HDL-c, CE 18:3/total cholesterol (EDTA) (mg/dL), CE 18:3/total-c/HDL-c, CE 20:3/apolipoprotein B (mg/dL), CE 20:3/LDL-c/HDL-c, CE 20:3/total-c/HDL-c, CE 20:5/apolipoprotein B (mg/dL), CE 20:5/HDL cholesterol (EDTA) (mg/dL), CE 20:5/LDL cholesterol (EDTA) (mg/dL), Cer(d18:0/22:0)/apolipoprotein B (mg/dL), Cer(d18:0/22:0)/LDL-

c/HDL-c, Cer(d18:0/22:0)/total-c/HDL-c, Cer(d18:0/24:0)/apolipoprotein A-I (mg/dL), Cer(d18:0/24:0)/apolipoprotein B (mg/dL), Cer(d18:0/24:0)/HDL cholesterol (EDTA) (mg/dL), Cer(d18:0/24:0)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:0/24:0)/LDL-c/HDL-c, Cer(d18:0/24:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:0/24:0)/total-c/HDL-c, LPC 18:2/apoA1/apoB, LPC 18:2/apolipoprotein B (mg/dL), LPC 18:2/HDL cholesterol (EDTA) (mg/dL), LPC 18:2/LDL cholesterol (EDTA) (mg/dL), LPC 18:2/LDL-c/HDL-c, LPC 18:2/total cholesterol (EDTA) (mg/dL), PC 16:0/20:3/apolipoprotein B (mg/dL), PC 16:0/20:3/HDL cholesterol (EDTA) (mg/dL), PC 16:0/20:3/LDL-c/HDL-c, PC 16:0/20:3/total-c/HDL-c, PC 16:0/20:4/apolipoprotein A-I (mg/dL), PC 16:0/20:4/apolipoprotein B (mg/dL), PC 16:0/20:4/LDL cholesterol (EDTA) (mg/dL), PC 16:0/20:4/LDL-c/HDL-c, PC 16:0/20:4/total cholesterol (EDTA) (mg/dL), PC 16:0/20:4/total-c/HDL-c, PC 18:0/18:1/LDL-c/HDL-c, PC 18:0/20:3/LDL-c/HDL-c, PC 18:0/20:3/total-c/HDL-c, PC 18:0/20:4/apoA1/apoB, Total LPC/LDL-c/HDL-c, Total LPC/total-c/HDL-c, Total PC/apolipoprotein B (mg/dL), Total PC/LDL-c/HDL-c, Total PC/total cholesterol (EDTA) (mg/dL) and Total PC/total-c/HDL-c.

In yet another alternative embodiment the invention relates to a method for evaluating the effectiveness of a treatment of CVD and/or one or more of its complications, such as AMI or CVD death, in a subject, wherein the subject is not undergoing statin treatment and wherein said method comprises determining in a sample from said subject one or more lipid-clinical concentration ratio(s), wherein (an) increased or decreased lipid-clinical concentration ratio(s) in said sample, when compared to a control sample, is (are) indicative of effectiveness of said treatment, wherein the one or more lipid-clinical concentration ratio(s) whose increase(s) is (are) compared to the control is (are) selected from (Tables 6b and 9b):
Cer(d18:1/16:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/16:0)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:1/16:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/18:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/18:0)/apolipoprotein B (mg/dL), Cer(d18:1/18:0)/HDL cholesterol (EDTA) (mg/dL), Cer(d18:1/18:0)/total

cholesterol (EDTA) (mg/dL), Cer(d18:1/18:0)/total-c/HDL-c, Cer(d18:1/18:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/20:0)/apolipoprotein B (mg/dL), Cer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL), Cer(d18:1/20:0)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/20:0)/total-c/HDL-c, Cer(d18:1/20:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/22:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/22:0)/apolipoprotein B (mg/dL), Cer(d18:1/22:0)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:1/22:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/22:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/24:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/24:0)/apolipoprotein B (mg/dL), Cer(d18:1/24:0)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:1/24:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL), Cer(d18:1/24:1)/apolipoprotein B (mg/dL), Cer(d18:1/24:1)/HDL cholesterol (EDTA) (mg/dL), Cer(d18:1/24:1)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:1/24:1)/LDL-c/HDL-c, Cer(d18:1/24:1)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/24:1)/total-c/HDL-c, Cer(d18:1/24:1)/triglycerides (EDTA) (mg/dL), GlcCer(d18:1/20:0)/apolipoprotein B (mg/dL), GlcCer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL), GlcCer(d18:1/24:1)/apolipoprotein B (mg/dL), GlcCer(d18:1/26:1)/apolipoprotein A-I (mg/dL), LacCer(d18:1/16:0)/triglycerides (EDTA) (mg/dL), LacCer(d18:1/18:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/18:0)/apolipoprotein B (mg/dL), LacCer(d18:1/18:0)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/20:0)/apoA1/apoB, LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/apolipoprotein B (mg/dL), LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/20:0)/LDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/20:0)/LDL-c/HDL-c, LacCer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/20:0)/total-c/HDL-c, LacCer(d18:1/20:0)/triglycerides (EDTA) (mg/dL), LacCer(d18:1/22:0)/apoA1/apoB, LacCer(d18:1/22:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/22:0)/apolipoprotein B (mg/dL), LacCer(d18:1/22:0)/HDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/22:0)/LDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/22:0)/total cholesterol (EDTA) (mg/dL),

LacCer(d18:1/24:1)/apolipoprotein A-I (mg/dL), LacCer(d18:1/24:1)/apolipoprotein B (mg/dL), LacCer(d18:1/24:1)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/24:1)/triglycerides (EDTA) (mg/dL), PC O-34:1/apolipoprotein B (mg/dL), PS O-16:0/18:2-alkenyl/triglycerides (EDTA) (mg/dL), PS O-16:1/18:2-alkyl/triglycerides (EDTA) (mg/dL), Total Cer/apolipoprotein A-I (mg/dL), Total Cer/apolipoprotein B (mg/dL), Total Cer/LDL cholesterol (EDTA) (mg/dL), Total Cer/total cholesterol (EDTA) (mg/dL), Total DAG/apolipoprotein A-I (mg/dL), Total DAG/triglycerides (EDTA) (mg/dL), Total GlcCer/apolipoprotein B (mg/dL), Total LacCer/apolipoprotein A-I (mg/dL), Total LacCer/apolipoprotein B (mg/dL) and Total LacCer/total cholesterol (EDTA) (mg/dL).

and wherein the one or more lipid-clinical concentration ratio(s) whose decrease is (are) compared to the control is (are) selected from (Tables 6b and 9b):

CE 14:0/apoA1/apoB, CE 14:0/apolipoprotein B (mg/dL), CE 14:0/LDL-c/HDL-c, CE 14:0/total-c/HDL-c, CE 16:1/apoA1/apoB, CE 18:3/apoA1/apoB, CE 18:3/apolipoprotein A-I (mg/dL), CE 18:3/apolipoprotein B (mg/dL), CE 18:3/HDL cholesterol (EDTA) (mg/dL), CE 18:3/LDL cholesterol (EDTA) (mg/dL), CE 18:3/LDL-c/HDL-c, CE 18:3/total cholesterol (EDTA) (mg/dL), CE 18:3/total-c/HDL-c, CE 20:5/triglycerides (EDTA) (mg/dL), Cer(d18:0/24:0)/apolipoprotein B (mg/dL), Cer(d18:0/24:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:0/24:0)/total-c/HDL-c, PC 18:0/20:4/apoA1/apoB, PC O-38:6/apolipoprotein A-I (mg/dL), Total LPC/apoA1/apoB and Total PC/apolipoprotein A-I (mg/dL).

In a preferred embodiment (for subjects that are either undergoing or not undergoing statin treatment), the one or more lipid-clinical concentration ratio(s) whose increase is (are) compared to the control is (are) selected from (Table 12):

Cer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Total Cer/apolipoprotein A-I (mg/dL), Total LacCer/apolipoprotein A-I (mg/dL), Cer(d18:1/18:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/22:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL) and Cer(d18:1/24:1)/apolipoprotein B (mg/dL).

In another preferred embodiment, the one or more lipid-clinical concentration ratio(s) whose decrease is (are) compared to the control is (are) selected from (Table 12): Cer(d18:0/24:0)/apolipoprotein B (mg/dL), Cer(d18:0/24:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:0/24:0)/apolipoprotein B (mg/dL), PC 16:0/20:4/apolipoprotein B (mg/dL) and Cer(d18:0/24:0)/apolipoprotein A-I (mg/dL).

In a particularly preferred embodiment, the lipid-clinical concentration ratio(s) whose increased is (are) compared to the control are selected from (Table 13): Cer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Total LacCer/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL) and Cer(d18:1/18:0)/apolipoprotein A-I (mg/dL).

For the purposes of the invention, and particularly for lipid-clinical concentration ratios, an Apolipoprotein A-I measurement may alternatively be an Apolipoprotein A-II measurement.

Claim 3 (note claims only have preferred embodiments) In yet another aspect the invention relates to a method of choosing an appropriate treatment of CVD and/or one or more of its complications, such as AMI or CVD death, in a subject, comprising determining in a sample from said subject the concentration of one or more lipid(s), wherein (an) increased or decreased concentration(s) in said sample, when compared to a control sample, is (are) indicative of said subject being in need of treatment or a change in, or supplementation of, an already administered treatment, wherein the one or more lipid(s) whose increase(s) in concentration is (are) compared to the control is (are) selected from (Tables 4a and 7a):
Cer(d18:1/18:0), Cer(d18:1/20:0), Cer(d18:1/24:1), GlcCer(d18:1/18:0), LacCer(d18:1/18:0), LacCer(d18:1/20:0), LacCer(d18:1/22:0), LacCer(d18:1/24:0), PC

O-32:0 (KDdiA-PC), PS O-16:0/18:2-alkenyl, PS O-16:1/18:2-alkyl, PS O-18:0/18:2-alkenyl (PS O-18:1/18:2-alkyl), PS O-18:2/16:0-alkenyl and Total LacCer;

and wherein the one or more lipid(s) whose decrease(s) in concentration is (are) compared to the control is (are) selected from (Tables 4a and 7a):

CE 14:0, CE 16:0, CE 17:1, CE 20:3, Cer(d18:0/22:0), Cer(d18:0/24:0), LPC 18:1, PC 16:0/18:2, PC 16:0/20:3, PC 16:0/20:4, PC 16:0/22:6, PC 18:0/18:1, PC 18:0/20:3, PC 18:0/20:4, PC 18:1/18:2, SM (d18:1/14:0) (d18:1/13:1-OH), SM (d18:1/23:0) (d18:1/22:1-OH), SM (d18:1/24:0) (d18:1/23:1-OH), Total CE, Total LPC and Total PC.

In yet another aspect the invention relates to a method of choosing an appropriate treatment of CVD and/or one or more of its complications, such as AMI or CVD death, in a subject, wherein the subject is not undergoing statin treatment and wherein said method comprises determining in a sample from said subject the concentration of one or more lipid(s), wherein (an) increased or decreased concentration(s) in said sample, when compared to a control sample, is (are) indicative of said subject being in need of treatment or a change in, or supplementation of, an already administered treatment, wherein the one or more lipid(s) whose increase(s) in concentration is (are) compared to the control is (are) selected from (Tables 4b and 7b):

Cer(d18:1/16:0), Cer(d18:1/18:0), Cer(d18:1/20:0), Cer(d18:1/22:0), Cer(d18:1/24:1), Cer(d18:1/26:1), GlcCer(d18:1/18:0), GlcCer(d18:1/20:0), GlcCer(d18:1/24:1), GlcCer(d18:1/26:1), LacCer(d18:1/18:0), LacCer(d18:1/20:0), LacCer(d18:1/22:0), LacCer(d18:1/24:0), LacCer(d18:1/24:1), PC O-32:0 (KDdiA-PC), PS O-16:0/18:2-alkenyl, PS O-16:1/18:2-alkyl, PS O-18:2/16:0-alkenyl, Total Cer, Total DAG and Total LacCer;

and wherein the one or more lipid(s) whose decrease(s) in concentration is (are) compared to the control is (are) selected from (Tables 4b and 7b):

CE 14:0, CE 17:1, CE 20:3, Cer(d18:0/24:0), LPC 18:1, PC 16:0/20:3, PC 16:0/20:4, PC 18:0/20:4, PC O-40:3, SM (d18:1/14:0) (d18:1/13:1-OH), Total LPC and Total PC.

In a preferred embodiment (for subjects that are either undergoing or not undergoing statin treatment), the one or more lipid(s) whose increase in concentration is (are) compared to the control is (are) selected from (Table 10):
Cer(d18:1/20:0), LacCer(d18:1/20:0), Cer(d18:1/24:1), LacCer(d18:1/24:1), PS O-18:2/16:0-alkenyl, PS O-16:1/18:2-alkyl, Total Cer, Total LacCer, GlcCer(d18:1/24:1), LacCer(d18:1/22:0) and Cer(d18:1/18:0).

In another preferred embodiment, the one or more lipid(s) whose decrease in concentration is (are) compared to the control is (are) selected from (Table 10):
Total PC, PC 16:0/20:4, Cer(d18:0/24:0), Total LPC, CE 14:0, CE 20:3, CE 17:1, PC 16:0/20:3, LPC 18:1, PC 18:0/20:3, PC 18:0/18:1 and Cer(d18:0/22:0).

In a particularly preferred embodiment, the one or more lipid(s) whose increase in concentration is (are) compared to the control is (are) selected from (Table 13):
Cer(d18:1/20:0), LacCer(d18:1/20:0), Cer(d18:1/24:1), LacCer(d18:1/24:1), LacCer(d18:1/22:0) and Cer(d18:1/18:0);
and the one or more lipid(s) whose decrease in concentration is (are) compared to the control is (are) selected from (Table 13): PC 16:0/20:4 and Cer(d18:0/24:0).

In an alternative embodiment the invention relates to a method of choosing an appropriate treatment of CVD and/or one or more of its complications, such as AMI or CVD death, in a subject, comprising determining in a sample from said subject one or more lipid-lipid ratio(s), wherein (an) increased or decreased lipid-lipid ratio(s) in said sample, when compared to a control sample, is (are) indicative of said subject being in need of treatment or a change in, or supplementation of, an already administered treatment, wherein the one or more lipid-lipid ratio(s) whose increase(s) is (are) compared to the control is (are) selected from (Tables 5a and 8a):
CE 16:0/CE 18:3, CE 18:2/CE 18:3, CE 19:1/Cer(d18:0/22:0), Cer(d18:1/16:0)/LPC 18:1, Cer(d18:1/16:0)/Total PC, Cer(d18:1/18:0)/LPC 16:0, Cer(d18:1/18:0)/LPC 18:1,

Cer(d18:1/18:0)/PC 16:0/18:1, Cer(d18:1/18:0)/PC 16:0/20:3, Cer(d18:1/18:0)/PC 16:0/20:4, Cer(d18:1/18:0)/PC 18:0/20:4, Cer(d18:1/18:0)/Total LPC, Cer(d18:1/18:0)/Total PC, Cer(d18:1/20:0)/PC 16:0/18:1, Cer(d18:1/20:0)/PC 16:0/20:3, Cer(d18:1/20:0)/PC 16:0/20:4, Cer(d18:1/20:0)/PC 18:0/20:4, Cer(d18:1/20:0)/PC 18:1/18:1, Cer(d18:1/20:0)/Total PC, Cer(d18:1/22:0)/LPC 18:2, Cer(d18:1/22:0)/PC 16:0/20:3, Cer(d18:1/22:0)/PC 16:0/20:4, Cer(d18:1/22:0)/Total PC, Cer(d18:1/24:1)/LPC 18:1, Cer(d18:1/24:1)/LPC 18:2, Cer(d18:1/24:1)/PC 16:0/18:1, Cer(d18:1/24:1)/PC 16:0/20:3, Cer(d18:1/24:1)/PC 16:0/20:4, Cer(d18:1/24:1)/PC 18:0/18:1, Cer(d18:1/24:1)/PC 18:0/20:3, Cer(d18:1/24:1)/PC 18:0/20:4, Cer(d18:1/24:1)/SM (d18:1/24:0) (d18:1/23:1-OH), Cer(d18:1/24:1)/Total CE, Cer(d18:1/24:1)/Total LPC, Cer(d18:1/24:1)/Total PC, Cer(d18:1/26:0)/PC O-40:0, GlcCer(d18:1/20:0)/PC 16:0/20:4, GlcCer(d18:1/20:0)/Total PC, GlcCer(d18:1/26:0)/Total CE, LacCer(d18:1/16:0)/Total LPC, LacCer(d18:1/18:0)/PC 16:0/18:1, LacCer(d18:1/18:0)/PC 16:0/20:3, LacCer(d18:1/18:0)/PC 18:0/18:1, LacCer(d18:1/18:0)/PC 18:0/20:3, LacCer(d18:1/18:0)/PC 18:1/18:1, LacCer(d18:1/18:0)/PC 18:1/18:2, LacCer(d18:1/18:0)/Total LPC, LacCer(d18:1/18:0)/Total PC, LacCer(d18:1/20:0)/PC 16:0/18:1, LacCer(d18:1/20:0)/PC 16:0/20:3, LacCer(d18:1/20:0)/PC 18:0/18:1, LacCer(d18:1/20:0)/PC 18:0/20:3 LacCer(d18:1/20:0)/PC 18:1/18:1, LacCer(d18:1/20:0)/PC 18:1/18:2, LacCer(d18:1/20:0)/PC 18:2/18:2, LacCer(d18:1/20:0)/SM (d18:1/17:1-OH), LacCer(d18:1/20:0)/SM (d18:1/18:0), LacCer(d18:1/20:0)/Total LPC, LacCer(d18:1/20:0)/Total PC, LacCer(d18:1/20:0)/Total SM, LacCer(d18:1/22:0)/PC 16:0/20:3, LacCer(d18:1/22:0)/PC 16:0/20:4, LacCer(d18:1/22:0)/PC 18:0/20:3, LacCer(d18:1/22:0)/SM (d18:1/14:0) (d18:1/13:1-OH), LacCer(d18:1/22:0)/Total LPC, LacCer(d18:1/22:0)/Total PC, LacCer(d18:1/24:0)/PC 16:0/20:3, LacCer(d18:1/24:0)/Total LPC, LacCer(d18:1/24:1)/Total LPC, LacCer(d18:1/24:1)/Total PC, LacCer(d18:1/24:1)/Total PC O, PC 16:0/16:0/PC 16:0/20:4, PC 16:0/16:0/Total PC, PC 16:0/18:2/Total PC, PC O-18:0/18:2-alkyl/PC O-36:5, PC O-32:0 (KDdiA-PC)/PC O-38:5, PS O-16:0/18:2-alkenyl/Total PS O, PS O-

16:1/18:2-alkyl/Total PS O, PS O-18:0/18:2-alkenyl (PS O-18:1/18:2-alkyl)/Total PS O, PS O-18:2/16:0-alkenyl/Total PS O, Total Cer/Total PC, Total LacCer/Total PC and Total LacCer/Total PC O;

and wherein one or more lipid-lipid ratio(s) whose decrease is (are) compared to the control is (are) selected from (Tables 5a and 8a):

CE 14:0/Cer(d18:1/24:1), CE 16:0/Cer(d18:1/24:1), CE 16:1/CE 19:1, CE 16:1/Cer(d18:1/18:0), CE 16:1/Cer(d18:1/20:0), CE 16:1/Cer(d18:1/24:1), CE 16:1/GlcCer(d18:1/18:0), CE 16:1/GlcCer(d18:1/20:0), CE 16:1/LacCer(d18:1/16:0), CE 16:1/LacCer(d18:1/18:0), CE 16:1/LacCer(d18:1/20:0), CE 16:1/LacCer(d18:1/22:0), CE 16:1/LacCer(d18:1/24:0), CE 16:1/PC 16:0/16:0, CE 16:1/Total LacCer, CE 17:1/Cer(d18:1/24:1), CE 17:1/GlcCer(d18:1/24:1), CE 17:1/LacCer(d18:1/18:0), CE 18:1/Total LacCer, CE 18:3/Cer(d18:1/16:0), CE 18:3/Cer(d18:1/18:0), CE 18:3/Cer(d18:1/20:0), CE 18:3/Cer(d18:1/22:0), CE 18:3/Cer(d18:1/24:0), CE 18:3/Cer(d18:1/24:1), CE 18:3/GlcCer(d18:1/18:0), CE 18:3/GlcCer(d18:1/20:0), CE 18:3/LacCer(d18:1/18:0), CE 18:3/LacCer(d18:1/20:0), CE 18:3/LacCer(d18:1/22:0), CE 18:3/LacCer(d18:1/24:0), CE 18:3/PC 16:0/16:0, CE 18:3/PC O-34:1, CE 18:3/PS O-16:0/18:1-alkenyl (PS O-16:1/18:1-alkyl), CE 18:3/PS O-16:0/18:2-alkenyl, CE 18:3/PS O-16:1/18:2-alkyl, CE 18:3/Total CE, CE 18:3/Total Cer, CE 18:3/Total LacCer, CE 20:3/Cer(d18:1/24:1), CE 20:3/LacCer(d18:1/20:0), Cer(d18:0/22:0)/Cer(d18:1/18:0), Cer(d18:0/22:0)/Cer(d18:1/20:0), Cer(d18:0/22:0)/Cer(d18:1/22:0), Cer(d18:0/22:0)/Cer(d18:1/24:1), Cer(d18:0/22:0)/LacCer(d18:1/24:0), Cer(d18:0/22:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/22:0)/PS O-16:1/18:2-alkyl, Cer(d18:0/22:0)/Total CE, Cer(d18:0/24:0)/Cer(d18:1/16:0), Cer(d18:0/24:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/Cer(d18:1/20:0), Cer(d18:0/24:0)/Cer(d18:1/22:0), Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/24:0)/GlcCer(d18:1/20:0), Cer(d18:0/24:0)/LacCer(d18:1/24:0), Cer(d18:0/24:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/24:0)/PS O-16:1/18:2-alkyl, Cer(d18:0/24:0)/SM (d18:1/17:0) (d18:1/16:1-OH), Cer(d18:0/24:0)/Total CE, Cer(d18:0/24:0)/Total Cer, Cer(d18:0/24:1)/Total CE, GlcCer(d18:1/26:0)/LacCer(d18:1/20:0), GlcCer(d18:1/26:0)/LacCer(d18:1/22:0), LPC

16:0/LacCer(d18:1/20:0), LPC 16:0/LacCer(d18:1/22:0), LPC 16:0/LacCer(d18:1/24:1), LPC 16:0/Total LacCer, LPC 18:1/LacCer(d18:1/20:0), LPC 18:2/LacCer(d18:1/20:0), LPC 18:2/PS O-16:0/18:2-alkenyl, LPC 18:2/PS O-16:1/18:2-alkyl, PC 16:0/20:3/PS O-16:0/18:2-alkenyl, PC 16:0/20:3/PS O-16:1/18:2-alkyl, PC 18:1/18:2/PS O-16:0/18:2-alkenyl, PC 18:1/18:2/PS O-16:1/18:2-alkyl, SM (d18:1/24:0) (d18:1/23:1-OH)/Total Cer and Total LPC/Total LacCer.

In an alternative embodiment the invention relates to a method of choosing an appropriate treatment of CVD and/or one or more of its complications, such as AMI or CVD death, in a subject, wherein the subject is not undergoing statin treatment and wherein said method comprises determining in a sample from said subject one or more lipid-lipid ratio(s), wherein (an) increased or decreased lipid-lipid ratio(s) in said sample, when compared to a control sample, is (are) indicative of said subject being in need of treatment or a change in, or supplementation of, an already administered treatment, wherein the one or more lipid-lipid ratio(s) whose increase(s) is (are) compared to the control is (are) selected from (Tables 5b and 8b):

CE 16:0/CE 18:3, CE 18:0/CE 18:3, CE 18:2/CE 18:3, Cer(d18:1/16:0)/LPC 18:1, Cer(d18:1/16:0)/Total PC, Cer(d18:1/18:0)/LPC 18:1, Cer(d18:1/18:0)/PC 16:0/18:1, Cer(d18:1/18:0)/PC 16:0/20:3, Cer(d18:1/18:0)/PC 16:0/20:4, Cer(d18:1/18:0)/PC 18:0/18:1, Cer(d18:1/18:0)/PC 18:0/20:4, Cer(d18:1/18:0)/PC 18:1/18:1, Cer(d18:1/18:0)/SM (d18:1/14:0) (d18:1/13:1-OH), Cer(d18:1/18:0)/SM (d18:1/17:2-OH), Cer(d18:1/18:0)/SM (d18:1/18:1), Cer(d18:1/18:0)/Total CE, Cer(d18:1/18:0)/Total LPC, Cer(d18:1/18:0)/Total PC, Cer(d18:1/20:0)/PC 16:0/18:1, Cer(d18:1/20:0)/PC 16:0/20:3, Cer(d18:1/20:0)/PC 16:0/20:4, Cer(d18:1/20:0)/PC 18:0/18:1, Cer(d18:1/20:0)/PC 18:0/20:4, Cer(d18:1/20:0)/PC 18:1/18:1, Cer(d18:1/20:0)/SM (d18:1/14:0) (d18:1/13:1-OH), Cer(d18:1/20:0)/Total LPC, Cer(d18:1/20:0)/Total PC, Cer(d18:1/20:0)/Total PC O, Cer(d18:1/22:0)/LPC 18:2, Cer(d18:1/22:0)/PC 16:0/20:3, Cer(d18:1/22:0)/PC 16:0/20:4, Cer(d18:1/22:0)/PC 18:0/20:4, Cer(d18:1/22:0)/Total PC, Cer(d18:1/24:1)/LPC 18:1, Cer(d18:1/24:1)/LPC 18:2, Cer(d18:1/24:1)/PC 16:0/18:1, Cer(d18:1/24:1)/PC 16:0/18:2,

Cer(d18:1/24:1)/PC 16:0/20:3, Cer(d18:1/24:1)/PC 16:0/20:4, Cer(d18:1/24:1)/PC 18:0/18:1, Cer(d18:1/24:1)/PC 18:0/18:2, Cer(d18:1/24:1)/PC 18:0/20:3, Cer(d18:1/24:1)/PC 18:0/20:4, Cer(d18:1/24:1)/PC 18:1/18:1, Cer(d18:1/24:1)/PC 18:1/18:2, Cer(d18:1/24:1)/PC O-40:3, Cer(d18:1/24:1)/SM (d18:1/17:1-OH), Cer(d18:1/24:1)/SM (d18:1/18:0), Cer(d18:1/24:1)/SM (d18:1/23:0) (d18:1/22:1-OH), Cer(d18:1/24:1)/SM (d18:1/24:0) (d18:1/23:1-OH), Cer(d18:1/24:1)/Total CE, Cer(d18:1/24:1)/Total LPC, Cer(d18:1/24:1)/Total PC, GlcCer(d18:1/26:0)/Total CE, GlcCer(d18:1/26:1)/Total CE, LacCer(d18:1/18:0)/Total PC, LacCer(d18:1/20:0)/PC 16:0/20:3, LacCer(d18:1/20:0)/PC 16:0/20:4, LacCer(d18:1/20:0)/PC 18:0/18:1, LacCer(d18:1/20:0)/PC 18:0/20:3, LacCer(d18:1/20:0)/PC 18:0/20:4, LacCer(d18:1/20:0)/PC 18:1/18:2, LacCer(d18:1/20:0)/SM (d18:1/17:1-OH), LacCer(d18:1/20:0)/SM (d18:1/18:0), LacCer(d18:1/20:0)/Total CE, LacCer(d18:1/20:0)/Total LPC, LacCer(d18:1/20:0)/Total PC, LacCer(d18:1/20:0)/Total SM, LacCer(d18:1/24:0)/Total LPC, PC 16:0/16:0/PC 16:0/20:4, PC 16:0/16:0/Total PC, PC O-32:0 (KDdiA-PC)/Total PC O, PS O-16:0/18:2-alkenyl/Total PC, PS O-16:0/18:2-alkenyl/Total PC O, PS O-16:0/18:2-alkenyl/Total PS O, PS O-16:1/18:2-alkyl/Total PC, PS O-16:1/18:2-alkyl/Total PC O, PS O-16:1/18:2-alkyl/Total PS O, PS O-18:2/16:0-alkenyl/Total PC O, PS O-18:2/16:0-alkenyl/Total PS O, SM (d18:1/17:0) (d18:1/16:1-OH)/Total PC O, Total Cer/Total PC, Total DAG/Total LPC, Total DAG/Total PC, Total DAG/Total PC O and Total LacCer/Total PC;

and wherein the one or more lipid-lipid ratio(s) whose decrease(s) is (are) compared to the control is (are) selected from (Tables 5b and 8b):

CE 14:0/Cer(d18:1/18:0), CE 14:0/Cer(d18:1/24:1), CE 14:0/Total DAG, CE 15:0/Cer(d18:1/20:0), CE 16:0/Cer(d18:1/18:0), CE 16:0/Cer(d18:1/24:1), CE 16:1/CE 19:1, CE 16:1/Cer(d18:1/18:0), CE 16:1/Cer(d18:1/20:0), CE 16:1/Cer(d18:1/24:1), CE 16:1/GlcCer(d18:1/24:1), CE 16:1/LacCer(d18:1/18:0), CE 16:1/LacCer(d18:1/24:0), CE 16:1/Total LacCer, CE 17:1/Cer(d18:1/18:0), CE 17:1/Cer(d18:1/24:1), CE 18:2/Cer(d18:1/20:0), CE 18:2/Cer(d18:1/24:1), CE 18:3/Cer(d18:1/16:0), CE

18:3/Cer(d18:1/18:0), CE 18:3/Cer(d18:1/20:0), CE 18:3/Cer(d18:1/22:0), CE 18:3/Cer(d18:1/24:0), CE 18:3/Cer(d18:1/24:1), CE 18:3/GlcCer(d18:1/20:0), CE 18:3/LacCer(d18:1/20:0), CE 18:3/LacCer(d18:1/22:0), CE 18:3/LacCer(d18:1/24:0), CE 18:3/PC 16:0/16:0, CE 18:3/PC O-34:1, CE 18:3/PS O-16:0/18:2-alkenyl, CE 18:3/PS O-16:1/18:2-alkyl, CE 18:3/Total CE, CE 18:3/Total Cer, CE 18:3/Total DAG, CE 18:3/Total LacCer, CE 20:3/Cer(d18:1/24:1), CE 20:3/LacCer(d18:1/20:0), CE 20:4/Cer(d18:1/18:0), CE 20:4/Cer(d18:1/24:1), CE 20:4/GlcCer(d18:1/20:0), CE 20:4/GlcCer(d18:1/24:1), CE 20:4/LacCer(d18:1/20:0), CE 20:5/LacCer(d18:1/20:0), Cer(d18:0/22:0)/Cer(d18:1/18:0), Cer(d18:0/22:0)/Cer(d18:1/20:0), Cer(d18:0/22:0)/Cer(d18:1/24:1), Cer(d18:0/22:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/22:0)/PS O-16:1/18:2-alkyl, Cer(d18:0/22:0)/Total CE, Cer(d18:0/22:0)/Total DAG, Cer(d18:0/22:0)/Total GlcCer, Cer(d18:0/24:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/Cer(d18:1/20:0), Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/24:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/24:0)/PS O-16:1/18:2-alkyl, Cer(d18:0/24:0)/Total CE, Cer(d18:0/24:0)/Total Cer, DAG 16:0/18:1/Total DAG, GlcCer(d18:1/26:0)/LacCer(d18:1/20:0), LPC 16:0/LacCer(d18:1/24:0), LPC 18:1/LacCer(d18:1/20:0), LPC 18:2/LacCer(d18:1/20:0), PC 16:0/20:3/PS O-16:0/18:2-alkenyl, PC 16:0/20:3/PS O-16:1/18:2-alkyl, PC 16:0/20:4/PS O-16:0/18:2-alkenyl, PC 16:0/20:4/PS O-16:1/18:2-alkyl, PC 16:0/20:4/Total DAG, PC 18:0/20:3/PS O-16:0/18:2-alkenyl, PC 18:0/20:3/PS O-16:1/18:2-alkyl, PC 18:0/20:3/PS O-18:2/16:0-alkenyl, PC 18:0/20:4/PS O-16:0/18:2-alkenyl, PC 18:0/20:4/PS O-16:1/18:2-alkyl, PC 18:1/18:2/PS O-16:0/18:2-alkenyl, PC 18:1/18:2/PS O-16:1/18:2-alkyl, PC 18:1/18:2/Total Cer, PC O-40:3/PS O-18:2/16:0-alkenyl, SM (d18:1/23:0) (d18:1/22:1-OH)/Total DAG, SM (d18:1/24:0) (d18:1/23:1-OH)/Total Cer, Total CE/Total DAG and Total LPC/Total LacCer.

In a preferred embodiment (for subjects that are either undergoing or not undergoing statin treatment), the one or more lipid-lipid ratio(s) whose increase is (are) compared to the control is (are) selected from (Table 11):
GlcCer(d18:1/26:1)/Total CE, Cer(d18:1/24:1)/Total PC, Cer(d18:1/24:1)/PC 16:0/20:4, Cer(d18:1/20:0)/PC 16:0/20:4, LacCer(d18:1/20:0)/PC 16:0/20:3, Total Cer/Total PC, Total LacCer/Total PC, LacCer(d18:1/20:0)/PC 18:1/18:2, PS O-16:0/18:2-alkenyl/Total PS O, Cer(d18:1/18:0)/PC 16:0/20:4, LacCer(d18:1/20:0)/Total LPC and LacCer(d18:1/20:0)/PC 16:0/20:4;

In another preferred embodiment, the one or more lipid-lipid ratio(s) whose decrease is (are) compared to the control is (are) selected from (Table 11):
Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/22:0)/Cer(d18:1/24:1), DAG 16:0/18:1/Total DAG, Cer(d18:0/24:0)/Cer(d18:1/22:0), Cer(d18:0/24:0)/Total CE, Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/24:0)/Total Cer,
Cer(d18:0/24:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/24:0)/LacCer(d18:1/24:0), Cer(d18:0/22:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/Cer(d18:1/22:0), Cer(d18:0/22:0)/Cer(d18:1/20:0), Cer(d18:0/22:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/22:0)/PS O-16:1/18:2-alkyl, GlcCer(d18:1/26:0)/LacCer(d18:1/20:0), Total LPC/Total LacCer and GlcCer(d18:1/26:0)/LacCer(d18:1/22:0).

In a particularly preferred embodiment, the one or more lipid-lipid ratio(s) whose increase is (are) compared to the control is (are) selected from (Table 13):
Cer(d18:1/24:1)/PC 16:0/20:4, LacCer(d18:1/20:0)/PC 16:0/20:3, PS O-16:0/18:2-alkenyl/Total PS O and Cer(d18:1/18:0)/PC 16:0/20:4;
and the one or more lipid-lipid ratio(s) whose decrease is (are) compared to the control is (are) selected from (Table 13):
GlcCer(d18:1/26:0)/LacCer(d18:1/20:0), DAG 16:0/18:1/Total DAG, Cer(d18:0/24:0)/Total Cer, Total LPC/Total LacCer, GlcCer(d18:1/26:0)/LacCer(d18:1/22:0), Cer(d18:0/24:0)/Cer(d18:1/24:1),

Cer(d18:0/24:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/24:0)/Cer(d18:1/22:0), Cer(d18:0/22:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/22:0)/PS O-16:1/18:2-alkyl and Cer(d18:0/24:0)/LacCer(d18:1/24:0).

In yet another embodiment the invention relates to a method of choosing an appropriate treatment of CVD and/or one or more of its complications, such as AMI or CVD death, in a subject, comprising determining in a sample from said subject one or more lipid-clinical concentration ratio(s), wherein (an) increased or decreased lipid-clinical concentration ratio(s) in said sample, when compared to a control sample, is (are) indicative of said subject being in need of treatment or a change in, or supplementation of, an already administered treatment, wherein the one or more lipid-clinical concentration ratio(s) whose increase is (are) compared to the control is (are) selected from (Tables 6a and 9a):

Cer(d18:1/16:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/18:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/18:0)/apolipoprotein B (mg/dL), Cer(d18:1/18:0)/HDL cholesterol (EDTA) (mg/dL), Cer(d18:1/18:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/18:0)/total-c/HDL-c, Cer(d18:1/18:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/20:0)/apolipoprotein B (mg/dL), Cer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL), Cer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/20:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/22:0)/apolipoprotein B (mg/dL), Cer(d18:1/22:0)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:1/22:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL), Cer(d18:1/24:1)/apolipoprotein B (mg/dL), Cer(d18:1/24:1)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:1/24:1)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/24:1)/total-c/HDL-c, Cer(d18:1/24:1)/triglycerides (EDTA) (mg/dL), GlcCer(d18:1/24:0)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/16:0)/triglycerides (EDTA) (mg/dL), LacCer(d18:1/18:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/18:0)/apolipoprotein B (mg/dL), LacCer(d18:1/18:0)/HDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/18:0)/LDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/18:0)/total

cholesterol (EDTA) (mg/dL), LacCer(d18:1/18:0)/total-c/HDL-c, LacCer(d18:1/18:0)/triglycerides (EDTA) (mg/dL), LacCer(d18:1/20:0)/apoA1/apoB, LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/apolipoprotein B (mg/dL), LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/20:0)/LDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/20:0)/LDL-c/HDL-c, LacCer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/20:0)/total-c/HDL-c, LacCer(d18:1/20:0)/triglycerides (EDTA) (mg/dL), LacCer(d18:1/22:0)/apoA1/apoB, LacCer(d18:1/22:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/22:0)/apolipoprotein B (mg/dL), LacCer(d18:1/22:0)/HDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/22:0)/LDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/22:0)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/22:0)/total-c/HDL-c, LacCer(d18:1/22:0)/triglycerides (EDTA) (mg/dL), LacCer(d18:1/24:0)/apoA1/apoB, LacCer(d18:1/24:1)/apolipoprotein A-I (mg/dL), LacCer(d18:1/24:1)/apolipoprotein B (mg/dL), LacCer(d18:1/24:1)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/24:1)/triglycerides (EDTA) (mg/dL), PC O-32:0 (KDdiA-PC)/apolipoprotein A-I (mg/dL), PC O-32:0 (KDdiA-PC)/triglycerides (EDTA) (mg/dL), PC O-34:1/triglycerides (EDTA) (mg/dL), PS O-16:0/18:1-alkenyl (PS O-16:1/18:1-alkyl)/triglycerides (EDTA) (mg/dL), PS O-16:0/18:2-alkenyl/triglycerides (EDTA) (mg/dL), PS O-16:1/18:2-alkyl/triglycerides (EDTA) (mg/dL), PS O-18:2/16:0-alkenyl/HDL cholesterol (EDTA) (mg/dL), PS O-18:2/16:0-alkenyl/triglycerides (EDTA) (mg/dL), Total Cer/apolipoprotein A-I (mg/dL), Total Cer/total cholesterol (EDTA) (mg/dL), Total Cer/triglycerides (EDTA) (mg/dL), Total GlcCer/apolipoprotein B (mg/dL), Total GlcCer/total cholesterol (EDTA) (mg/dL), Total LacCer/apolipoprotein A-I (mg/dL), Total LacCer/apolipoprotein B (mg/dL), Total LacCer/total cholesterol (EDTA) (mg/dL) and Total LacCer/triglycerides (EDTA) (mg/dL);

and wherein the one or more lipid-clinical concentration ratio(s) whose decrease is (are) compared to the control is (are) selected from (Tables 6a and 9a):

CE 14:0/apolipoprotein B (mg/dL), CE 14:0/LDL cholesterol (EDTA) (mg/dL), CE 14:0/LDL-c/HDL-c, CE 14:0/total cholesterol (EDTA) (mg/dL), CE 14:0/total-c/HDL-

c, CE 16:1/apolipoprotein B (mg/dL), CE 16:1/HDL cholesterol (EDTA) (mg/dL), CE 16:1/LDL cholesterol (EDTA) (mg/dL), CE 16:1/total cholesterol (EDTA) (mg/dL), CE 17:1/LDL-c/HDL-c, CE 18:3/apoA1/apoB, CE 18:3/apolipoprotein A-I (mg/dL), CE 18:3/apolipoprotein B (mg/dL), CE 18:3/HDL cholesterol (EDTA) (mg/dL), CE 18:3/LDL cholesterol (EDTA) (mg/dL), CE 18:3/LDL-c/HDL-c, CE 18:3/total cholesterol (EDTA) (mg/dL), CE 18:3/total-c/HDL-c, CE 20:3/apolipoprotein B (mg/dL), CE 20:3/LDL-c/HDL-c, CE 20:3/total-c/HDL-c, CE 20:5/apolipoprotein B (mg/dL), CE 20:5/HDL cholesterol (EDTA) (mg/dL), CE 20:5/LDL cholesterol (EDTA) (mg/dL), Cer(d18:0/22:0)/apolipoprotein B (mg/dL), Cer(d18:0/22:0)/LDL-c/HDL-c, Cer(d18:0/22:0)/total-c/HDL-c, Cer(d18:0/24:0)/apolipoprotein A-I (mg/dL), Cer(d18:0/24:0)/apolipoprotein B (mg/dL), Cer(d18:0/24:0)/HDL cholesterol (EDTA) (mg/dL), Cer(d18:0/24:0)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:0/24:0)/LDL-c/HDL-c, Cer(d18:0/24:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:0/24:0)/total-c/HDL-c, LPC 18:2/apoA1/apoB, LPC 18:2/apolipoprotein B (mg/dL), LPC 18:2/HDL cholesterol (EDTA) (mg/dL), LPC 18:2/LDL cholesterol (EDTA) (mg/dL), LPC 18:2/LDL-c/HDL-c, LPC 18:2/total cholesterol (EDTA) (mg/dL), PC 16:0/20:3/apolipoprotein B (mg/dL), PC 16:0/20:3/HDL cholesterol (EDTA) (mg/dL), PC 16:0/20:3/LDL-c/HDL-c, PC 16:0/20:3/total-c/HDL-c, PC 16:0/20:4/apolipoprotein A-I (mg/dL), PC 16:0/20:4/apolipoprotein B (mg/dL), PC 16:0/20:4/LDL cholesterol (EDTA) (mg/dL), PC 16:0/20:4/LDL-c/HDL-c, PC 16:0/20:4/total cholesterol (EDTA) (mg/dL), PC 16:0/20:4/total-c/HDL-c, PC 18:0/18:1/LDL-c/HDL-c, PC 18:0/20:3/LDL-c/HDL-c, PC 18:0/20:3/total-c/HDL-c, PC 18:0/20:4/apoA1/apoB, Total LPC/LDL-c/HDL-c, Total LPC/total-c/HDL-c, Total PC/apolipoprotein B (mg/dL), Total PC/LDL-c/HDL-c, Total PC/total cholesterol (EDTA) (mg/dL) and Total PC/total-c/HDL-c.

In yet another embodiment the invention relates to a method of choosing an appropriate treatment of CVD and/or one or more of its complications, such as AMI or CVD death, in a subject, wherein the subject is not undergoing statin treatment and wherein said method comprises determining in a sample from said subject one or more lipid-clinical

concentration ratio(s), wherein (an) increased or decreased lipid-clinical concentration ratio(s) in said sample, when compared to a control sample, is (are) indicative of said subject being in need of treatment or a change in, or supplementation of, an already administered treatment, wherein the one or more lipid-clinical concentration ratio(s) whose increase is (are) compared to the control is (are) selected from (Tables 6b and 9b):

Cer(d18:1/16:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/16:0)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:1/16:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/18:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/18:0)/apolipoprotein B (mg/dL), Cer(d18:1/18:0)/HDL cholesterol (EDTA) (mg/dL), Cer(d18:1/18:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/18:0)/total-c/HDL-c, Cer(d18:1/18:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/20:0)/apolipoprotein B (mg/dL), Cer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL), Cer(d18:1/20:0)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/20:0)/total-c/HDL-c, Cer(d18:1/20:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/22:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/22:0)/apolipoprotein B (mg/dL), Cer(d18:1/22:0)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:1/22:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/22:0)/triglycerides (EDTA) (mg/dL), Cer(d18:1/24:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/24:0)/apolipoprotein B (mg/dL), Cer(d18:1/24:0)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:1/24:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL), Cer(d18:1/24:1)/apolipoprotein B (mg/dL), Cer(d18:1/24:1)/HDL cholesterol (EDTA) (mg/dL), Cer(d18:1/24:1)/LDL cholesterol (EDTA) (mg/dL), Cer(d18:1/24:1)/LDL-c/HDL-c, Cer(d18:1/24:1)/total cholesterol (EDTA) (mg/dL), Cer(d18:1/24:1)/total-c/HDL-c, Cer(d18:1/24:1)/triglycerides (EDTA) (mg/dL), GlcCer(d18:1/20:0)/apolipoprotein B (mg/dL), GlcCer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL), GlcCer(d18:1/24:1)/apolipoprotein B (mg/dL), GlcCer(d18:1/26:1)/apolipoprotein A-I (mg/dL), LacCer(d18:1/16:0)/triglycerides (EDTA) (mg/dL), LacCer(d18:1/18:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/18:0)/apolipoprotein B

(mg/dL), LacCer(d18:1/18:0)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/20:0)/apoA1/apoB, LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/apolipoprotein B (mg/dL), LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/20:0)/LDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/20:0)/LDL-c/HDL-c, LacCer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/20:0)/total-c/HDL-c, LacCer(d18:1/20:0)/triglycerides (EDTA) (mg/dL), LacCer(d18:1/22:0)/apoA1/apoB, LacCer(d18:1/22:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/22:0)/apolipoprotein B (mg/dL), LacCer(d18:1/22:0)/HDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/22:0)/LDL cholesterol (EDTA) (mg/dL), LacCer(d18:1/22:0)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/24:1)/apolipoprotein A-I (mg/dL), LacCer(d18:1/24:1)/apolipoprotein B (mg/dL), LacCer(d18:1/24:1)/total cholesterol (EDTA) (mg/dL), LacCer(d18:1/24:1)/triglycerides (EDTA) (mg/dL), PC O-34:1/apolipoprotein B (mg/dL), PS O-16:0/18:2-alkenyl/triglycerides (EDTA) (mg/dL), PS O-16:1/18:2-alkyl/triglycerides (EDTA) (mg/dL), Total Cer/apolipoprotein A-I (mg/dL), Total Cer/apolipoprotein B (mg/dL), Total Cer/LDL cholesterol (EDTA) (mg/dL), Total Cer/total cholesterol (EDTA) (mg/dL), Total DAG/apolipoprotein A-I (mg/dL), Total DAG/triglycerides (EDTA) (mg/dL), Total GlcCer/apolipoprotein B (mg/dL), Total LacCer/apolipoprotein A-I (mg/dL), Total LacCer/apolipoprotein B (mg/dL) and Total LacCer/total cholesterol (EDTA) (mg/dL).

and wherein the one or more lipid-clinical concentration ratio(s) whose decrease is (are) compared to the control is (are) selected from (Tables 6b and 9b):

CE 14:0/apoA1/apoB, CE 14:0/apolipoprotein B (mg/dL), CE 14:0/LDL-c/HDL-c, CE 14:0/total-c/HDL-c, CE 16:1/apoA1/apoB, CE 18:3/apoA1/apoB, CE 18:3/apolipoprotein A-I (mg/dL), CE 18:3/apolipoprotein B (mg/dL), CE 18:3/HDL cholesterol (EDTA) (mg/dL), CE 18:3/LDL cholesterol (EDTA) (mg/dL), CE 18:3/LDL-c/HDL-c, CE 18:3/total cholesterol (EDTA) (mg/dL), CE 18:3/total-c/HDL-c, CE 20:5/triglycerides (EDTA) (mg/dL), Cer(d18:0/24:0)/apolipoprotein B (mg/dL), Cer(d18:0/24:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:0/24:0)/total-c/HDL-c, PC

18:0/20:4/apoA1/apoB, PC O-38:6/apolipoprotein A-I (mg/dL), Total LPC/apoA1/apoB and Total PC/apolipoprotein A-I (mg/dL).

In a preferred embodiment (for subjects that are either undergoing or not undergoing statin treatment), the one or more lipid-clinical concentration ratio(s) whose increase is (are) compared to the control is (are) selected from (Table 12):
Cer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Total Cer/apolipoprotein A-I (mg/dL), Total LacCer/apolipoprotein A-I (mg/dL), Cer(d18:1/18:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/22:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL) and Cer(d18:1/24:1)/apolipoprotein B (mg/dL).

In another preferred embodiment, the one or more lipid-clinical concentration ratio(s) whose decrease is (are) compared to the control is (are) selected from (Table 12):
Cer(d18:0/24:0)/apolipoprotein B (mg/dL), Cer(d18:0/24:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:0/24:0)/apolipoprotein B (mg/dL), PC 16:0/20:4/apolipoprotein B (mg/dL) and Cer(d18:0/24:0)/apolipoprotein A-I (mg/dL).

In a particularly preferred embodiment, the one or more lipid-clinical concentration ratio(s) whose increase is (are) compared to the control is (are) selected from (Table 13):
Cer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Total LacCer/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL) and Cer(d18:1/18:0)/apolipoprotein A-I (mg/dL).

For the purposes of the invention, and particularly for lipid-clinical concentration ratios, an Apolipoprotein A-I measurement may alternatively be an Apolipoprotein A-II measurement.

Claim 5In one embodiment of the invention, the treatment the effectiveness of which is to be evaluated or which is to be chosen as appropriate in accordance with the methods described and claimed herein, is a lipid modifying treatment.

Claim 7For the purposes of the invention, at least one lipid concentration, lipid-lipid ratio or lipid-clinical concentration ratio from Tables 4-13, or combinations thereof, may be determined to assess whether the patient is at risk to develop one or more of CVD complications such as AMI or CVD death; to evaluate the effectiveness of the treatment of CVD and/or one or more of its complications, such as AMI or CVD death in a subject; or to choose an appropriate treatment of CVD and/or one or more of its complications, such as AMI or CVD death in a subject. However, it is also possible, and may be advantageous, to determine at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, or at least 8 lipid concentrations, lipid-lipid ratios or lipid-clinical concentration ratios from Tables 4-13, or combinations thereof, in this regard. Where more than one lipidomic markers are determined and used for the assessment, it may be advantageous that a specific lipid concentration, lipid-lipid ratio, lipid-clinical concentration ratio or combination thereof, is given greater weight than others in the above-mentioned assessment, evaluation or choice.

Preferred embodiments of the invention are methods wherein the one or more lipid(s) or lipid ratio(s), or combination thereof, comprise(s): (particularly preferred lipid species and ratios in claim 6) Cer(d18:1/20:0), LacCer(d18:1/20:0), Cer(d18:1/24:1), LacCer(d18:1/24:1), LacCer(d18:1/22:0), Cer(d18:1/18:0), PC 16:0/20:4, Cer(d18:0/24:0), Cer(d18:1/24:1)/PC 16:0/20:4, LacCer(d18:1/20:0)/PC 16:0/20:3, PS O-16:0/18:2-alkenyl/Total PS O, Cer(d18:1/18:0)/PC 16:0/20:4, GlcCer(d18:1/26:0)/LacCer(d18:1/20:0), DAG 16:0/18:1/Total DAG, Cer(d18:0/24:0)/Total Cer, Total LPC/Total LacCer, GlcCer(d18:1/26:0)/LacCer(d18:1/22:0), Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/24:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/24:0)/Cer(d18:1/22:0), Cer(d18:0/22:0)/PS O-16:0/18:2-alkenyl,

Cer(d18:0/22:0)/PS O-16:1/18:2-alkyl, Cer(d18:0/24:0)/LacCer(d18:1/24:0), Cer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Total LacCer/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL) and Cer(d18:1/18:0)/apolipoprotein A-I (mg/dL).

In the context of the present invention, CVD is typically characterized by coronary artery disease, peripheral artery disease, a stroke and/or CVD death. The CVD in the subject whose sample is analyzed in accordance with the invention may be atherosclerosis-induced. However, the invention also embodies methods involving subjects who are at risk of developing CVD, but who may or may not have atherosclerosis.

In a further embodiment, the methods of the invention may further comprise determining the serum level of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), Apolipoprotein B (ApoB) and/or Apolipoprotein C-III in the subject's sample. In one embodiment of the invention, the subject does not have elevated serum levels of one or more of total cholesterol, low-density lipoprotein cholesterol (LDL-C), Apolipoprotein C-III or Apolipoprotein B (ApoB), or a decreased serum level of HDL-cholesterol (HDL-C).

As mentioned above, for the purposes of the present invention, a control sample may be obtained from (a) CAD patient(s) or a group of CAD patients that has/have remained free of any major CVD complications e.g., by mixing a variety of samples from said population. If a group of CAD patients is used then several lipid profiles from a population are combined and the lipidomic marker is created from this combination. The levels or amounts of the individual lipids or the lipid-lipid ratios or lipid-clinical concentration ratios in the sample from a subject are compared to the levels or amounts of the lipids or lipid ratios in the control for determining the risk of one or more of CVD complications, such as AMI or CVD death, in said subject.

The invention encompasses the analysis of lipid concentrations, lipid-lipid ratios and/or lipid-clinical concentration ratios in samples from a subject that has been or is being treated with one or more statins and/or any other HMG-CoA reductase inhibitor.

Alternatively, the invention encompasses the analysis of lipid concentrations, lipid-lipid ratios and/or lipid-clinical concentration ratios in samples from a subject that has not yet undergone statin therapy or therapy with any other HMG-CoA reductase inhibitor.

In accordance with the aspects and embodiments of the invention described and claimed herein, the statin may be one selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, fluvastatin XL, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.

Collecting information on a lipidomic marker or a lipidomic profile from a subject's biological sample can be performed via various chemical and high resolution analytical techniques. Suitable analytical techniques include but are not limited to mass spectrometry and nuclear resonance spectroscopy. Any high resolution technique capable of resolving individual lipids or lipid classes and providing structural information of the same can be used to collect the lipid profile from the biological sample. For methods of the present invention the level of the lipid is determined by using mass spectrometry, nuclear magnetic resonance spectroscopy, fluorescence spectroscopy or dual polarisation interferometry, a high performance separation method such as HPLC or UPLC and/or an immunoassay such as an ELISA. According to an alternative or further embodiment an analyte in a sample can be detected and/or quantified by combining the analyte with a binding moiety capable of specifically binding the analyte. The binding moiety can include, for example, a member of a ligand-receptor pair, i.e., a pair of molecules capable of having a specific binding interaction. The binding moiety can also include, for example, a member of a specific binding pair, such as antibody-antigen, enzyme-substrate, nucleic acid-based ligands,

other protein ligands, or other specific binding pairs known in the art. In a preferred embodiment, the lipidomic profile is collected with mass spectrometry (MS), wherein the MS instrument may be coupled to direct infusion methods and high performance separation methods such as HPLC or HPLC. The amount of the individual lipids or lipid classes in the collected lipidomic profile is used when comparing the collected lipid profile to a control.

The methods of the present invention may be used for determining a risk of said patient to develop CVD complications, particularly severe CVD complications such as death and myocardial infarction (MI), including acute myocardial infarction (AMI).

In one embodiment of the invention, a method for treating or preventing CVD complications, such as AMI or CVD death, in a subject in need thereof is provided. The method comprises administering a therapeutically effective dose of a drug capable of modulating one or more of the lipid concentration(s), lipid-lipid ratio(s) or lipid-clinical concentration ratio(s) described in Tables 4-13, wherein the dose is such that said one or more lipid concentration(s), lipid-lipid ratio(s) or lipid-clinical concentration ratio(s) in a sample of said subject does not significantly change when compared to (a) corresponding lipid concentration(s), (a) corresponding lipid-lipid ratio(s) or (a) corresponding lipid-clinical concentration ratio(s) in a control, e.g., a control sample. In a preferred embodiment, the drug is a statin or another HMG CoA reductase inhibitor. Particularly preferred statins in this regard are atorvastatin, cerivastatin, fluvastatin, fluvastatin XL, lovastatin, pitavastatin, pravastatin, rosuvastatin or simvastatin. In another preferred embodiment, the drug is niacin (nicotinic acid); a cholesterol absorption inhibitor, such as ezetimibe or SCH-48461; a cholesteryl ester transfer protein (CETP) inhibitor, such as torcetrapib, anacetrapib or JTT-705; a bile acids sequestrant, such as colesevelam, cholestyramine and colestipol; or a fibrate, such as fenofibrate, gemfibrozil, clofibrate, and bezafibrate. Alternatively, it may also be a phytosterol.

Also embodied by the present invention is a lipid as described herein, e.g. a lipid from any of Tables 4, 7, 10 or 13, for use in preventing or treating a subject at risk to develop CVD complications such as AMI or CVD death, wherein the said lipid is to be taken as a dietary supplement or a medicament. A corresponding method of treatment is likewise encompassed. Likewise, the invention also encompasses a modulator for use for modulating a lipid concentration, lipid-lipid ratio or lipid-clinical concentration ratio as described herein, e.g., in Tables 4-13, in a subject at risk to develop CVD and/or one or more of its complications such as AMI or CVD death. A corresponding method of treatment is likewise encompassed. In a further embodiment, the said modulator is a small molecule, an antisense RNA, a small interfering RNA (siRNA) or a natural or modified lipid.

In one embodiment of the present invention, an antibody against any one of the lipids in Tables 4-13 is used for predicting one or more CVD complications such as AMI or CVD death. In another embodiment of the invention, the antibody may be used for preventing or treating one or more of the above complications in a subject.

Any of the methods, drugs, lipids or antibodies of the present invention may be used for a subject which is at risk to develop or has suffered from one or more CVD complications such as acute myocardial infarction and/or a cardiovascular death. For the purposes of the invention, CVD complication(s) includes severe CVD complication(s), particularly death.

Also encompassed by the present invention is a kit for predicting CVD complications or for performing any of the methods or uses of the present invention, wherein the kit comprises a lipid standard chosen from the lipids in Tables 4, 7, 10 or 13, one or more control lipidomic markers, an antibody against one of the said lipids, and reagents for performing the method.

Brief Description of the Figures

Figure 1.

This figure demonstrates the importance of molecular lipid measurements. Two examples are given in this figure to illustrate that two closely related molecular lipids may have a very different or even opposite effect on CVD complications. First quadrangles are used to indicate two Lactosylceramides (LacCer). LacCer (18:1/20:0) is a significant predictor for CVD Death, while closely related LacCer (18:1/16:0) has only limited or no value as a risk predictor. Second example proves that that two lipid species from the same lipid class may have even an opposite effect on CVD events. PC (18:0/20:4) proved to be a protective lipid against CVD death while PC (16:0/16:0) seems to increase CVD complications.

Detailed Description of the Invention

Definitions:

Coronary vascular disease / cardiovascular disease (CVD) has its general meaning in the art and is used to classify numerous conditions that affect the heart, heart valves, blood, and vasculature of the body, including CAD. In the present invention the terms CVD and CAD may be used interchangeably. Cardiovascular diseases include endothelial dysfunction, coronary artery disease, angina pectoris, myocardial infarction, atherosclerosis, congestive heart failure, hypertension, cerebrovascular disease, stroke, transient ischemic attacks, deep vein thrombosis, peripheral artery disease, cardiomyopathy, arrhythmias, aortic stenosis, and aneurysm. Such diseases frequently involve atherosclerosis. In a preferred embodiment of the invention, the cardiovascular disease is a cardiovascular disease associated with atherosclerosis.

CAD is coronary artery disease, AMI is acute myocardial infarction, ACS is acute coronary syndrome, CAC is coronary artery calcification, RCT is reverse cholesterol transport, LDL is low density lipoprotein, HDL is high density lipoprotein, LDL-C is

low density lipoprotein cholesterol, HDL-C is high density lipoprotein cholesterol, ApoA is Apolipoprotein A, ApoB is Apolipoprotein B, ApoC is apolipoprotein C, MS is mass spectrometry, HPLC is high performance liquid chromatography, and UPLC is ultra performance liquid chromatography.

As used herein, "a subject" includes all mammals, including without limitation humans, but also non-human primates, dogs, cats, horses, sheep, goats, cows, rabbits, pigs and rodents.

A "sample" is defined as any biological sample obtained from a subject or a group or population of subjects. For the purposes of the present invention, the biological sample may be whole blood, blood serum, or blood plasma. It may also be a tissue sample. However, a preferred embodiment is wherein the biological sample is plasma or serum. Taking a blood sample of a patient is a part of normal clinical practice. The blood sample can be taken in connection with e.g. measuring the cholesterol levels in the patients. The collected blood sample can be prepared and serum or plasma can be separated with techniques well known to a person skilled in the art. Vena blood samples can be collected from patients using a needle and a BD Vacutainer® Plastic Tubes or Vacutainer® Plus Plastic Tubes (BD Vacutainer® SST^{TM} Tubes contain spray-coated silia and a polymer gel for serum separation). Serum can be separated by centrifugation at 1300 RCF for 10 min at room temperature and stored in small plastic tubes at -80°C.

For the purposes of the present invention, lipids from the Lipidomic analysis were named according to the following nomenclature: CE is cholesteryl ester, Cer is ceramide, DAG is diacylglycerol, PC O is ether-linked PC, GD is disialogangliosides, GlcCer is galactosyl- and glucosylceramides, GM is monosialogangliosides, LacCer is lactosylceramides, LPC is lysophosphatidylcholine, PC is Phosphatidylcholine, PE is Phosphatidylethanolamine, PI is Phosphatidylinositol, SM is Sphingomyelin, S1P is sphingosine-1-phosphate.

The nomenclature X:Y indicates, X number of total carbon atoms in the fatty acid(s) portions of the molecule, and Y the total number of double bonds in the fatty acid portion(s) of the molecule.

The nomenclature A/B indicates, for a molecule of DAG and PC, A and B types of fatty acid moieties attached to the glycerol backbone of the molecule.

The nomenclature (dC/A) indicates, for a molecule of Cer, , GlcCer, , LacCer and SM, C the type of long-chain base with an amide-linked, A, fatty acid moiety.

The wording "compared to a control sample" as used herein will be understood to include embodiments where control samples are actually analyzed in respect of a lipidomic marker of interest, i.e., in respect of the concentration of one or more of the lipid(s), the lipid-lipid ratios, or the lipid-clinical concentration ratios or combinations thereof as specifically described herein in connection with the various aspects and embodiments of the present invention. It will be appreciated, however, that the above wording also includes embodiments where the corresponding information on said lipidomic marker in said control sample is merely taken from the literature, or has been previously determined, calculated or extrapolated, or is yet to be determined, calculated or extrapolated.

As used herein, the term "antibody" includes monoclonal and polyclonal antibodies, whole antibodies, antibody fragments, and antibody sub-fragments that exhibit specific binding to a said lipid. Thus, suitable "antibodies" can be whole immunoglobulins of any class, e.g., IgG, IgM, IgA, IgD, IgE, chimeric antibodies or hybrid antibodies with dual or multiple antigen or epitope specificities, or fragments, e.g., $F(ab')_2$, Fab', Fab and the like, including hybrid fragments, and additionally includes any immunoglobulin or any natural, synthetic or genetically engineered protein that acts like an antibody by binding to a specific antigen to form a complex. The term "antibody" encompasses antigen-binding fragments of antibodies (e.g., single chain antibodies, Fab fragments,

$F(ab')_2$, a Fd fragment, a Fv fragment and dAb fragments) as well as complete antibodies. For example, Fab molecules can be expressed and assembled in a genetically transformed host like E. coli. A lambda vector system is available thus to express a population of Fab's with a potential diversity equal to or exceeding that of subject generating the predecessor antibody. See Huse WD, *et al.*, *Science* 1989, 246:1275-81. Such Fab's are included in the definition of "antibody." The ability of a given molecule, including an antibody fragment or sub-fragment, to act like an antibody and specifically bind to a specific antigen can be determined by binding assays known in the art, for example, using the antigen of interest as the binding partner.

Antibodies against lipids in accordance with the present invention may be prepared by methods well known to those skilled in the art. For example, mice may be immunized with a lipid with adjuvant. Splenocytes are harvested as a pool from the mice that were administered 3 immunizations at 2-week intervals with test bleeds performed on alternate weeks for serum antibody titers. Splenocytes are prepared as 3 aliquots that are either used immediately in fusion experiments or stored in liquid nitrogen for use in future fusions.

Fusion experiments are then performed according to the procedure of Stewart & Fuller, *J. Immunol. Methods* 1989, 123:45-53. Supernatants from wells with growing hybrids are screened by enzyme-linked immunosorbent assay (ELISA) for monoclonal antibody (MAb) secretors on 96-well ELISA plates coated with the said lipid. ELISA positive cultures are cloned by limiting dilutions, typically resulting in hybridomas established from single colonies after 2 serial cloning experiments.

Examples

Example 1

Materials and Methods

This study is a sub-cohort of the LURIC study that is a large scale prospective study on cardiovascular epidemiology. LURIC database contains clinical information over 3000 patients including baseline coronary angiography, clinically used biomarker data and also e.g. CVD mortality data for the follow-up period (3 years). In this biomarker study the inventors compared CAD cases (n=62) that died during the follow-up due to CVD with patients (n=173) having a stable CAD. Subjects with a significant atherosclerosis level in the angiogram but no CVD related death during the follow-up were used as controls, while the case group had similarly a significant atherosclerosis based on the angiography at baseline and in addition they died during the follow-up due to acute cardiovascular events. A statistical analysis was performed separately also for cases (n=48) and controls (n=124) that were not treated with statins. The clinical characteristics are described in Table 1.

Table 1. Background characteristics for LURIC patients analyzed with lipidomics

Variable	**Controls (n=173)**	**Cases (n=62)**
Age (average)	60	67
LDL-C (mg/dL)	122	117.5
HDL-C (mg/dL)	37.2	35.3
DM2 patients	62 (36%)	36 (58%)
Hypertensive patients	101 (58%)	39 (63%)
Lipid lowering users	49 (28%)	14 (23%)
Smokers (active or quit less than 3 years before sampling)	46 (27%)	8 (13%)

Definition of Cases: All cases had a significant vessel disease (>= 20% stenosis) in coronary angiogram and they all died due to CVD during the follow-up.

Definition of Controls: All controls had a significant vessel disease (>= 20% stenosis) in coronary angiogram, but they did not die due to CVD during the follow-up.

Example 2

Analytical Methods

Mass Spectrometry Driven Lipidomics

Direct infusion coupled to tandem mass spectrometry, *i.e.* shotgun lipidomics, and two liquid chromatography tandem mass spectrometry (LC-MS/MS) approaches, *i.e.* ceramide and cerebroside lipidomics and ganglioside lipidomics, were used to identify lipid biomarkers for coronary artery disease (CVD) risk by analyzing molecular lipid species in human serum, plasma, and carotid artery plaques. The applied methods were optimized especially for quantification of molecular cholesteryl esters (CE), phosphatidylcholines (PC), lysophosphatidylcholines (LPC) and other lysophospholipids (LPL), ether-linked phosphatidylcholines (PC O) and other ether-linked phospholipids (PL O), phosphatidylserines (PS), phosphatidylethanolamines (PE), phosphatidylglycerols (PG), phosphatidylinositols (PI), phosphatidic acids (PA), diacylglycerols (DAG), ceramides (Cer), glucosylceramides (GlcCer) and lactosylceramides (LacCer).

The following materials were used according to the methods. HPLC or LC-MS grade of chloroform, methanol, water, acetonitrile, formic acid, methanol, isopropanol, ammonium acetate, acetic acid, potassium chloride and butylated hydroxytoluene (BHT) were purchased from Sigma-Aldrich (St. Louis, MO, USA).

HPLC column (Acquity BEH C18, 2.1 × 50 mm id. 1.7 µm) was purchased from Waters (Milford, MA, USA). HPLC pre-column (Widepore C18 4 x 2.0mm) was purchased from Phenomenex (Torrance, CA, USA). All labware used for the extraction

were resistant to chloroform. Aerosol resistant filter tips (Molecular BioProducts) and Eppendorf 2 ml safe-lock tubes, 96-well twin.tec PCR plates, and Pierce-it-lite thermo-sealing foils were purchased from VWR International (West Chester, PA, USA). CO-RE Filter Tips and 96-well 2 ml Whatman Uniplates were purchased from Hamilton Robotics (Bonaduz, Switzerland). Synthetic lipid standards were purchased from Avanti Polar Lipids (Alabaster, AL, USA) and from Matreya (Pleasant Gap, PA, USA).

Lipids were extracted in chloroform:methanol according to the following protocols. Samples were spiked with known amounts of non-endogenous synthetic internal standards for data normalization and endogenous lipid quantification. In shotgun lipidomics analysis; LPC 17:0, PC 17:0/17:0, PA 17:0/17:0, PE 17:0/17:0, PG 17:0/17:0, PS 17:0/17:0, DAG 17:0/17:0, D6-CE 18:0, in ceramide and cerebroside lipidomics; Cer d18:1/17:0, D3-LacCer d18:1/16:0, and D3-GlcCer d18:1/16:0, were used as internal standards. Post-extract spiked non-endogenous synthetic external standards were used for quality controlling. Stock solutions of standards were prepared by dissolving appropriately weighed amounts of each standard in chloroform:methanol (2:1, V:V) to achieve a final concentration of 500 μM. An internal standard mixture containing each of the standard stock was created and used in lipid extraction.

Samples and quality control samples for each extraction batch were thawed on ice. The carotid artery plaque samples were weighed on ice by using a cryo-box and homogenized in ice-cold 70% methanol in water. The Mixer Mill 301 Teflon adapters were kept at -20°C. Homogenization was performed at 15-25 Hz for 2-15 minutes with Mixer Mill 301 (Retch GmbH, Germany).

Lipid extraction of human samples was carried out in automated fashion using a Hamilton MICROLAB STAR system (Hamilton Robotics, Switzerland). Well-mixed samples were aliquoted into a 96-well 2 ml Whatman Uniplate containing ice-cold methanol and 0.1% BHT. 5 μl of serum and plasma and 30 μl of carotid artery plaques were used for shotgun- and ceramide and cerebroside lipidomics and 100 μl of serum

and plasma and 200 µl of carotid artery plaques was used for ganglioside lipidomics. The samples were mixed thoroughly after each step in the extraction protocol. The extraction proceeded at room temperature by adding an appropriate volume of internal standard mixture and chloroform, and methanol and water in the case of ganglioside lipidomics. In shotgun and ceramide and cerebroside lipidomics, the organic phase separation was facilitated by adding 20 mM acetic acid and centrifuging the plate for 5 min at 500 × g. The organic phase was transferred into a new 96-well 2 ml Whatman Uniplate. The remaining water-containing phase was washed by adding appropriate volume of chloroform followed by centrifugation. The two organic phases were pooled and evaporated under N_2 until dryness. The lipid extracts were then re-dissolved in chloroform:methanol (1:2, v:v) including the addition of the synthetic external standard. In ganglioside lipidomics, after thorough mixing the supernatant was collected after 30 min centrifugation at 2000 x g. The remaining pellet was re-extracted with appropriate volume of water and chloroform:methanol (1:2, v:v) and the supernatant was collected in the same way as above. The pooled supernatant was subjected to solvent partitioning by addition of water and inversion of the sample tubes. The upper phase was collected after 30 min centrifugation at 2000 x g. The lower phase was thoroughly re-extracted with potassium chloride and the produced upper phase was collected as mentioned above. The upper phases were pooled and evaporated under N_2 until dryness. The lipid extracts were then re-dissolved in chloroform:methanol (1:2, v:v). The extracts were stored in 2 ml safe-lock Eppendorf tubes at -20°C prior to MS analysis. Required volumes of lipid extracts were aliquoted into an Eppendorf 96-well twin.tec PCR plate and the plate was heat-sealed with aluminum foil to avoid evaporation.

In shotgun lipidomics, lipid extracts were analyzed on a hybrid triple quadrupole/linear ion trap mass spectrometer (QTRAP 5500, AB Sciex) equipped with a robotic nanoflow ion source (NanoMate HD, Advion Biosciences). The instruments were operated in positive and negative ion modes. In positive ion the spray voltage was set to 1.0 to 1.4 kV and in negative ion mode to -1.0 to -1.4 kV. A gas pressure of 0.3-0.8 psi

was used and the interface heater was set at 60°C. The collision energy (CE) and declustering potential (DP) was optimized for each lipid class using synthetic standards. The mass spectrometer was operated in unit resolution mode using a scan speed of 200 Da/s. Molecular lipids were analyzed in both positive and negative ion modes using multiple precursor ion scanning (MPIS) and neutral loss scanning (NLS). The used precursor ion and neutral loss scans in positive mode and negative mode are summarized in Table 2.

Table 2. Shotgun lipidomics.

Lipid Class	**Characteristic Fragment**	**PIS or NL $[M+H]^+$ (m/z)**
PC/SM/LPC	Phosphorylcholine	184.1
DAG	FA 14:1	283.25
DAG	FA 14:0	285.25
DAG	FA 16:2	309.25
DAG	FA 16:1	311.25
DAG	FA 16:0	313.25
DAG	FA 17:0	327.25
DAG	FA 18:3	335.25
DAG	FA 18:2	337.25
DAG	FA 18:1	339.25
DAG	FA 18:0	341.25
DAG	FA 20:5	359.25
DAG	FA 20:4	361.25
DAG	FA 20:3	363.25
DAG	FA 20:2	365.25
DAG	FA 20:1	367.25
CE	Cholestadiene	369.35
d6-CE	d6-Cholestadiene	375.35
DAG	FA 22:6	385.30
DAG	FA 22:5	387.30
DAG	FA 22:4	389.30

DAG	FA 22:3	391.30
PE/PE-O	phosphorylethanolamine	NL 141.0
PS	phosphorylserine	NL 185.0
PG	phosphorylglycerol $+NH_4$	NL 189.0
PI	phosphorylinositol $+NH_4$	NL 277.1

Lipid Class	Characteristic Fragment	PIS or NL $[M-H]^-$ (m/z)
PA/PG/PS/PI	Glycerophosphate $-H_20$	153.000
PC/LPC	Phosphorylcholine	168.000
PA/PG/PS/PI/PC/LPC	FA 10:1	169.100
PA/PG/PS/PI/PC/LPC	FA 10:0	171.100
PA/PG/PS/PI/PC/LPC	FA 11:1	183.100
PA/PG/PS/PI/PC/LPC	FA 11:0	185.200
PE	dilyso PE $-H_20$	196.000
PA/PG/PS/PI/PC/LPC	FA 12:1	197.200
PA/PG/PS/PI/PC/LPC	FA 12:0	199.200
PA/PG/PS/PI/PC/LPC	FA 13:1	211.200
PA/PG/PS/PI/PC/LPC	FA 13:0	213.200
PA/PG/PS/PI/PC/LPC	FA 14:2	223.200
PA/PG/PS/PI/PC/LPC	FA 14:1	225.200
PA/PG/PS/PI/PC/LPC	FA 14:0	227.200
PA/PG/PS/PI/PC/LPC	FA 15:2, O-16:2	237.200
PA/PG/PS/PI/PC/LPC	FA 15:1, O-16:1	239.200
PI	PI-H_2O	241.000
PA/PG/PS/PI/PC/LPC	FA 15:0	241.200
PA/PG/PS/PI/PC/LPC	FA 16:2	251.200
PA/PG/PS/PI/PC/LPC	FA 16:1	253.200
PA/PG/PS/PI/PC/LPC	FA 16:0	255.200
PA/PG/PS/PI/PC/LPC	FA 20:5-CO_2	257.200
PC/LPC	D3-FA 16:0	258.200
PA/PG/PS/PI/PC/LPC	FA 20:4-CO_2	259.200
PA/PG/PS/PI/PC/LPC	FA 17:2	265.200

PA/PG/PS/PI/PC/LPC	O-18:2	265.300
PA/PG/PS/PI/PC/LPC	FA 17:1	267.200
PA/PG/PS/PI/PC/LPC	FA 17:0	269.300
PA/PG/PS/PI/PC/LPC	FA 18:3	277.200
PA/PG/PS/PI/PC/LPC	FA 18:2	279.200
PA/PG/PS/PI/PC/LPC	FA 18:1	281.300
PA/PG/PS/PI/PC/LPC	FA 18:0	283.300
PA/PG/PS/PI/PC/LPC	FA 22:5-CO_2	285.300
PA/PG/PS/PI/PC/LPC	FA 22:4-CO_2	287.300
PA/PG/PS/PI/PC/LPC	FA 19:2	293.300
PA/PG/PS/PI/PC/LPC	FA 19:1	295.300
PA/PG/PS/PI/PC/LPC	FA 19:0	297.300
PA/PG/PS/PI/PC/LPC	FA 20:5	301.200
PA/PG/PS/PI/PC/LPC	FA 20:4	303.200
PA/PG/PS/PI/PC/LPC	FA 20:3	305.200
PA/PG/PS/PI/PC/LPC	FA 20:2	307.300
PA/PG/PS/PI/PC/LPC	FA 20:1	309.300
PA/PG/PS/PI/PC/LPC	FA 20:0	311.300
PA/PG/PS/PI/PC/LPC	FA 22:6	327.200
PA/PG/PS/PI/PC/LPC	FA 22:5	329.200
PA/PG/PS/PI/PC/LPC	FA 22:4	331.300
PA/PG/PS/PI/PC/LPC	FA 22:3	333.300
PA/PG/PS/PI/PC/LPC	FA 22:2	335.300
PA/PG/PS/PI/PC/LPC	FA 22:1	337.300
PA/PG/PS/PI/PC/LPC	FA 22:0	339.300
SGalCer	HSO_4	96.9
PS	Serine -H_2O	NL 87.1

In ceramide and cerebroside lipidomics, the high performance liquid chromatography (HPLC) analyses were conducted in the following way. Chromatographic apparatus consisted of a CTC HTC PAL autosampler (CTC Analytics AG, Switzerland), a Rheos

Allegro UHPLC pump (Flux Instruments AG, Switzerland), an external column heater set to 60°C for ceramide and cerebroside lipidomics and 45°C for ganglioside lipidomics, and the Acquity BEH C18 column with an in-line pre-column. The extracted samples, 10 µl of each, were injected into the pre-column followed by the analytical column and delivered to the mass spectrometer at a flow rate of 500 µl/min. In ceramide and cerebroside lipidomics, A gradient was used for lipid analyte separation with solvent A comprising 10 mM ammonium acetate in HPLC grade water containing 0.1% formic acid and solvent B of 10 mM ammonium acetate in acetonitrile:isopropanol (4:3, V:V) containing 0.1% formic acid. The gradient was constructed in the following way: 0 min – 65% B; 2 min – 65% B; 2.5 min – 75% B; 17.5 min – 100% B; 22.5 min – 100% B; 22.6 min – 65% B; 25 min – 65% B.

The lipid extracts were analyzed by HPLC-MS/MS. The MS analysis was performed on a hybrid triple quadrupole/linear ion trap mass spectrometer equipped with the Turbo V™ Ion Source (4000 QTRAP, AB Sciex). The instrument was operating in positive and negative ion modes. The ion source voltage was set to 5500V for ceramide and cerebroside lipidomics and to -4500V for ganglioside lipidomics, and source temperature at 400°C. The collision energy (CE) and declustering potential (DP) was optimized for each lipid class using synthetic standards. A 20 sec dwell time was applied for each scan. Multiple reaction monitoring (MRM) scan mode was used. MRM transitions for each lipid species are summarized in table 3.

Table 3. Ceramide and cerebroside lipidomics.

Lipid	**$[M+H]^+$ (m/z)**	**Product $[M+H]^+$ (m/z)**
Cer(d18:0/16:0)	540.5	266.25
Cer(d18:0/18:0)	568.6	266.25
Cer(d18:0/20:0)	596.6	266.25
Cer(d18:0/22:0)	624.6	266.25
Cer(d18:0/24:0)	652.7	266.25
Cer(d18:0/24:1)	650.6	266.25

Cer(d18:0/26:0)	680.7	266.25
Cer(d18:0/26:1)	678.7	266.25
Cer(d18:1/16:0)	538.5	264.25
Cer(d18:1/18:0)	566.5	264.25
Cer(d18:1/20:0)	594.6	264.25
Cer(d18:1/22:0)	622.6	264.25
Cer(d18:1/24:0)	650.6	264.25
Cer(d18:1/24:1)	648.6	264.25
Cer(d18:1/26:0)	678.7	264.25
Cer(d18:1/26:1)	676.7	264.25
GlcCer(d18:0/16:0)	702.6	266.25
GlcCer(d18:0/18:0)	730.6	266.25
GlcCer(d18:0/20:0)	758.6	266.25
GlcCer(d18:0/22:0)	786.7	266.25
GlcCer(d18:0/24:0)	814.7	266.25
GlcCer(d18:0/24:1)	812.7	266.25
GlcCer(d18:0/26:0)	842.7	266.25
GlcCer(d18:0/26:1)	840.7	266.25
GlcCer(d18:1/16:0)	700.6	264.25
GlcCer(d18:1/18:0)	728.6	264.25
GlcCer(d18:1/20:0)	756.6	264.25
GlcCer(d18:1/22:0)	784.7	264.25
GlcCer(d18:1/24:0)	812.7	264.25
GlcCer(d18:1/24:1)	810.7	264.25
GlcCer(d18:1/26:0)	840.7	264.25
GlcCer(d18:1/26:1)	838.7	264.25
LacCer(d18:1/16:0)	862.6	264.25
LacCer(d18:1/18:0)	890.7	264.25
LacCer(d18:1/20:0)	918.7	264.25
LacCer(d18:1/22:0)	946.7	264.25
LacCer(d18:1/24:0)	974.7	264.25

LacCer(d18:1/24:1)	972.7	264.25
LacCer(d18:1/26:0)	1002.8	264.25
LacCer(d18:1/26:1)	1000.8	264.25
LacCer(d18:0/16:0)	864.6	266.25
LacCer(d18:0/18:0)	892.7	266.25
LacCer(d18:0/20:0)	920.7	266.25
LacCer(d18:0/22:0)	948.7	266.25
LacCer(d18:0/24:0)	976.7	266.25
LacCer(d18:0/24:1)	974.7	266.25
LacCer(d18:0/26:0)	1004.8	266.25
LacCer(d18:0/26:1)	1002.8	266.25
Cer(d18:1/16:0)-OH	554.5	264.25
Cer(d18:1/18:0)-OH	582.5	264.25
Cer(d18:1/20:0)-OH	610.6	264.25
Cer(d18:1/22:0)-OH	638.6	264.25
Cer(d18:1/24:0)-OH	666.6	264.25
Cer(d18:1/24:1)-OH	664.6	264.25
Cer(d18:1/26:0)-OH	694.7	264.25
Cer(d18:1/26:1)-OH	692.7	264.25
IS D3-LacCer d18:1/16:0	865.6	264.25
IS D3-GluCer d18:1/16:0	703.7	264.25
IS Cer d18:1/17:0	552.5	264.25
ES Cer d17:1/18:0	552.5	250.25

The data processing was done in the following way. Initially the retention time (in LC mode) and identification of each peak was done using endogenous standards and by Information Dependent Acquisition (IDA) experiments where applicable. The raw data were processed according to peak detected and retention time (in LC mode) in automated fashion. A stringent cutoff was applied for separating background noise

from actual lipid peaks. Each sample was controlled and only accepted when fulfilling the stringent acceptance criteria. Peak area counts (cps) of detected peaks were converted into a list of corresponding lipid names. Lipids were normalized to their respective internal standard and sample volume or tissue weight to retrieve their concentrations.

Several quality controls were used in the lipidomic analyses. A calibration line using synthetic or isolated standards was obtained prior to sample analysis. Synthetic standards were chosen based on application and had similar properties to the endogenous lipids or analyte(s) of interest. The calibration line consisted of a minimum of five standards points covering the expected quantification range. A sample extracted without standard and standards extracted with no matrix, were included with the calibration line.

The calibration line was used to determine the dynamic quantification range for each lipid class monitored, *e.g.*, the linear quantification limits. As the internal standards used behave in the same way as endogenous lipids they were used for quantifying endogenous lipid species. The calibration lines were based on the same internal standards that were used for quantification of the endogenous lipids.

In each sample extracted for lipids, the ratio of synthetic internal standards (IS) to corresponding post-extract spiked external standard (ES) was determined. The peak area (cps) ratio of internal to external standard (IS/ES) was used for calculating the Coefficient of Variation (CV) across all samples. The IS/ES ratio enabled the calculation of lipid extraction recovery.

Instrument control (IC) was included at the start, middle and end of each run. IC sample analyzed was an extracted reference plasma sample and a set of standards to monitor the instrument's performance, *i.e.*, the intra- and inter-assay variation.

For each platform, a stringent cutoff was applied for separating background noise from actual lipid peaks. Each sample was controlled and only accepted when fulfilling the stringent acceptance criteria. Masses and counts of detected peaks were converted into a list of corresponding lipid names. Lipids were normalized to their respective internal standard and sample volume to retrieve their concentrations.

Statistical analyses

Percentage changes in lipid concentrations between control and case groups were calculated as follows:

100 * (AVG[C] in case group – AVG[C] in control group)/AVG[C] in control group

Statistical significance was assigned based on standard t-test p-values.

In addition, ROC curves were used for finding lipid molecules and concentration cutoffs that separate the best cases from controls. Selectivity is calculated as a number of correctly identified cases divided by the total number of cases. Specificity is calculated as a number of correctly identified controls divided by the total number of controls. Selectivity and specificity was calculated for each lipid concentration, lipid to lipid ratio and ratio of lipid to clinical concentrations.

Example 3

Ethics

The LURIC study was approved by the ethics review committee at the "Landesärztekammer Rheinland-Pfalz" (Mainz, Germany). Written informed consent was obtained from each of the participants.

Results

In this LURIC study sub-cohort, the traditional biomarkers including LDL-cholesterol and HDL–cholesterol concentrations were practically identical in both groups and therefore were not predictive of CVD-related mortality in this study.

Multiple lipidomic markers appeared as significant predictors of CVD death (Tables 4-13). A total of 151 molecular lipids were quantified. The significant predictors were selected based on the top fifty candidates from each category, when available. The biomarker candidates based on molecular lipid concentrations are presented in Tables 4, 7, 10 and 13. The candidates were selected according to the following criteria: t-test p-value ≤ 0.05 or sensitivity $\geq 60\%$ and specificity $\geq 60\%$. From traditional clinical chemistry only apolipoprotein A1 and total cholesterol reached statistical significance with p-value lower than 0.05, but % change was less than 10% between controls and cases, other clinical values did not show any statistical significance. The predictive value of new lipidomic biomarkers was increased when their levels were expressed as distinct lipid-lipid ratios or lipid-clinical ratios (e.g. LDL-C or HDL-C). The top biomarker candidates are presented in Table 13. Top candidates from each category, when available, were selected based on the following selection criteria: t-test p-value ≤ 0.05 and sensitivity $\geq 60\%$ and specificity $\geq 60\%$.

Importance of detailed molecular lipid analyses

Recent evolvement of mass spectrometry driven lipid analysis approaches has made it possible to resolve complex lipidomes to their molecular lipid species level at high-throughput and quality required for analyses of clinical cohorts. As a result of the high sensitivity and selectivity of the methods, a lipidome-wide analysis of minute sample amounts has become feasible. Present technologies are capable of identifying lipids with different sum compositions, *i.e.* phosphatidylcholine (PC) 34:1, but more important is the identification of molecular lipid species, e.g. PC 16:0/18:1. In the latter analysis, information of the type of fatty acids and their positions attached to the glycerol backbone making up the particular PC molecule is retrieved.

The seminal work of Shinzawa-Itoh and colleagues showed by highly sophisticated experiments that the oxygen transfer mechanism in cytochrome c oxidase requires a specific phosphatidylglycerol molecular lipid with palmitate and vaccenate at the *sn*-1

and *sn*-2 positions respectively on the glycerol backbone (Shinzawa-Itoh K, Aoyama H, Muramoto K *et al: Structures and physiological roles of 13 integral lipids of bovine heart cytochrome c oxidase. EMBO* J 2007, 26:1713-1725). In line with other studies, this undoubtedly indicates that the lipid structure is an essential determinant of the biological effect. Therefore, molecular lipidomics is an essential for biomarker discovery. Figure 1 illustrates the importance of molecular lipid data by comparing the biomarker value of two PC and LacCer molecules in predicting CVD mortality in the LURIC cohort. The data reveals that while LacCer(d18:1/20:0) is a significant CVD predictor, LacCer (d18:1/18:16:0) has low biomarker potential. In addition, two PC molecules PC (18:0/20:4) and PC (18:0/16:0) have even opposite effects on CVD complications. Thus, it is always necessary to identify and quantify all lipid species for lipid classes of interest including but not limited to cholesterol esters, different phopsholipid classes, ceramides, cerebrosides (lactosylceramides, glycosylceramides), and gangliosides.

Table 4. Significant lipids in LURIC study sorted by p-value. Lipid names, p-values and % change for negative correlation are presented. Table 4a shows significant lipids from all study subjects. The significant lipids from subjects not undergoing statin treatment are listed in table 4b.

4a) Significant lipids in LURIC study sorted by p-value from all study subjects.

Lipid name	p-value	Percentage change
Positive correlation		
LacCer(d18:1/20:0)	0,00008	29,52421
LacCer(d18:1/22:0)	0,00046	22,75541
LacCer(d18:1/18:0)	0,00094	26,78692
Cer(d18:1/18:0)	0,00177	23,30373
Cer(d18:1/20:0)	0,00302	17,32385
LacCer(d18:1/24:1)	0,00361	24,72456
PS O-18:2/16:0-alkenyl	0,00571	49,89286
PS O-16:0/18:2-alkenyl	0,00670	49,99084
PS O-16:1/18:2-alkyl	0,00670	49,99084

Cer(d18:1/24:1)	0,01142	14,88898
Total LacCer	0,01669	13,83938
PS O-18:0/18:2-alkenyl (PS O-18:1/18:2-alkyl)	0,02899	40,93773
LacCer(d18:1/24:0)	0,04425	15,80958
PC O-32:0 (KDdiA-PC)	0,04546	17,40815
GlcCer(d18:1/18:0)	0,04913	12,83156
Negative correlation		
Total PC	0,00011	-16,07367
PC 16:0/20:4	0,00077	-18,06547
Total LPC	0,00126	-17,02070
CE 14:0	0,00181	-22,73309
PC 16:0/20:3	0,00191	-18,78110
Cer(d18:0/24:0)	0,00254	-27,27562
PC 18:0/20:4	0,00303	-16,02110
CE 20:3	0,00312	-19,02446
CE 17:1	0,00694	-16,90145
PC 18:0/20:3	0,00726	-17,20664
PC 18:0/18:1	0,00765	-18,18002
Cer(d18:0/22:0)	0,01158	-22,37263
PC 16:0/22:6	0,01180	-16,65050
LPC 18:1	0,01457	-14,45827
SM (d18:1/23:0) (d18:1/22:1-OH)	0,01920	-14,02360
CE 16:0	0,02427	-10,63490
Total CE	0,02745	-11,83333
SM (d18:1/24:0) (d18:1/23:1-OH)	0,02784	-13,83715
PC 18:1/18:2	0,03666	-10,83371

4b) Significant lipids in LURIC study sorted by p-value from subjects not undergoing statin treatment.

Lipid name	p-value	Percentage change
Positive correlation		
Cer(d18:1/20:0)	0,00004	28,00357
Cer(d18:1/18:0)	0,00009	34,32550
LacCer(d18:1/20:0)	0,00010	32,91154
Cer(d18:1/24:1)	0,00039	23,37606
LacCer(d18:1/22:0)	0,00048	25,61851
LacCer(d18:1/18:0)	0,00144	29,19850
LacCer(d18:1/24:1)	0,00199	29,83279
PS O-18:2/16:0-alkenyl	0,00432	33,81177
Cer(d18:1/22:0)	0,00473	18,32126

PS O-16:0/18:2-alkenyl	0,00590	32,17190
PS O-16:1/18:2-alkyl	0,00590	32,17190
Total DAG	0,00794	31,67365
Cer(d18:1/16:0)	0,00952	16,71359
Total Cer	0,00932	15,44601
Total LacCer	0,01105	16,00541
LacCer(d18:1/24:0)	0,01989	19,85622
GlcCer(d18:1/20:0)	0,02288	17,74772
PC O-32:0 (KDdiA-PC)	0,02467	22,23265
GlcCer(d18:1/18:0)	0,02584	16,12961
GlcCer(d18:1/24:1)	0,03290	18,89331
GlcCer(d18:1/26:1)	0,04702	17,52675
Cer(d18:1/26:1)	0,04802	13,59618
Negative correlation		
Total PC	0,00921	-12,44220
CE 14:0	0,01090	-21,01258
CE 20:3	0,02157	-16,03606
CE 17:1	0,02204	-15,93952
PC 16:0/20:4	0,02256	-14,96966
PC 18:0/20:4	0,03376	-13,60917
Cer(d18:0/24:0)	0,03376	-21,87004
Total LPC	0,03443	-12,91576
PC 16:0/20:3	0,04337	-13,43056

Table 5. Table of significant lipid to lipid ratios in LURIC study sorted by p-value. Lipid names, p-values, % change both for positive and negative correlation are presented. Table 5a shows significant lipids from all study subjects. The significant lipids from subjects not undergoing statin treatment are listed in table 5b.

5a) Significant lipid to lipid ratios in LURIC study sorted by p-value from all study subjects.

Lipid name / lipid name	p-value	Percentage change
Positive correlation		
GlcCer(d18:1/26:0)/Total CE	0,0000000	12,8050228
GlcCer(d18:1/26:1)/Total CE	0,0000000	29,5576923
PS O-16:0/18:2-alkenyl/Total PS O	0,0000000	26,0723978

PS O-16:1/18:2-alkyl/Total PS O	0,0000000	26,0723978
PS O-18:2/16:0-alkenyl/Total PS O	0,0000000	28,7826715
Cer(d18:1/24:1)/Total PC	0,0000000	38,6612692
PC 16:0/16:0/Total PC	0,0000000	26,1328496
LacCer(d18:1/20:0)/Total PC	0,0000000	55,3076855
Cer(d18:1/24:1)/PC 16:0/20:4	0,0000000	52,6701270
Cer(d18:1/20:0)/Total PC	0,0000000	40,0940286
LacCer(d18:1/18:0)/Total PC	0,0000000	53,5855166
Cer(d18:1/18:0)/Total PC	0,0000000	48,2586905
Cer(d18:1/18:0)/PC 16:0/20:4	0,0000000	65,7060860
Cer(d18:1/24:1)/PC 16:0/18:1	0,0000000	34,2415459
PS O-18:0/18:2-alkenyl (PS O-18:1/18:2-alkyl)/Total PS O	0,0000000	18,7146206
Total LacCer/Total PC	0,0000001	40,0389043
Cer(d18:1/24:1)/PC 16:0/20:3	0,0000001	39,6033049
Cer(d18:1/22:0)/Total PC	0,0000001	31,3604924
Cer(d18:1/20:0)/PC 16:0/20:4	0,0000001	55,6619154
LacCer(d18:1/22:0)/Total PC	0,0000001	48,7385500
LacCer(d18:1/20:0)/PC 16:0/20:3	0,0000001	57,2475183
Cer(d18:1/18:0)/PC 16:0/20:3	0,0000002	53,4975004
LacCer(d18:1/20:0)/PC 18:0/20:3	0,0000002	56,3125345
LacCer(d18:1/18:0)/PC 18:0/20:3	0,0000002	58,4642532
Cer(d18:1/22:0)/PC 16:0/20:4	0,0000002	42,5755107
LacCer(d18:1/20:0)/PC 18:0/18:1	0,0000004	50,6042672
Cer(d18:1/24:1)/LPC 18:1	0,0000004	37,9852355
LacCer(d18:1/20:0)/PC 16:0/18:1	0,0000004	46,3528827
LacCer(d18:1/20:0)/PC 18:1/18:1	0,0000004	49,6378601
Cer(d18:1/18:0)/PC 16:0/18:1	0,0000004	42,1348344
Cer(d18:1/18:0)/PC 18:0/20:4	0,0000005	55,4207048
Cer(d18:1/24:1)/PC 18:0/20:4	0,0000005	40,7129933
Cer(d18:1/20:0)/PC 16:0/20:3	0,0000005	44,8451813
LacCer(d18:1/18:0)/PC 18:0/18:1	0,0000006	50,0860210
Cer(d18:1/20:0)/PC 16:0/18:1	0,0000006	35,2897482
LacCer(d18:1/20:0)/PC 18:1/18:2	0,0000007	47,4807020
Cer(d18:1/24:1)/Total LPC	0,0000007	37,5873387
Total Cer/Total PC	0,0000007	28,8638001
Cer(d18:1/20:0)/PC 18:0/20:4	0,0000007	46,2204972
LacCer(d18:1/18:0)/PC 18:1/18:1	0,0000007	47,3110220
LacCer(d18:1/18:0)/PC 16:0/20:3	0,0000007	55,5925567
LacCer(d18:1/24:1)/Total PC	0,0000008	56,5726916
Cer(d18:1/24:1)/PC 18:0/18:1	0,0000008	38,3563305
Cer(d18:1/24:1)/PC 18:0/20:3	0,0000013	39,6802706

LacCer(d18:1/22:0)/PC 16:0/20:4	0,0000013	57,8428560
LacCer(d18:1/18:0)/PC 16:0/18:1	0,0000014	45,2070855
LacCer(d18:1/22:0)/PC 18:0/20:3	0,0000014	50,7183795
Cer(d18:1/20:0)/PC 18:1/18:1	0,0000016	40,1833717
LacCer(d18:1/18:0)/PC 18:1/18:2	0,0000017	46,5169450
Cer(d18:1/22:0)/PC 16:0/20:3	0,0000018	33,7513783
Negative correlation		
Cer(d18:0/22:0)/Total CE	0,0000000	-11,7767698
Cer(d18:0/24:0)/Total CE	0,0000000	-18,9531828
Cer(d18:0/24:1)/Total CE	0,0000000	-1,2444181
CE 18:3/Cer(d18:1/24:1)	0,0000000	-35,9591235
Cer(d18:0/24:0)/Cer(d18:1/24:1)	0,0000004	-36,1288066
CE 18:3/Total Cer	0,0000021	-30,3105704
CE 18:3/PC 16:0/16:0	0,0000028	-30,4716021
CE 18:3/LacCer(d18:1/20:0)	0,0000028	-44,3063424
CE 20:3/Cer(d18:1/24:1)	0,0000034	-28,1216690
CE 18:3/PS O-16:0/18:2-alkenyl	0,0000036	-38,5094276
CE 18:3/PS O-16:1/18:2-alkyl	0,0000036	-38,5094276
CE 18:3/Total LacCer	0,0000037	-34,1308012
CE 18:3/Cer(d18:1/20:0)	0,0000037	-33,6203392
LPC 18:2/LacCer(d18:1/20:0)	0,0000040	-41,6604394
Cer(d18:0/24:0)/Total Cer	0,0000049	-31,4531758
Cer(d18:0/24:0)/Cer(d18:1/18:0)	0,0000052	-40,2960344
Cer(d18:0/24:0)/PS O-16:0/18:2-alkenyl	0,0000059	-40,8329837
Cer(d18:0/24:0)/PS O-16:1/18:2-alkyl	0,0000059	-40,8329837
Cer(d18:0/22:0)/Cer(d18:1/24:1)	0,0000064	-32,1886967
Cer(d18:0/24:0)/LacCer(d18:1/24:0)	0,0000067	-37,0287234
Cer(d18:0/22:0)/Cer(d18:1/18:0)	0,0000071	-36,5400374
CE 14:0/Cer(d18:1/24:1)	0,0000076	-29,9054883
CE 18:3/Cer(d18:1/16:0)	0,0000079	-32,5598715
CE 18:3/Cer(d18:1/18:0)	0,0000082	-38,1543108
Cer(d18:0/24:0)/Cer(d18:1/20:0)	0,0000087	-35,4631184
CE 18:3/GlcCer(d18:1/20:0)	0,0000087	-36,4665498
CE 18:3/Cer(d18:1/22:0)	0,0000101	-30,6595286
Cer(d18:0/24:0)/Cer(d18:1/22:0)	0,0000105	-32,4086711
Cer(d18:0/22:0)/PS O-16:0/18:2-alkenyl	0,0000114	-37,4226868
Cer(d18:0/22:0)/PS O-16:1/18:2-alkyl	0,0000114	-37,4226868
CE 18:3/PC O-34:1	0,0000122	-33,4941413
CE 18:3/Total CE	0,0000151	-20,2882080
PC 16:0/20:3/PS O-16:0/18:2-alkenyl	0,0000154	-29,5280580
PC 16:0/20:3/PS O-16:1/18:2-alkyl	0,0000154	-29,5280580

PC 18:1/18:2/PS O-16:0/18:2-alkenyl	0,0000155	-23,7129392
PC 18:1/18:2/PS O-16:1/18:2-alkyl	0,0000155	-23,7129392
Cer(d18:0/22:0)/Cer(d18:1/20:0)	0,0000165	-31,5266149
CE 18:3/LacCer(d18:1/22:0)	0,0000174	-37,1525849
LPC 18:2/PS O-16:0/18:2-alkenyl	0,0000175	-30,3450779
LPC 18:2/PS O-16:1/18:2-alkyl	0,0000175	-30,3450779
CE 17:1/Cer(d18:1/24:1)	0,0000186	-24,8594478
CE 16:0/Cer(d18:1/24:1)	0,0000188	-19,2509390
CE 18:3/GlcCer(d18:1/18:0)	0,0000221	-35,5601491
CE 18:3/LacCer(d18:1/18:0)	0,0000326	-37,4416706
CE 18:3/PS O-16:0/18:1-alkenyl (PS O-16:1/18:1-alkyl)	0,0000326	-34,1672013
CE 18:3/Cer(d18:1/24:0)	0,0000331	-27,4645341
Cer(d18:0/22:0)/Cer(d18:1/22:0)	0,0000377	-28,0899033
LPC 16:0/LacCer(d18:1/20:0)	0,0000391	-35,6188222
Cer(d18:0/24:0)/Cer(d18:1/16:0)	0,0000446	-34,6695918
Total LPC/Total LacCer	0,0000469	-26,0881987

5b) Significant lipid to lipid ratios in LURIC study sorted by p-value from subjects not undergoing statin treatment

Lipid name / Lipid name	**p-value**	**Percentage change**
Positive correlation		
GlcCer(d18:1/26:0)/Total CE	0,000000	13,329316
GlcCer(d18:1/26:1)/Total CE	0,000000	35,356592
PS O-16:0/18:2-alkenyl/Total PS O	0,000000	26,426208
PS O-16:1/18:2-alkyl/Total PS O	0,000000	26,426208
PS O-18:2/16:0-alkenyl/Total PS O	0,000000	29,590682
Cer(d18:1/24:1)/Total PC	0,000000	43,040800
Cer(d18:1/24:1)/PC 16:0/20:4	0,000000	59,876132
Cer(d18:1/24:1)/PC 18:0/20:4	0,000000	46,504629
Cer(d18:1/20:0)/Total PC	0,000000	46,216544
PC 16:0/16:0/Total PC	0,000000	28,139641
Total DAG/Total LPC	0,000000	57,426180
Cer(d18:1/18:0)/PC 16:0/20:4	0,000000	73,073704
Cer(d18:1/18:0)/Total PC	0,000000	53,769121
Cer(d18:1/22:0)/Total PC	0,000000	34,704834
Cer(d18:1/22:0)/PC 16:0/20:4	0,000000	47,860118
Cer(d18:1/20:0)/PC 16:0/20:4	0,000000	64,045788
LacCer(d18:1/20:0)/Total PC	0,000000	55,686130
Cer(d18:1/18:0)/PC 18:0/20:4	0,000000	61,943925
Cer(d18:1/20:0)/PC 18:0/20:4	0,000000	53,941480

Cer(d18:1/24:1)/PC 16:0/18:1	0,000000	35,646899
Cer(d18:1/24:1)/PC 16:0/20:3	0,000000	44,382440
Cer(d18:1/18:0)/PC 16:0/20:3	0,000001	61,224227
Cer(d18:1/20:0)/PC 16:0/20:3	0,000001	52,891307
Cer(d18:1/24:1)/PC 18:0/18:1	0,000001	42,115354
Cer(d18:1/22:0)/PC 18:0/20:4	0,000001	36,949978
Cer(d18:1/20:0)/PC 18:0/18:1	0,000004	47,396000
SM (d18:1/17:0) (d18:1/16:1-OH)/Total PC O	0,000004	39,660537
PC O-32:0 (KDdiA-PC)/Total PC O	0,000005	46,418572
Cer(d18:1/20:0)/PC 16:0/18:1	0,000005	37,704904
Cer(d18:1/24:1)/LPC 18:1	0,000005	40,092181
Cer(d18:1/24:1)/PC 18:1/18:1	0,000005	38,720001
Cer(d18:1/18:0)/PC 16:0/18:1	0,000006	44,307054
LacCer(d18:1/18:0)/Total PC	0,000006	50,539560
Cer(d18:1/20:0)/PC 18:1/18:1	0,000006	44,664936
Cer(d18:1/18:0)/PC 18:0/18:1	0,000006	54,563687
LacCer(d18:1/20:0)/PC 18:0/20:4	0,000007	66,072520
Cer(d18:1/24:1)/PC 18:0/20:3	0,000007	44,320399
LacCer(d18:1/20:0)/PC 16:0/20:3	0,000008	56,972652
Cer(d18:1/22:0)/PC 16:0/20:3	0,000008	37,291136
PC 16:0/16:0/PC 16:0/20:4	0,000009	42,512740
PS O-16:0/18:2-alkenyl/Total PC	0,000009	53,059092
PS O-16:1/18:2-alkyl/Total PC	0,000009	53,059092
LacCer(d18:1/20:0)/PC 18:0/20:3	0,000009	55,403274
Total Cer/Total PC	0,000011	29,949121
Total LacCer/Total PC	0,000012	37,815865
Total DAG/Total PC	0,000012	57,897424
Cer(d18:1/18:0)/PC 18:1/18:1	0,000012	49,427440
LacCer(d18:1/20:0)/PC 18:1/18:2	0,000013	48,432788
Total DAG/Total PC O	0,000014	52,258466
Cer(d18:1/24:1)/Total LPC	0,000014	38,684740
Negative correlation	**p-value**	**Percentage change**
Cer(d18:0/22:0)/Total CE	0,000000	-6,628640
Cer(d18:0/24:0)/Total CE	0,000000	-13,307278
DAG 16:0/18:1/Total DAG	0,000000	-17,305276
CE 18:3/Cer(d18:1/24:1)	0,000000	-37,975733
CE 16:0/Cer(d18:1/24:1)	0,000001	-23,257135
Cer(d18:0/24:0)/Cer(d18:1/24:1)	0,000003	-36,760563
CE 20:4/Cer(d18:1/24:1)	0,000004	-28,636879
CE 20:3/Cer(d18:1/24:1)	0,000007	-30,787067
CE 14:0/Cer(d18:1/24:1)	0,000008	-32,409429

Cer(d18:0/22:0)/Cer(d18:1/24:1)	0,000011	-34,086320
CE 20:4/Cer(d18:1/18:0)	0,000017	-31,313949
CE 18:3/LacCer(d18:1/20:0)	0,000017	-45,652383
CE 18:3/Cer(d18:1/20:0)	0,000019	-34,938575
CE 17:1/Cer(d18:1/24:1)	0,000020	-27,626744
CE 18:3/Cer(d18:1/18:0)	0,000022	-39,797182
CE 18:3/PS O-16:0/18:2-alkenyl	0,000023	-40,724368
CE 18:3/PS O-16:1/18:2-alkyl	0,000023	-40,724368
CE 18:3/PC O-34:1	0,000025	-36,379680
CE 18:3/Total DAG	0,000025	-40,454303
CE 18:3/PC 16:0/16:0	0,000026	-31,169278
CE 18:2/Cer(d18:1/24:1)	0,000027	-23,500781
Cer(d18:0/22:0)/Cer(d18:1/18:0)	0,000031	-38,447200
CE 18:3/Total Cer	0,000034	-30,424215
Cer(d18:0/22:0)/PS O-16:0/18:2-alkenyl	0,000045	-37,930990
Cer(d18:0/22:0)/PS O-16:1/18:2-alkyl	0,000045	-37,930990
LPC 18:2/LacCer(d18:1/20:0)	0,000045	-40,925010
PC 18:0/20:4/PS O-16:0/18:2-alkenyl	0,000046	-31,467609
PC 18:0/20:4/PS O-16:1/18:2-alkyl	0,000046	-31,467609
PC 16:0/20:4/Total DAG	0,000046	-36,637600
CE 16:0/Cer(d18:1/18:0)	0,000047	-26,423623
Cer(d18:0/22:0)/Cer(d18:1/20:0)	0,000051	-32,923442
PC 16:0/20:3/PS O-16:0/18:2-alkenyl	0,000051	-30,612669
PC 16:0/20:3/PS O-16:1/18:2-alkyl	0,000051	-30,612669
Cer(d18:0/24:0)/Cer(d18:1/18:0)	0,000052	-41,966868
CE 17:1/Cer(d18:1/18:0)	0,000062	-30,441023
CE 20:4/LacCer(d18:1/20:0)	0,000062	-34,937892
Cer(d18:0/24:0)/Cer(d18:1/20:0)	0,000077	-36,424116
CE 18:3/GlcCer(d18:1/20:0)	0,000078	-38,775015
PC 16:0/20:4/PS O-16:0/18:2-alkenyl	0,000079	-31,649115
PC 16:0/20:4/PS O-16:1/18:2-alkyl	0,000079	-31,649115
Cer(d18:0/24:0)/PS O-16:0/18:2-alkenyl	0,000082	-40,069396
Cer(d18:0/24:0)/PS O-16:1/18:2-alkyl	0,000082	-40,069396
Cer(d18:0/24:0)/Total Cer	0,000091	-30,775984
Cer(d18:0/22:0)/Total DAG	0,000096	-39,183597
CE 18:3/Cer(d18:1/16:0)	0,000101	-32,942871
PC 18:1/18:2/PS O-16:0/18:2-alkenyl	0,000106	-24,667433
PC 18:1/18:2/PS O-16:1/18:2-alkyl	0,000106	-24,667433
CE 18:3/Cer(d18:1/22:0)	0,000109	-30,876034
CE 14:0/Cer(d18:1/18:0)	0,000117	-35,001327
PC 18:0/20:3/PS O-16:0/18:2-alkenyl	0,000119	-29,825217

Table 6. Table of significant lipid to clinical ratios in LURIC study sorted by p-value. Lipid names and clinical measurement, p-values and percentage change both for positive and negative correlation are presented. Table 6a shows significant lipids from all study subjects. The significant lipids from subjects not undergoing statin treatment are listed in table 6b

6a) Significant lipid to clinical ratios in LURIC study sorted by p-value from all study subjects.

Lipid name / clinical measurement	p-value	Percentage change
Positive correlation		
LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL)	0,00000	43,04967
LacCer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL)	0,00000	41,46919
LacCer(d18:1/22:0)/total cholesterol (EDTA) (mg/dL)	0,00000	32,24669
LacCer(d18:1/20:0)/triglycerides (EDTA) (mg/dL)	0,00001	54,05564
LacCer(d18:1/22:0)/apolipoprotein A-I (mg/dL)	0,00001	32,96039
Cer(d18:1/18:0)/triglycerides (EDTA) (mg/dL)	0,00001	40,06643
Cer(d18:1/18:0)/total cholesterol (EDTA) (mg/dL)	0,00002	31,56099
LacCer(d18:1/20:0)/apolipoprotein B (mg/dL)	0,00002	37,03057
Cer(d18:1/20:0)/triglycerides (EDTA) (mg/dL)	0,00003	34,46408
Cer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL)	0,00003	25,23403
LacCer(d18:1/18:0)/triglycerides (EDTA) (mg/dL)	0,00004	52,60972
LacCer(d18:1/24:1)/triglycerides (EDTA) (mg/dL)	0,00004	60,79934
LacCer(d18:1/22:0)/apolipoprotein B (mg/dL)	0,00004	29,83861
Cer(d18:1/20:0)/apolipoprotein A-I (mg/dL)	0,00004	31,35691
LacCer(d18:1/18:0)/total cholesterol (EDTA) (mg/dL)	0,00005	38,87517
Cer(d18:1/24:1)/triglycerides (EDTA) (mg/dL)	0,00005	32,27486
LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL)	0,00006	39,32664
LacCer(d18:1/22:0)/triglycerides (EDTA) (mg/dL)	0,00006	49,54525
LacCer(d18:1/18:0)/apolipoprotein A-I (mg/dL)	0,00007	41,61371
LacCer(d18:1/24:1)/total cholesterol (EDTA) (mg/dL)	0,00007	36,35465
Total LacCer/total cholesterol (EDTA) (mg/dL)	0,00008	23,69633
Cer(d18:1/18:0)/apolipoprotein A-I (mg/dL)	0,00008	37,38237
Cer(d18:1/24:1)/total cholesterol (EDTA) (mg/dL)	0,00011	21,94547
Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL)	0,00011	27,12684
Cer(d18:1/18:0)/apolipoprotein B (mg/dL)	0,00017	27,27914
LacCer(d18:1/20:0)/total-c/HDL-c	0,00018	33,48550

LacCer(d18:1/24:1)/apolipoprotein A-I (mg/dL)	0,00018	36,33201
Total LacCer/triglycerides (EDTA) (mg/dL)	0,00022	38,52220
LacCer(d18:1/24:1)/apolipoprotein B (mg/dL)	0,00022	33,98045
LacCer(d18:1/18:0)/apolipoprotein B (mg/dL)	0,00022	33,69302
LacCer(d18:1/22:0)/HDL cholesterol (EDTA) (mg/dL)	0,00024	29,19905
Total LacCer/apolipoprotein A-I (mg/dL)	0,00025	25,87122
PC O-32:0 (KDdiA-PC)/triglycerides (EDTA) (mg/dL)	0,00029	48,31010
LacCer(d18:1/20:0)/LDL cholesterol (EDTA) (mg/dL)	0,00031	31,95659
Cer(d18:1/22:0)/triglycerides (EDTA) (mg/dL)	0,00037	28,23304
Total Cer/triglycerides (EDTA) (mg/dL)	0,00043	26,80115
LacCer(d18:1/22:0)/LDL cholesterol (EDTA) (mg/dL)	0,00050	24,24011
Cer(d18:1/20:0)/apolipoprotein B (mg/dL)	0,00052	20,79615
LacCer(d18:1/22:0)/total-c/HDL-c	0,00061	27,84411
Total LacCer/apolipoprotein B (mg/dL)	0,00065	20,63257
PC O-34:1/triglycerides (EDTA) (mg/dL)	0,00066	38,80785
PC O-32:0 (KDdiA-PC)/apolipoprotein A-I (mg/dL)	0,00066	36,57664
Cer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL)	0,00067	30,67863
LacCer(d18:1/18:0)/total-c/HDL-c	0,00073	30,67436
PS O-18:2/16:0-alkenyl/HDL cholesterol (EDTA) (mg/dL)	0,00073	57,54661
LacCer(d18:1/18:0)/HDL cholesterol (EDTA) (mg/dL)	0,00079	38,04132
Cer(d18:1/16:0)/triglycerides (EDTA) (mg/dL)	0,00083	28,51323
Cer(d18:1/18:0)/HDL cholesterol (EDTA) (mg/dL)	0,00085	36,16483
Cer(d18:1/18:0)/total-c/HDL-c	0,00087	21,75165
LacCer(d18:1/20:0)/apoA1/apoB	0,00090	32,36387
Negative correlation		
CE 18:3/apolipoprotein B (mg/dL)	0,00016	-25,31907
CE 18:3/total cholesterol (EDTA) (mg/dL)	0,00026	-23,67665
CE 18:3/LDL cholesterol (EDTA) (mg/dL)	0,00052	-27,21759
CE 18:3/apolipoprotein A-I (mg/dL)	0,00054	-23,09816
CE 18:3/LDL-c/HDL-c	0,00060	-31,33346
CE 18:3/apoA1/apoB	0,00068	-27,55825
CE 18:3/total-c/HDL-c	0,00070	-27,28733
CE 18:3/HDL cholesterol (EDTA) (mg/dL)	0,00072	-24,04060
Cer(d18:0/24:0)/apolipoprotein B (mg/dL)	0,00181	-26,25271
CE 14:0/LDL-c/HDL-c	0,00241	-27,07756
Cer(d18:0/24:0)/total cholesterol (EDTA) (mg/dL)	0,00281	-24,73116
Cer(d18:0/24:0)/total-c/HDL-c	0,00347	-27,84469
CE 14:0/total-c/HDL-c	0,00356	-23,22809
PC 16:0/20:3/total-c/HDL-c	0,00364	-19,07121
CE 14:0/apolipoprotein B (mg/dL)	0,00375	-19,76414
Total PC/LDL-c/HDL-c	0,00402	-21,24583

Cer(d18:0/24:0)/LDL-c/HDL-c	0,00502	-33,76759
Total PC/apolipoprotein B (mg/dL)	0,00513	-12,91145
Total PC/total-c/HDL-c	0,00535	-16,13350
CE 20:3/LDL-c/HDL-c	0,00547	-21,16631
PC 16:0/20:4/apolipoprotein B (mg/dL)	0,00576	-15,39247
PC 16:0/20:4/total-c/HDL-c	0,00682	-18,06323
Cer(d18:0/22:0)/LDL-c/HDL-c	0,00748	-29,05891
Total PC/total cholesterol (EDTA) (mg/dL)	0,00760	-10,60231
Cer(d18:0/22:0)/total-c/HDL-c	0,00765	-23,72182
PC 16:0/20:3/LDL-c/HDL-c	0,00784	-22,56336
PC 18:0/20:3/total-c/HDL-c	0,00794	-17,83335
CE 14:0/total cholesterol (EDTA) (mg/dL)	0,00816	-17,44260
CE 20:3/total-c/HDL-c	0,00819	-17,34055
PC 16:0/20:4/LDL-c/HDL-c	0,00828	-21,49898
CE 17:1/LDL-c/HDL-c	0,00832	-21,33179
CE 14:0/LDL cholesterol (EDTA) (mg/dL)	0,00832	-20,55966
Cer(d18:0/24:0)/LDL cholesterol (EDTA) (mg/dL)	0,00848	-30,08563
LPC 18:2/LDL-c/HDL-c	0,00873	-21,70580
Total LPC/LDL-c/HDL-c	0,00881	-20,39287
PC 18:0/20:3/LDL-c/HDL-c	0,00947	-22,19538
Cer(d18:0/24:0)/apolipoprotein A-I (mg/dL)	0,01052	-22,39254
Cer(d18:0/22:0)/apolipoprotein B (mg/dL)	0,01094	-21,02661
CE 20:3/apolipoprotein B (mg/dL)	0,01105	-15,18746
PC 16:0/20:4/total cholesterol (EDTA) (mg/dL)	0,01131	-13,37554
Total LPC/total-c/HDL-c	0,01183	-16,82334
LPC 18:2/apoA1/apoB	0,01189	-19,23316
PC 16:0/20:3/apolipoprotein B (mg/dL)	0,01273	-15,11848
CE 16:1/apolipoprotein B (mg/dL)	0,01456	-26,99397
Cer(d18:0/24:0)/HDL cholesterol (EDTA) (mg/dL)	0,01507	-23,10073
CE 16:1/LDL cholesterol (EDTA) (mg/dL)	0,01581	-29,68280
PC 18:0/18:1/LDL-c/HDL-c	0,01581	-25,72002
CE 20:5/HDL cholesterol (EDTA) (mg/dL)	0,01584	-23,45029
CE 20:5/apolipoprotein B (mg/dL)	0,01619	-27,03163
LPC 18:2/LDL cholesterol (EDTA) (mg/dL)	0,01648	-17,26480

6b) Significant lipid to clinical ratios in LURIC study sorted by p-value from subjects not undergoing statin treatment.

Lipid name / Clinical measurement	p-value	Percentage change
Positive correlation		

Cer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL)	0,00000	38,78716
Cer(d18:1/20:0)/apolipoprotein B (mg/dL)	0,00000	35,29473
Cer(d18:1/18:0)/total cholesterol (EDTA) (mg/dL)	0,00000	44,87416
Cer(d18:1/24:1)/total cholesterol (EDTA) (mg/dL)	0,00000	31,81230
Cer(d18:1/18:0)/apolipoprotein B (mg/dL)	0,00000	41,46939
Cer(d18:1/20:0)/apolipoprotein A-I (mg/dL)	0,00000	43,22923
Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL)	0,00000	36,15491
LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL)	0,00001	47,52465
Cer(d18:1/18:0)/apolipoprotein A-I (mg/dL)	0,00001	49,43693
LacCer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL)	0,00001	47,43498
Cer(d18:1/22:0)/total cholesterol (EDTA) (mg/dL)	0,00001	26,21569
LacCer(d18:1/22:0)/total cholesterol (EDTA) (mg/dL)	0,00001	36,57029
Cer(d18:1/24:1)/apolipoprotein B (mg/dL)	0,00001	29,03655
LacCer(d18:1/22:0)/apolipoprotein A-I (mg/dL)	0,00001	35,92744
Cer(d18:1/18:0)/triglycerides (EDTA) (mg/dL)	0,00002	45,88769
Cer(d18:1/20:0)/triglycerides (EDTA) (mg/dL)	0,00002	41,38147
LacCer(d18:1/20:0)/apolipoprotein B (mg/dL)	0,00002	43,58427
Total Cer/total cholesterol (EDTA) (mg/dL)	0,00002	22,69184
Total DAG/triglycerides (EDTA) (mg/dL)	0,00003	42,61436
LacCer(d18:1/20:0)/LDL cholesterol (EDTA) (mg/dL)	0,00003	42,53680
Cer(d18:1/18:0)/total-c/HDL-c	0,00003	32,87649
Cer(d18:1/24:1)/triglycerides (EDTA) (mg/dL)	0,00004	37,38060
Cer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL)	0,00004	44,64484
LacCer(d18:1/22:0)/apolipoprotein B (mg/dL)	0,00004	35,19942
Cer(d18:1/22:0)/apolipoprotein B (mg/dL)	0,00005	24,23877
LacCer(d18:1/24:1)/total cholesterol (EDTA) (mg/dL)	0,00006	43,51653
LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL)	0,00006	45,00931
Total LacCer/total cholesterol (EDTA) (mg/dL)	0,00007	27,38505
Cer(d18:1/18:0)/HDL cholesterol (EDTA) (mg/dL)	0,00008	50,71310
Cer(d18:1/24:1)/HDL cholesterol (EDTA) (mg/dL)	0,00008	36,69128
LacCer(d18:1/20:0)/triglycerides (EDTA) (mg/dL)	0,00009	53,20068
LacCer(d18:1/24:1)/apolipoprotein B (mg/dL)	0,00009	42,74199
Cer(d18:1/20:0)/total-c/HDL-c	0,00010	26,38965
LacCer(d18:1/22:0)/LDL cholesterol (EDTA) (mg/dL)	0,00010	31,99739
Cer(d18:1/22:0)/apolipoprotein A-I (mg/dL)	0,00011	28,85911
LacCer(d18:1/24:1)/triglycerides (EDTA) (mg/dL)	0,00013	64,74061
Total Cer/apolipoprotein B (mg/dL)	0,00015	21,06506
Total Cer/apolipoprotein A-I (mg/dL)	0,00016	25,36811
Cer(d18:1/16:0)/total cholesterol (EDTA) (mg/dL)	0,00016	27,48182
LacCer(d18:1/24:1)/apolipoprotein A-I (mg/dL)	0,00017	41,35186
Cer(d18:1/20:0)/LDL cholesterol (EDTA) (mg/dL)	0,00018	35,64759

LacCer(d18:1/18:0)/total cholesterol (EDTA) (mg/dL)	0,00019	42,30922
LacCer(d18:1/22:0)/HDL cholesterol (EDTA) (mg/dL)	0,00020	33,63345
LacCer(d18:1/18:0)/apolipoprotein A-I (mg/dL)	0,00022	44,38352
Cer(d18:1/18:0)/LDL cholesterol (EDTA) (mg/dL)	0,00023	42,34532
Total LacCer/apolipoprotein A-I (mg/dL)	0,00031	28,05057
Total LacCer/apolipoprotein B (mg/dL)	0,00035	24,82894
Cer(d18:1/22:0)/triglycerides (EDTA) (mg/dL)	0,00039	32,11726
LacCer(d18:1/20:0)/total-c/HDL-c	0,00040	37,19117
Cer(d18:1/16:0)/apolipoprotein A-I (mg/dL)	0,00042	30,73655
Negative correlation		
CE 18:3/apoA1/apoB	0,00213	-27,06449
CE 18:3/apolipoprotein A-I (mg/dL)	0,00385	-21,63982
CE 18:3/apolipoprotein B (mg/dL)	0,00576	-21,66212
CE 18:3/total cholesterol (EDTA) (mg/dL)	0,00593	-20,58905
CE 18:3/HDL cholesterol (EDTA) (mg/dL)	0,00621	-21,44255
CE 18:3/total-c/HDL-c	0,01166	-23,94433
CE 18:3/LDL-c/HDL-c	0,01395	-25,96634
CE 18:3/LDL cholesterol (EDTA) (mg/dL)	0,01410	-22,13225
CE 14:0/total-c/HDL-c	0,02379	-20,97683
CE 14:0/LDL-c/HDL-c	0,03038	-22,86773
Cer(d18:0/24:0)/apolipoprotein B (mg/dL)	0,03428	-21,10483
CE 14:0/apolipoprotein B (mg/dL)	0,03640	-16,53355
Cer(d18:0/24:0)/total-c/HDL-c	0,04122	-23,22174
Cer(d18:0/24:0)/total cholesterol (EDTA) (mg/dL)	0,04309	-19,71324
CE 14:0/apoA1/apoB	0,04354	-18,62921
CE 16:1/apoA1/apoB	0,04511	-23,73367

The biomarker ability of measured lipids was assessed also by calculating the sensitivity and specificity values for each lipid and their ratios to other lipids or classical biomarkers such as LDL-C and apolipoproteins. This ROC curve analysis revealed a number of biomarker candidates that have equal of higher than 60% sensitivity and specificity for predicting CVD complications (Tables 7-9).

Table 7. Significant lipids in LURIC study sorted by top sensitivity and specificity. Table 7a shows significant lipids from all study subjects. The significant lipids from subjects not undergoing statin treatment are listed in table 7b.

7a) Significant lipids in LURIC study sorted by top sensitivity and specificity from all study subjects.

Lipid name	Sensitivity	Specificity	Percentage change
Positive correlation			
LacCer(d18:1/20:0)	66,03774	63,70370	29,52421
Total LacCer	63,15789	60,12270	13,83938
Cer(d18:1/24:1)	61,40351	60,12270	14,88898
Negative correlation			
Total PC	71,92982	63,29114	-16,07367
PC 16:0/20:3	71,42857	60,75949	-18,78110
Total LPC	70,17544	60,75949	-17,02070
PC 18:0/20:3	66,03774	63,05732	-17,20664
LPC 18:1	64,91228	60,12658	-14,45827
SM (d18:1/14:0) (d18:1/13:1-OH)	63,79310	60,50955	-10,49341
Cer(d18:0/22:0)	61,40351	61,34969	-22,37263
PC 16:0/18:2	61,40351	60,12658	-8,30551
PC 16:0/22:6	60,37736	61,14650	-16,65050

7b) Significant lipids in LURIC study sorted by top sensitivity and specificity from subjects not undergoing statin treatment.

Lipid name	Sensitivity	Specificity	Percentage change
Positive correlation			
LacCer(d18:1/20:0)	70,45455	60,00000	29,52421
Cer(d18:1/24:1)	69,56522	60,34483	14,88898
Cer(d18:1/20:0)	65,21739	64,65517	17,32385
Cer(d18:1/22:0)	60,86957	62,93103	10,65433
GlcCer(d18:1/24:1)	60,86957	62,06897	12,75066
LacCer(d18:1/22:0)	60,00000	61,76471	22,75541
Negative correlation			
Total PC	69,56522	61,60714	-16,07367
PC 16:0/20:3	64,44444	60,71429	-18,78110
SM (d18:1/14:0) (d18:1/13:1-OH)	63,82979	60,71429	-10,49341
LPC 18:1	63,04348	60,71429	-14,45827
Total LPC	63,04348	60,71429	-17,02070
PC O-40:3	60,97561	60,43956	-1,88354
PC 16:0/20:4	60,86957	60,71429	-18,06547

Table 8. Table of significant lipid to lipid ratios in LURIC study sorted by top sensitivity and specificity. Table 8a shows significant lipids from all study subjects. The significant lipids from subjects not undergoing statin treatment are listed in table 8b.

8a) Table of significant lipid to lipid ratios in LURIC study sorted by top sensitivity and specificity from all study subjects.

Lipid name / Lipid name	Sensitivity	Specificity	Percentage change
Positive correlation			
PS O-16:0/18:2-alkenyl/Total PS O	98,24561	63,92405	26,07240
PS O-16:1/18:2-alkyl/Total PS O	98,24561	63,92405	26,07240
PS O-18:2/16:0-alkenyl/Total PS O	85,45455	70,66667	28,78267
LacCer(d18:1/20:0)/PC 16:0/20:3	80,39216	65,11628	57,24752
CE 18:2/CE 18:3	79,31034	60,37736	26,34366
LacCer(d18:1/20:0)/Total LPC	78,84615	61,24031	53,68111
LacCer(d18:1/20:0)/Total PC	78,84615	64,34109	55,30769
LacCer(d18:1/20:0)/PC 18:0/20:3	77,08333	60,15625	56,31253
Cer(d18:1/24:1)/LPC 18:2	75,92593	63,69427	48,79017
CE 16:0/CE 18:3	75,86207	60,37736	25,64615
LacCer(d18:1/20:0)/Total SM	75,47170	60,60606	29,12486
Cer(d18:1/16:0)/Total PC	75,00000	61,14650	32,91697
Cer(d18:1/18:0)/PC 16:0/20:4	75,00000	63,05732	65,70609
Cer(d18:1/18:0)/Total LPC	75,00000	61,14650	45,10211
Cer(d18:1/24:1)/SM (d18:1/24:0) (d18:1/23:1-OH)	75,00000	62,42038	36,77357
Cer(d18:1/24:1)/Total LPC	75,00000	63,05732	37,58734
Cer(d18:1/24:1)/Total PC	75,00000	60,50955	38,66127
LacCer(d18:1/18:0)/Total LPC	75,00000	60,13072	55,13308
LacCer(d18:1/20:0)/SM (d18:1/17:1-OH)	75,00000	62,60163	36,30844
LacCer(d18:1/20:0)/SM (d18:1/18:0)	75,00000	62,60163	36,30844
Total Cer/Total PC	75,00000	63,92405	28,86380
LacCer(d18:1/24:0)/Total LPC	74,54545	61,94030	36,27249
LacCer(d18:1/20:0)/PC 18:2/18:2	74,46809	60,31746	47,81762
PC 16:0/16:0/Total PC	73,68421	65,18987	26,13285
Cer(d18:1/22:0)/Total PC	73,21429	61,78344	31,36049
GlcCer(d18:1/20:0)/Total PC	73,21429	60,50955	36,81380
LacCer(d18:1/16:0)/Total LPC	73,21429	60,50955	26,35547

LacCer(d18:1/18:0)/Total PC	73,21429	61,43791	53,58552
LacCer(d18:1/22:0)/SM (d18:1/14:0) (d18:1/13:1-OH)	73,21429	60,00000	30,07361
Total LacCer/Total PC	73,21429	60,50955	40,03890
LacCer(d18:1/20:0)/PC 16:0/18:1	73,07692	62,01550	46,35288
LacCer(d18:1/20:0)/PC 18:1/18:2	73,07692	60,46512	47,48070
Cer(d18:1/26:0)/PC O-40:0	72,72727	62,22222	9,97951
LacCer(d18:1/22:0)/Total LPC	72,72727	64,92537	41,61463
LacCer(d18:1/24:1)/Total LPC	72,72727	60,44776	45,29327
PC O-18:0/18:2-alkyl/PC O-36:5	72,72727	61,18421	25,99402
PC O-32:0 (KDdiA-PC)/PC O-38:5	72,54902	61,36364	34,00112
Cer(d18:1/22:0)/LPC 18:2	72,22222	61,78344	41,72749
LacCer(d18:1/22:0)/PC 16:0/20:3	72,22222	66,41791	51,38070
LacCer(d18:1/24:0)/PC 16:0/20:3	72,22222	61,19403	39,48118
Cer(d18:1/24:1)/Total CE	71,92982	61,39241	31,32927
PC 16:0/16:0/PC 16:0/20:4	71,92982	61,39241	38,61464
PC 16:0/18:2/Total PC	71,92982	60,75949	8,88941
Total LacCer/Total PC O	71,92982	60,24845	17,49430
Cer(d18:1/16:0)/LPC 18:1	71,42857	63,69427	30,55279
Cer(d18:1/18:0)/LPC 16:0	71,42857	61,14650	40,41256
Cer(d18:1/18:0)/LPC 18:1	71,42857	61,78344	45,33865
GlcCer(d18:1/20:0)/PC 16:0/20:4	71,42857	60,50955	46,04915
LacCer(d18:1/24:1)/Total PC O	71,42857	60,14493	21,09716
CE 19:1/Cer(d18:0/22:0)	71,15385	60,14493	39,21301
Negative correlation			
CE 18:3/LacCer(d18:1/20:0)	84,90566	62,87879	-44,30634
CE 18:3/Cer(d18:1/24:1)	80,70175	60,12658	-35,95912
Cer(d18:0/24:0)/Total Cer	80,70175	60,12270	-31,45318
LPC 18:2/LacCer(d18:1/20:0)	80,00000	64,34109	-41,66044
CE 18:3/Total CE	79,31034	61,00629	-20,28821
GlcCer(d18:1/26:0)/LacCer(d18:1/20:0)	79,16667	61,40351	-23,71130
CE 16:1/Cer(d18:1/20:0)	78,94737	61,39241	-33,84979
CE 16:1/Cer(d18:1/24:1)	77,19298	61,39241	-36,17234
CE 16:1/LacCer(d18:1/18:0)	77,19298	60,38961	-37,93756
CE 18:3/Cer(d18:1/20:0)	77,19298	60,75949	-33,62034
LPC 18:1/LacCer(d18:1/20:0)	76,92308	63,56589	-34,40451
CE 18:3/LacCer(d18:1/22:0)	76,78571	61,02941	-37,15258
CE 16:1/CE 19:1	75,47170	60,86957	-66,77151
CE 16:1/Cer(d18:1/18:0)	75,43860	61,39241	-39,42716
CE 16:1/LacCer(d18:1/16:0)	75,43860	60,12658	-30,53235
CE 16:1/Total LacCer	75,43860	60,75949	-34,87060
CE 18:3/PC 16:0/16:0	75,43860	60,00000	-30,47160

CE 18:3/PS O-16:0/18:2-alkenyl	75,43860	60,64516	-38,50943
CE 18:3/PS O-16:1/18:2-alkyl	75,43860	60,64516	-38,50943
CE 18:3/Total LacCer	75,43860	63,29114	-34,13080
Cer(d18:0/24:0)/Cer(d18:1/22:0)	75,43860	66,25767	-32,40867
CE 16:1/LacCer(d18:1/22:0)	75,00000	61,02941	-37,29505
CE 16:1/LacCer(d18:1/24:0)	75,00000	60,29412	-36,84318
GlcCer(d18:1/26:0)/LacCer(d18:1/22:0)	75,00000	60,86957	-20,64622
LPC 16:0/LacCer(d18:1/20:0)	75,00000	61,24031	-35,61882
Total LPC/Total LacCer	75,00000	61,78344	-26,08820
LPC 16:0/LacCer(d18:1/24:1)	74,54545	60,44776	-24,61533
CE 17:1/GlcCer(d18:1/24:1)	74,07407	60,25641	-24,94421
CE 16:1/GlcCer(d18:1/18:0)	73,68421	60,12658	-36,48698
CE 16:1/GlcCer(d18:1/20:0)	73,68421	60,75949	-38,30453
CE 16:1/PC 16:0/16:0	73,68421	60,64516	-29,10430
CE 18:1/Total LacCer	73,68421	60,12658	-20,87773
CE 18:3/Cer(d18:1/16:0)	73,68421	67,08861	-32,55987
CE 18:3/Cer(d18:1/22:0)	73,68421	61,39241	-30,65953
CE 20:3/Cer(d18:1/24:1)	73,68421	61,39241	-28,12167
Cer(d18:0/22:0)/Cer(d18:1/24:1)	73,68421	61,96319	-32,18870
Cer(d18:0/24:0)/Cer(d18:1/18:0)	73,68421	63,80368	-40,29603
Cer(d18:0/24:0)/Cer(d18:1/24:1)	73,68421	65,64417	-36,12881
Cer(d18:0/24:0)/GlcCer(d18:1/20:0)	73,68421	60,73620	-40,34621
CE 16:1/LacCer(d18:1/20:0)	73,58491	62,12121	-39,47654
CE 20:3/LacCer(d18:1/20:0)	73,58491	62,12121	-35,94789
CE 18:3/LacCer(d18:1/24:0)	73,21429	62,50000	-35,91095
CE 18:3/PS O-16:0/18:1-alkenyl (PS O-16:1/18:1-alkyl)	73,21429	60,64516	-34,16720
Cer(d18:0/22:0)/LacCer(d18:1/24:0)	73,21429	60,00000	-31,24173
Cer(d18:0/24:0)/LacCer(d18:1/24:0)	73,21429	62,85714	-37,02872
LPC 16:0/Total LacCer	73,21429	61,78344	-24,37341
SM (d18:1/24:0) (d18:1/23:1-OH)/Total Cer	73,21429	61,14650	-13,97590
Cer(d18:0/24:0)/SM (d18:1/17:0) (d18:1/16:1-OH)	72,91667	60,00000	-44,87505
LPC 16:0/LacCer(d18:1/22:0)	72,72727	67,16418	-27,47521
CE 17:1/LacCer(d18:1/18:0)	72,22222	60,52632	-27,90709

8b) Table of significant lipid to lipid ratios in LURIC study sorted by top sensitivity and specificity from subjects not undergoing statin treatment.

Lipid name / Lipid name	Sensitivity	Specificity	Percentage change
Positive correlation			
PS O-16:0/18:2-alkenyl/Total PS O	97,82609	62,50000	26,42621
PS O-16:1/18:2-alkyl/Total PS O	88,63636	72,64151	29,59068
PS O-18:2/16:0-alkenyl/Total PS O	81,39535	62,16216	51,68188
Cer(d18:1/24:1)/LPC 18:2	80,85106	60,52632	24,84398
CE 18:2/CE 18:3	80,00000	62,16216	73,07370
Cer(d18:1/18:0)/PC 16:0/20:4	80,00000	60,36036	27,45405
Cer(d18:1/24:1)/PC 16:0/18:2	80,00000	62,16216	38,68474
Cer(d18:1/24:1)/Total LPC	80,00000	62,16216	43,04080
Cer(d18:1/24:1)/Total PC	79,06977	68,42105	82,44735
LacCer(d18:1/20:0)/PC 16:0/20:4	78,57143	64,21053	56,97265
LacCer(d18:1/20:0)/PC 16:0/20:3	77,77778	60,36036	34,07762
Cer(d18:1/16:0)/Total PC	77,77778	60,36036	45,52166
Cer(d18:1/18:0)/LPC 18:1	77,77778	60,17699	32,27927
Cer(d18:1/24:1)/SM (d18:1/24:0) (d18:1/23:1-OH)	77,50000	60,43956	20,46959
Cer(d18:1/24:1)/PC O-40:3	76,74419	60,00000	49,56627
LacCer(d18:1/20:0)/Total LPC	76,74419	63,15789	55,68613
LacCer(d18:1/20:0)/Total PC	76,08696	60,17699	49,43112
Cer(d18:1/18:0)/Total CE	76,08696	60,71429	28,98221
Cer(d18:1/20:0)/SM (d18:1/14:0) (d18:1/13:1-OH)	76,08696	60,86957	29,01076
Cer(d18:1/20:0)/Total PC O	76,08696	60,17699	39,34990
Cer(d18:1/24:1)/Total CE	76,08696	61,60714	20,69456
PS O-16:0/18:2-alkenyl/Total PC O	76,08696	61,60714	20,69456
PS O-16:1/18:2-alkyl/Total PC O	75,55556	60,36036	26,36925
Cer(d18:1/16:0)/LPC 18:1	75,55556	63,06306	44,40414
Cer(d18:1/18:0)/Total LPC	75,55556	63,06306	34,70483
Cer(d18:1/22:0)/Total PC	75,55556	61,60714	29,94912
Total Cer/Total PC	75,00000	61,61616	27,48798
LacCer(d18:1/20:0)/Total SM	75,00000	67,01031	34,46432
LacCer(d18:1/24:0)/Total LPC	75,00000	60,37736	21,65448
PS O-18:2/16:0-alkenyl/Total PC O	74,46809	61,40351	25,51627
CE 16:0/CE 18:3	74,46809	65,13761	29,77017
CE 18:0/CE 18:3	74,41860	60,36036	44,40272
Cer(d18:1/22:0)/LPC 18:2	74,41860	64,21053	48,43279
LacCer(d18:1/20:0)/PC 18:1/18:2	74,41860	60,86957	34,96305
LacCer(d18:1/20:0)/SM (d18:1/17:1-OH)	74,41860	60,86957	34,96305
LacCer(d18:1/20:0)/SM (d18:1/18:0)	74,35897	62,76596	55,40327
LacCer(d18:1/20:0)/PC 18:0/20:3			

Cer(d18:1/18:0)/SM (d18:1/14:0) (d18:1/13:1-OH)	73,91304	74,10714	34,95249
Cer(d18:1/18:0)/SM (d18:1/17:2-OH)	73,91304	60,00000	25,13954
Cer(d18:1/18:0)/SM (d18:1/18:1)	73,91304	60,00000	25,13954
Cer(d18:1/24:1)/SM (d18:1/23:0) (d18:1/22:1-OH)	73,91304	60,71429	29,95139
PC 16:0/16:0/PC 16:0/20:4	73,91304	60,71429	42,51274
Cer(d18:1/20:0)/Total LPC	73,33333	61,26126	36,63159
Cer(d18:1/24:1)/PC 16:0/20:4	73,33333	62,16216	59,87613
Cer(d18:1/24:1)/PC 18:0/18:2	73,33333	62,16216	29,37710
Cer(d18:1/24:1)/PC 18:1/18:2	73,33333	61,26126	36,88389
Cer(d18:1/24:1)/SM (d18:1/17:1-OH)	73,33333	64,42308	23,41916
Cer(d18:1/24:1)/SM (d18:1/18:0)	73,33333	64,42308	23,41916
LacCer(d18:1/20:0)/PC 18:0/18:1	73,17073	62,10526	50,18761
LacCer(d18:1/20:0)/Total CE	72,72727	62,62626	53,71776
Negative correlation			
DAG 16:0/18:1/Total DAG	88,88889	61,16505	-17,30528
CE 18:3/LacCer(d18:1/20:0)	86,36364	66,66667	-45,65238
LPC 18:2/LacCer(d18:1/20:0)	82,92683	62,10526	-40,92501
CE 18:3/Cer(d18:1/24:1)	82,60870	61,06195	-37,97573
GlcCer(d18:1/26:0)/LacCer(d18:1/20:0)	80,48780	64,77273	-26,83109
CE 14:0/Total DAG	80,00000	61,16505	-39,38279
CE 18:3/Total CE	78,72340	62,28070	-19,58872
PC 18:0/20:3/PS O-16:0/18:2-alkenyl	78,57143	60,36036	-29,82522
PC 18:0/20:3/PS O-16:1/18:2-alkyl	78,57143	60,36036	-29,82522
CE 16:1/Cer(d18:1/24:1)	78,26087	61,06195	-37,53854
CE 18:3/PS O-16:0/18:2-alkenyl	78,26087	60,90909	-40,72437
CE 18:3/PS O-16:1/18:2-alkyl	78,26087	60,90909	-40,72437
CE 18:3/Total LacCer	78,26087	60,17699	-32,64187
Cer(d18:0/24:0)/Total Cer	78,26087	62,06897	-30,77598
GlcCer(d18:1/26:0)/LacCer(d18:1/22:0)	78,04878	61,79775	-21,27116
CE 18:3/LacCer(d18:1/22:0)	77,77778	63,63636	-34,76187
CE 20:3/LacCer(d18:1/20:0)	77,27273	60,60606	-36,58675
PC O-40:3/PS O-18:2/16:0-alkenyl	76,92308	62,79070	-28,59638
LPC 18:1/LacCer(d18:1/20:0)	76,74419	60,00000	-33,84809
CE 16:0/Cer(d18:1/24:1)	76,08696	61,06195	-23,25713
CE 16:1/Cer(d18:1/18:0)	76,08696	63,71681	-41,11023
CE 16:1/Cer(d18:1/20:0)	76,08696	66,37168	-34,98271
CE 16:1/GlcCer(d18:1/24:1)	76,08696	60,17699	-39,81218
CE 16:1/LacCer(d18:1/18:0)	76,08696	60,36036	-37,28535
CE 18:3/Cer(d18:1/20:0)	76,08696	63,71681	-34,93858
CE 18:3/Cer(d18:1/22:0)	76,08696	61,94690	-30,87603
Cer(d18:0/22:0)/Cer(d18:1/24:1)	76,08696	61,20690	-34,08632

Cer(d18:0/22:0)/Total GlcCer	76,08696	60,34483	-28,95910
Cer(d18:0/24:0)/Cer(d18:1/20:0)	76,08696	60,34483	-36,42412
PC 18:0/20:3/PS O-18:2/16:0-alkenyl	75,60976	60,95238	-29,83126
CE 16:1/LacCer(d18:1/24:0)	75,55556	60,60606	-36,83943
CE 18:3/LacCer(d18:1/24:0)	75,55556	60,60606	-37,84417
PC 18:1/18:2/Total Cer	75,55556	60,71429	-19,58862
SM (d18:1/23:0) (d18:1/22:1-OH)/Total DAG	75,55556	63,10680	-37,45206
SM (d18:1/24:0) (d18:1/23:1-OH)/Total Cer	75,55556	61,94690	-11,07113
Total CE/Total DAG	75,55556	66,01942	-31,35698
Total LPC/Total LacCer	75,55556	69,36937	-23,44706
CE 16:1/CE 19:1	75,00000	60,82474	-56,18741
CE 20:5/LacCer(d18:1/20:0)	75,00000	61,61616	-37,54401
LPC 16:0/LacCer(d18:1/24:0)	75,00000	60,82474	-25,29458
CE 15:0/Cer(d18:1/20:0)	74,41860	60,57692	-21,94830
CE 16:0/Cer(d18:1/18:0)	73,91304	61,06195	-26,42362
CE 16:1/Total LacCer	73,91304	63,71681	-33,50629
CE 18:2/Cer(d18:1/20:0)	73,91304	61,94690	-19,85408
CE 18:3/Cer(d18:1/24:0)	73,91304	61,40351	-28,00256
CE 18:3/GlcCer(d18:1/20:0)	73,91304	65,48673	-38,77502
CE 18:3/PC 16:0/16:0	73,91304	63,63636	-31,16928
CE 20:3/Cer(d18:1/24:1)	73,91304	61,06195	-30,78707
CE 20:4/GlcCer(d18:1/20:0)	73,91304	62,83186	-30,95570
CE 20:4/GlcCer(d18:1/24:1)	73,91304	61,06195	-28,82844

Table 9. Table of significant lipid to clinical ratios in LURIC study sorted by top sensitivity and specificity. Table 9a shows significant lipids from all study subjects. The significant lipids from subjects not undergoing statin treatment are listed in table 9b.

9a) Table of significant lipid to clinical ratios in LURIC study sorted by top sensitivity and specificity from all study subjects.

Lipid name / Clinical measurement	Sensitivity	Specificity	Percentage change
Positive correlation			
LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL)	75,47170	61,48148	43,04967
Cer(d18:1/24:1)/total cholesterol (EDTA) (mg/dL)	70,17544	60,73620	21,94547

Cer(d18:1/24:1)/triglycerides (EDTA) (mg/dL)	70,17544	60,12270	32,27486
LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL)	69,81132	62,22222	39,32664
LacCer(d18:1/20:0)/apoA1/apoB	67,92453	61,48148	32,36387
LacCer(d18:1/22:0)/HDL cholesterol (EDTA) (mg/dL)	67,85714	60,00000	29,19905
Cer(d18:1/16:0)/triglycerides (EDTA) (mg/dL)	66,66667	61,34969	28,51323
Cer(d18:1/22:0)/apolipoprotein B (mg/dL)	66,66667	60,12270	14,20773
Cer(d18:1/24:1)/apolipoprotein B (mg/dL)	66,66667	62,57669	18,05222
Total Cer/total cholesterol (EDTA) (mg/dL)	66,66667	65,85366	15,12131
LacCer(d18:1/20:0)/LDL-c/HDL-c	66,03774	60,74074	23,54484
LacCer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL)	66,03774	62,96296	41,46919
LacCer(d18:1/20:0)/total-c/HDL-c	66,03774	60,00000	33,48550
Cer(d18:1/18:0)/triglycerides (EDTA) (mg/dL)	64,91228	60,73620	40,06643
Cer(d18:1/22:0)/total cholesterol (EDTA) (mg/dL)	64,91228	61,34969	17,20335
Cer(d18:1/24:1)/total-c/HDL-c	64,91228	61,34969	13,34657
GlcCer(d18:1/24:0)/total cholesterol (EDTA) (mg/dL)	64,91228	61,96319	17,04608
LacCer(d18:1/18:0)/apolipoprotein A-I (mg/dL)	64,91228	60,37736	41,61371
LacCer(d18:1/18:0)/total cholesterol (EDTA) (mg/dL)	64,91228	61,00629	38,87517
Total LacCer/total cholesterol (EDTA) (mg/dL)	64,91228	65,03067	23,69633
LacCer(d18:1/22:0)/apoA1/apoB	64,28571	62,85714	24,17423
LacCer(d18:1/22:0)/apolipoprotein A-I (mg/dL)	64,28571	62,85714	32,96039
LacCer(d18:1/22:0)/total cholesterol (EDTA) (mg/dL)	64,28571	60,00000	32,24669
LacCer(d18:1/24:0)/apoA1/apoB	64,28571	62,14286	15,23336
LacCer(d18:1/20:0)/LDL cholesterol (EDTA) (mg/dL)	64,15094	61,48148	31,95659
LacCer(d18:1/20:0)/apolipoprotein B (mg/dL)	64,15094	60,00000	37,03057
PS O-18:2/16:0-alkenyl/triglycerides (EDTA) (mg/dL)	63,63636	63,33333	99,88127
Cer(d18:1/20:0)/apolipoprotein B (mg/dL)	63,15789	60,12270	20,79615
Cer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL)	63,15789	61,96319	25,23403
Cer(d18:1/22:0)/LDL cholesterol (EDTA) (mg/dL)	63,15789	60,12270	11,30545
Cer(d18:1/24:1)/LDL cholesterol (EDTA) (mg/dL)	63,15789	60,12270	14,20759
PS O-16:0/18:2-alkenyl/triglycerides (EDTA) (mg/dL)	63,15789	63,29114	97,78843
PS O-16:1/18:2-alkyl/triglycerides (EDTA) (mg/dL)	63,15789	63,29114	97,78843
Total GlcCer/total cholesterol (EDTA) (mg/dL)	63,15789	60,73620	17,56924
Total LacCer/apolipoprotein A-I (mg/dL)	63,15789	61,34969	25,87122
Total LacCer/apolipoprotein B (mg/dL)	63,15789	61,96319	20,63257
LacCer(d18:1/24:1)/triglycerides (EDTA) (mg/dL)	62,50000	62,14286	60,79934
PS O-16:0/18:1-alkenyl (PS O-16:1/18:1-alkyl)/triglycerides (EDTA) (mg/dL)	62,50000	61,39241	65,88734
Cer(d18:1/20:0)/triglycerides (EDTA) (mg/dL)	61,40351	60,73620	34,46408
Cer(d18:1/22:0)/triglycerides (EDTA) (mg/dL)	61,40351	63,19018	28,23304
Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL)	61,40351	65,03067	27,12684
LacCer(d18:1/16:0)/triglycerides (EDTA) (mg/dL)	61,40351	64,41718	25,01312
LacCer(d18:1/18:0)/HDL cholesterol (EDTA) (mg/dL)	61,40351	60,37736	38,04132

LacCer(d18:1/18:0)/LDL cholesterol (EDTA) (mg/dL)	61,40351	64,15094	28,50180
LacCer(d18:1/18:0)/apolipoprotein B (mg/dL)	61,40351	61,00629	33,69302
LacCer(d18:1/18:0)/triglycerides (EDTA) (mg/dL)	61,40351	62,26415	52,60972
Total Cer/apolipoprotein A-I (mg/dL)	61,40351	63,41463	19,09944
Total GlcCer/apolipoprotein B (mg/dL)	61,40351	60,12270	14,92180
Total LacCer/triglycerides (EDTA) (mg/dL)	61,40351	62,57669	38,52220
LacCer(d18:1/22:0)/apolipoprotein B (mg/dL)	60,71429	65,00000	29,83861
Negative correlation			
CE 18:3/total-c/HDL-c	67,24138	62,89308	-27,28733
LPC 18:2/apolipoprotein B (mg/dL)	65,45455	60,12658	-16,19596
Total PC/apolipoprotein B (mg/dL)	64,91228	61,39241	-12,91145
Total PC/total cholesterol (EDTA) (mg/dL)	64,91228	60,75949	-10,60231
CE 16:1/HDL cholesterol (EDTA) (mg/dL)	63,79310	61,63522	-22,01197
CE 18:3/HDL cholesterol (EDTA) (mg/dL)	63,79310	62,26415	-24,04060
CE 18:3/LDL cholesterol (EDTA) (mg/dL)	63,79310	62,26415	-27,21759
LPC 18:2/LDL-c/HDL-c	63,63636	61,39241	-21,70580
Total PC/total-c/HDL-c	63,15789	60,12658	-16,13350
PC 16:0/20:3/HDL cholesterol (EDTA) (mg/dL)	62,50000	62,65823	-11,45558
PC 16:0/20:3/apolipoprotein B (mg/dL)	62,50000	60,12658	-15,11848
CE 16:1/apolipoprotein B (mg/dL)	62,06897	62,26415	-26,99397
CE 16:1/total cholesterol (EDTA) (mg/dL)	62,06897	60,37736	-24,28770
CE 18:3/LDL-c/HDL-c	62,06897	62,89308	-31,33346
CE 18:3/apolipoprotein A-I (mg/dL)	62,06897	60,37736	-23,09816
LPC 18:2/HDL cholesterol (EDTA) (mg/dL)	61,81818	60,75949	-16,07209
LPC 18:2/apoA1/apoB	61,81818	63,92405	-19,23316
PC 16:0/20:4/LDL cholesterol (EDTA) (mg/dL)	61,40351	60,12658	-15,98292
PC 16:0/20:4/apolipoprotein A-I (mg/dL)	61,40351	60,75949	-12,23661
PC 16:0/20:4/total cholesterol (EDTA) (mg/dL)	61,40351	61,39241	-13,37554
Total PC/LDL-c/HDL-c	61,40351	62,65823	-21,24583
PC 16:0/20:3/total-c/HDL-c	60,71429	61,39241	-19,07121
PC 18:0/20:4/apoA1/apoB	60,71429	62,02532	-13,36540
CE 18:3/apoA1/apoB	60,34483	60,37736	-27,55825
CE 18:3/apolipoprotein B (mg/dL)	60,34483	61,00629	-25,31907
CE 20:5/HDL cholesterol (EDTA) (mg/dL)	60,34483	60,37736	-23,45029
CE 20:5/LDL cholesterol (EDTA) (mg/dL)	60,34483	60,37736	-25,93288
LPC 18:2/LDL cholesterol (EDTA) (mg/dL)	60,00000	62,02532	-17,26480
LPC 18:2/total cholesterol (EDTA) (mg/dL)	60,00000	62,65823	-14,92954

9b) Table of significant lipid to clinical ratios in LURIC study sorted by top sensitivity and specificity from subjects not undergoing statin treatment.

Lipid name / Clinical measurement	Sensitivity	Specificity	Percentage change
Positive correlation			
Cer(d18:1/24:1)/apolipoprotein B (mg/dL)	82,60870	62,06897	18,05222
Cer(d18:1/24:1)/total cholesterol (EDTA) (mg/dL)	80,43478	61,20690	21,94547
LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL)	77,27273	67,00000	43,04967
Cer(d18:1/22:0)/LDL cholesterol (EDTA) (mg/dL)	73,91304	60,34483	11,30545
Total Cer/LDL cholesterol (EDTA) (mg/dL)	73,91304	62,39316	8,25598
Total Cer/total cholesterol (EDTA) (mg/dL)	73,91304	70,08547	15,12131
LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL)	72,72727	61,00000	39,32664
LacCer(d18:1/20:0)/apoA1/apoB	72,72727	60,00000	32,36387
Cer(d18:1/22:0)/total cholesterol (EDTA) (mg/dL)	71,73913	61,20690	17,20335
Cer(d18:1/24:1)/LDL cholesterol (EDTA) (mg/dL)	71,73913	61,20690	14,20759
Cer(d18:1/24:1)/total-c/HDL-c	71,73913	60,34483	13,34657
Total Cer/apolipoprotein A-I (mg/dL)	71,73913	61,53846	19,09944
Total Cer/apolipoprotein B (mg/dL)	71,73913	61,53846	12,34421
LacCer(d18:1/20:0)/LDL cholesterol (EDTA) (mg/dL)	70,45455	61,00000	31,95659
LacCer(d18:1/20:0)/LDL-c/HDL-c	70,45455	61,00000	23,54484
Cer(d18:1/20:0)/LDL cholesterol (EDTA) (mg/dL)	69,56522	60,34483	18,51094
Cer(d18:1/20:0)/apolipoprotein B (mg/dL)	69,56522	68,10345	20,79615
Cer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL)	69,56522	71,55172	25,23403
Cer(d18:1/20:0)/total-c/HDL-c	69,56522	60,34483	14,96816
Cer(d18:1/22:0)/apolipoprotein B (mg/dL)	69,56522	65,51724	14,20773
Cer(d18:1/24:0)/total cholesterol (EDTA) (mg/dL)	69,56522	60,68376	11,30123
Cer(d18:1/24:1)/LDL-c/HDL-c	69,56522	62,93103	5,34922
Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL)	69,56522	60,34483	27,12684
Cer(d18:1/24:1)/triglycerides (EDTA) (mg/dL)	69,56522	63,79310	32,27486
GlcCer(d18:1/24:1)/apolipoprotein B (mg/dL)	69,56522	61,20690	17,03707
Total DAG/apolipoprotein A-I (mg/dL)	68,88889	60,19417	15,46034
LacCer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL)	68,18182	61,00000	41,46919
PC O-34:1/apolipoprotein B (mg/dL)	68,18182	60,00000	22,73127
Cer(d18:1/16:0)/LDL cholesterol (EDTA) (mg/dL)	67,39130	62,06897	10,42412
Cer(d18:1/18:0)/total-c/HDL-c	67,39130	61,20690	21,75165
Cer(d18:1/18:0)/triglycerides (EDTA) (mg/dL)	67,39130	64,65517	40,06643
Cer(d18:1/24:0)/LDL cholesterol (EDTA) (mg/dL)	67,39130	62,39316	4,69599
Cer(d18:1/24:0)/apolipoprotein A-I (mg/dL)	67,39130	61,53846	14,67208
GlcCer(d18:1/20:0)/total cholesterol (EDTA) (mg/dL)	67,39130	60,34483	20,60005
Total GlcCer/apolipoprotein B (mg/dL)	67,39130	60,34483	14,92180
Total LacCer/total cholesterol (EDTA) (mg/dL)	67,39130	62,93103	23,69633
LacCer(d18:1/22:0)/apoA1/apoB	66,66667	61,76471	24,17423

LacCer(d18:1/22:0)/apolipoprotein A-I (mg/dL)	66,66667	60,78431	32,96039
LacCer(d18:1/20:0)/apolipoprotein B (mg/dL)	65,90909	61,00000	37,03057
LacCer(d18:1/20:0)/total-c/HDL-c	65,90909	62,00000	33,48550
Cer(d18:1/16:0)/triglycerides (EDTA) (mg/dL)	65,21739	62,06897	28,51323
Cer(d18:1/22:0)/apolipoprotein A-I (mg/dL)	65,21739	66,37931	21,04730
Cer(d18:1/24:0)/apolipoprotein B (mg/dL)	65,21739	62,39316	9,26738
GlcCer(d18:1/20:0)/apolipoprotein B (mg/dL)	65,21739	60,34483	17,00627
GlcCer(d18:1/26:1)/apolipoprotein A-I (mg/dL)	65,21739	61,60714	21,90520
LacCer(d18:1/16:0)/triglycerides (EDTA) (mg/dL)	65,21739	60,34483	25,01312
LacCer(d18:1/18:0)/apolipoprotein B (mg/dL)	65,21739	61,40351	33,69302
LacCer(d18:1/18:0)/total cholesterol (EDTA) (mg/dL)	65,21739	62,28070	38,87517
PS O-16:0/18:2-alkenyl/triglycerides (EDTA) (mg/dL)	65,21739	61,60714	97,78843
PS O-16:1/18:2-alkyl/triglycerides (EDTA) (mg/dL)	65,21739	61,60714	97,78843
Negative correlation			
CE 18:3/total-c/HDL-c	68,08511	62,28070	-27,28733
CE 18:3/LDL-c/HDL-c	63,82979	60,52632	-31,33346
CE 18:3/apoA1/apoB	61,70213	64,03509	-27,55825
CE 20:5/triglycerides (EDTA) (mg/dL)	61,70213	60,52632	-15,26342
PC O-38:6/apolipoprotein A-I (mg/dL)	60,86957	62,03704	-3,87776
Total LPC/apoA1/apoB	60,86957	60,71429	-14,81039
Total PC/apolipoprotein A-I (mg/dL)	60,86957	62,50000	-8,50761
PC 18:0/20:4/apoA1/apoB	60,00000	64,28571	-13,36540

The preferred lipid molecules of the invention were selected as follows: a) it was likely to be biologically meaningful, b) it preferably belongs to a family of lipids that are behaving similarly, c) it is expressed in meaningful & measurable concentrations, d) it has very significant p-value or good AUC-value (>0.65) and for most also the %-change is substantial (>20%), and e) it appeared significant in different tests. About 15 lipids or lipid ratios, each with either a positive or negative CVD correlation, were selected based on the highest p-values and best sensitivity and specificity subjectively ensuring the balanced representation of all lipid classes. Sensitivity and specificity thresholds were annotated in cases where the threshold of 60 and 70 were reached, respectively. The preferred embodiment lipids, lipid-lipid ratios and lipid-clinical ratios are presented in tables 10-13.

Table 10. The preferred embodiment lipids selected from significant lipids detected from LURIC sample set.

Lipid name	p-value	Percentage change	Sensitivity	Specificity
Positive correlation				
Cer(d18:1/20:0)	0,00004	28,00357		
LacCer(d18:1/20:0)	0,00010	32,91154	70,45455	60,00000
Cer(d18:1/24:1)	0,00039	23,37606	69,56522	60,34483
LacCer(d18:1/24:1)	0,00199	29,83279		
PS O-18:2/16:0-alkenyl	0,00432	33,81177		
PS O-16:1/18:2-alkyl	0,00590	32,17190		
Total Cer	0,00932	15,44601		
Total LacCer	0,01105	16,00541		
GlcCer(d18:1/24:1)		12,75066	60,86957	62,06897
LacCer(d18:1/22:0)	0,00046	22,75541		
Cer(d18:1/18:0)	0,00009	34,32550		
Negative correlation				
Total PC	0,00921	-12,44220		
PC 16:0/20:4	0,02256	-14,96966		
Cer(d18:0/24:0)	0,03376	-21,87004		
Total LPC	0,03443	-12,91576		
CE 14:0	0,01090	-21,01258		
CE 20:3	0,02157	-16,03606		
CE 17:1	0,02204	-15,93952		
PC 16:0/20:3		-18,78110	64,44444	60,71429
LPC 18:1		-14,45827	63,04348	60,71429
PC 18:0/20:3	0,00726	-17,20664		
PC 18:0/18:1	0,00765	-18,18002		
Cer(d18:0/22:0)	0,01158	-22,37263		

Table 11. Preferred embodiments from significant lipid to lipid ratios detected from LURIC sample set.

Lipid name / Lipid name	p-value	Percentage change	Sensitivity	Specificity
Positive correlation				
GlcCer(d18:1/26:1)/Total CE	0,000000	35,356592		
Cer(d18:1/24:1)/Total PC	0,000000	43,040800		
Cer(d18:1/24:1)/PC 16:0/20:4	0,000000	59,876132		
Cer(d18:1/20:0)/PC 16:0/20:4	0,000000	64,045788		
LacCer(d18:1/20:0)/PC 16:0/20:3	0,000008	56,972652	80,39216	65,11628
Total Cer/Total PC	0,000011	29,949121		

Total LacCer/Total PC	0,000012	37,815865		
LacCer(d18:1/20:0)/PC 18:1/18:2	0,000013	48,432788		
PS O-16:0/18:2-alkenyl/Total PS O		26,42621	97,82609	62,50000
Cer(d18:1/18:0)/PC 16:0/20:4		73,07370	80,00000	62,16216
LacCer(d18:1/20:0)/Total LPC		53,68111	78,84615	61,24031
LacCer(d18:1/20:0)/PC 16:0/20:4		82,44735	79,06977	68,42105
Negative correlation				
Cer(d18:0/24:0)/Cer(d18:1/24:1)	0,000003	-36,760563		
Cer(d18:0/22:0)/Cer(d18:1/24:1)	0,000011	-34,086320		
DAG 16:0/18:1/Total DAG		-17,30528	88,88889	61,16505
Cer(d18:0/24:0)/Cer(d18:1/22:0)		-32,40867	75,43860	66,25767
Cer(d18:0/24:0)/Total CE	0,0000000	-18,9531828		
Cer(d18:0/24:0)/Cer(d18:1/24:1)	0,000003	-36,760563		
Cer(d18:0/24:0)/Total Cer	0,0000049	-31,4531758		
Cer(d18:0/24:0)/Cer(d18:1/18:0)	0,0000052	-40,2960344		
Cer(d18:0/24:0)/PS O-16:0/18:2-alkenyl	0,0000059	-40,8329837		
Cer(d18:0/24:0)/LacCer(d18:1/24:0)	0,0000067	-37,0287234		
Cer(d18:0/22:0)/Cer(d18:1/18:0)	0,0000071	-36,5400374		
Cer(d18:0/24:0)/Cer(d18:1/22:0)	0,0000105	-32,4086711		
Cer(d18:0/22:0)/Cer(d18:1/20:0)	0,0000165	-31,5266149		
Cer(d18:0/22:0)/PS O-16:0/18:2-alkenyl	0,000045	-37,930990		
Cer(d18:0/22:0)/PS O-16:1/18:2-alkyl	0,000045	-37,930990		
GlcCer(d18:1/26:0)/LacCer(d18:1/20:0)		-26,83109	80,48780	64,77273
Total LPC/Total LacCer	0,0000469	-26,08820		
GlcCer(d18:1/26:0)/LacCer(d18:1/22:0)		-21,27116	78,04878	61,79775

Table 12. Preferred embodiments from significant lipid to clinical ratios from LURIC sample set.

Lipid name / Clinical measurement	p-value	Percentage change	Sensitivity	Specificity
Positive correlation				
Cer(d18:1/20:0)/apolipoprotein A-I (mg/dL)	0,00000	43,22923		
Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL)	0,00000	36,15491	69,56522	60,34483
LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL)	0,00001	47,52465	77,27273	67,00000
Total Cer/apolipoprotein A-I (mg/dL)	0,00016	25,36811		
Total LacCer/apolipoprotein A-I (mg/dL)	0,00031	28,05057	71,73913	61,53846
Cer(d18:1/18:0)/apolipoprotein A-I (mg/dL)	0,00001	49,43693		
LacCer(d18:1/22:0)/apolipoprotein A-I (mg/dL)	0,00001	35,92744		
LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL)		39,32664	72,72727	61,00000
Cer(d18:1/24:1)/apolipoprotein B (mg/dL)		18,05222	82,60870	62,06897
Negative correlation				

Cer(d18:0/24:0)/apolipoprotein B (mg/dL)	0,03428	-21,10483
Cer(d18:0/24:0)/total cholesterol (EDTA) (mg/dL)	0,04309	-19,71324
Cer(d18:0/24:0)/apolipoprotein B (mg/dL)	0,00181	-26,25271
PC 16:0/20:4/apolipoprotein B (mg/dL)	0,00576	-15,39247
Cer(d18:0/24:0)/apolipoprotein A-I (mg/dL)	0,01052	-22,39254

Table 13. Top candidates from each category, if available, are listed. The best candidates were selected based on following criteria: t-test p-value $\leq$ 0.05 and sensitivity $\geq$ 60% and specificity $\geq$ 60%.

Measurement name	**p-value**	**Percentage change**
Positive correlation		
Cer(d18:1/20:0)	0,00004	28,00357
LacCer(d18:1/20:0)	0,00010	32,91154
Cer(d18:1/24:1)	0,00039	23,37606
LacCer(d18:1/24:1)	0,00199	29,83279
LacCer(d18:1/22:0)	0,00046	22,75541
Cer(d18:1/18:0)	0,00009	34,32550
Cer(d18:1/24:1)/PC 16:0/20:4	0,000000	59,876132
LacCer(d18:1/20:0)/PC 16:0/20:3	0,000008	56,972652
PS O-16:0/18:2-alkenyl/Total PS O		26,42621
Cer(d18:1/18:0)/PC 16:0/20:4	0,000000	73,073704
Cer(d18:1/20:0)/apolipoprotein A-I (mg/dL)	0,00000	43,22923
Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL)	0,00000	36,15491
LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL)	0,00001	47,52465
Total LacCer/apolipoprotein A-I (mg/dL)	0,00031	28,05057
LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL)		39,32664
Cer(d18:1/18:0)/apolipoprotein A-I (mg/dL)	0,00001	49,43693
Negative correlation		
PC 16:0/20:4	0,02256	-14,96966
Cer(d18:0/24:0)	0,03376	-21,87004
GlcCer(d18:1/26:0)/LacCer(d18:1/20:0)		-26,83109
DAG 16:0/18:1/Total DAG		-17,30528
Cer(d18:0/24:0)/Total Cer		-31,45318
Total LPC/Total LacCer		-26,08820
GlcCer(d18:1/26:0)/LacCer(d18:1/22:0)		-21,27116
Cer(d18:0/24:0)/Cer(d18:1/24:1)	0,0000004	-36,1288066
Cer(d18:0/24:0)/Cer(d18:1/18:0)	0,0000052	-40,2960344
Cer(d18:0/24:0)/PS O-16:0/18:2-alkenyl	0,0000059	-40,8329837
Cer(d18:0/24:0)/Cer(d18:1/22:0)	0,0000105	-32,4086711
Cer(d18:0/22:0)/PS O-16:0/18:2-alkenyl	0,000045	-37,930990

Cer(d18:0/22:0)/PS O-16:1/18:2-alkyl	0,000045	-37,930990
Cer(d18:0/24:0)/LacCer(d18:1/24:0)	0,0000067	-37,0287234

Lipidomic analysis proved to be efficient in identifying novel plasma biomarkers for CVD complications.

Molecular lipid to molecular lipid ratio could be an important indicator of cellular lipid metabolism including e.g., enzyme activities in the lipid metabolism pathways. Thus, these ratios may provide more information as the absolute plasma concentrations of the molecular lipids alone. As the absolute molecular lipid plasma concentration differences in general between healthy individuals and atherosclerotic patients seem to be between 30-70%, it might be reasonable to calculate and use different ratios instead of absolute concentrations only. As lipoprotein particles (e.g. LDL, HDL, and VLDL) are serving as carriers for most of the lipids in the blood stream it is appropriate to relate molecular lipid concentrations to lipoprotein data. Thus, the molecular lipid to HDL-cholesterol, LDL-cholesterol, apolipoprotein A-I and apolipoprotein B ratios were calculated. In fact, a number of ratios between the concentrations of different molecular lipids outperformed absolute plasma concentrations as disease biomarkers in CVD patients.

As the detected lipids are carried in the lipoprotein particles (LDL, VLDL and HDL) it is obvious that the corresponding lipoprotein fraction concentrations will even improve the prediction potential of molecular lipids from the results of the present study in total serum/plasma samples.

The lipid lowering drug efficiency measurements have so far been based on LDL-C and HDL-C assays. As the inventors have herein observed more potential biomarkers that predict the development of high-risk CVD complications better than these classical analyses, future drug efficiency profiling should be based on new sensitive and specific

biomarkers that are more directly related to the risk of severe CVD-related complications rather than to LDL-C.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific embodiments described herein both in the Examples in the body of the entire patent description. Such equivalents are considered to be within the scope of this invention and are covered by the following claims.

CLAIMS

1. A method for determining whether a subject is at risk to develop one or more CVD complications such as acute myocardial infarction (AMI) and/or CVD death, comprising

   a. determining in a sample from said subject the concentration(s) of one or more lipid(s), wherein (an) increased or decreased concentration(s) in said sample, when compared to a control sample, is (are) indicative of said subject having an increased risk of developing one or more CVD complications, such as AMI or CVD death,
   wherein the one or more lipid(s) whose increase(s) in concentration is (are) compared to the control is (are) selected from:
   Cer(d18:1/20:0), LacCer(d18:1/20:0), Cer(d18:1/24:1), LacCer(d18:1/24:1), PS O-18:2/16:0-alkenyl, PS O-16:1/18:2-alkyl, Total Cer, Total LacCer, GlcCer(d18:1/24:1), LacCer(d18:1/22:0) and Cer(d18:1/18:0);
   and wherein the one or more lipid(s) whose decrease(s) in concentration is (are) compared to the control is (are) selected from:
   Total PC, PC 16:0/20:4, Cer(d18:0/24:0), Total LPC, CE 14:0, CE 20:3, CE 17:1, PC 16:0/20:3, LPC 18:1, PC 18:0/20:3, PC 18:0/18:1 and Cer(d18:0/22:0);
   or

   b. determining in a sample from said subject one or more lipid-lipid ratio(s), wherein (an) increased or decreased lipid-lipid ratio(s) in said sample, when compared to a control sample, is (are) indicative of said subject having an increased risk of developing one or more CVD complications, such as AMI or CVD death,
   wherein the one or more lipid-lipid ratio(s) whose increase(s) is (are) compared to the control is (are) selected from:

GlcCer(d18:1/26:1)/Total CE, Cer(d18:1/24:1)/Total PC, Cer(d18:1/24:1)/PC 16:0/20:4, Cer(d18:1/20:0)/PC 16:0/20:4, LacCer(d18:1/20:0)/PC 16:0/20:3, Total Cer/Total PC, Total LacCer/Total PC, LacCer(d18:1/20:0)/PC 18:1/18:2, PS O-16:0/18:2-alkenyl/Total PS O, , Cer(d18:1/18:0)/PC 16:0/20:4, LacCer(d18:1/20:0)/Total LPC and LacCer(d18:1/20:0)/PC 16:0/20:4; and wherein the one or more lipid-lipid ratio(s) whose decrease(s) is (are) compared to the control is (are) selected from: Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/22:0)/Cer(d18:1/24:1), DAG 16:0/18:1/Total DAG, Cer(d18:0/24:0)/Cer(d18:1/22:0), Cer(d18:0/24:0)/Total CE, Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/24:0)/Total Cer, Cer(d18:0/24:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/24:0)/LacCer(d18:1/24:0), Cer(d18:0/22:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/Cer(d18:1/22:0), Cer(d18:0/22:0)/Cer(d18:1/20:0), Cer(d18:0/22:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/22:0)/PS O-16:1/18:2-alkyl, GlcCer(d18:1/26:0)/LacCer(d18:1/20:0), Total LPC/Total LacCer and GlcCer(d18:1/26:0)/LacCer(d18:1/22:0);

or

c. determining in a sample from said subject one or more lipid-clinical concentration ratio(s), wherein (an) increased or decreased lipid-clinical concentration ratio(s) in said sample, when compared to a control sample, is (are) indicative of said subject having an increased risk of developing one or more CVD complications, such as AMI or CVD death,

wherein the one or more lipid-clinical concentration ratio(s) whose increase(s) is (are) compared to the control is (are) selected from: Cer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL),

LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Total Cer/apolipoprotein A-I (mg/dL), Total LacCer/apolipoprotein A-I (mg/dL), Cer(d18:1/18:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/22:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL) and Cer(d18:1/24:1)/apolipoprotein B (mg/dL);
and wherein the one or more lipid-clinical concentration ratio(s) whose decrease(s) is (are) compared to the control is (are) selected from: Cer(d18:0/24:0)/apolipoprotein B (mg/dL), Cer(d18:0/24:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:0/24:0)/apolipoprotein B (mg/dL), PC 16:0/20:4/apolipoprotein B (mg/dL) and Cer(d18:0/24:0)/apolipoprotein A-I (mg/dL).

2. A method for evaluating the effectiveness of a treatment of CVD and/or one or more of its complications, such as AMI or CVD death, in a subject, comprising

a. determining in a sample from said subject the concentration(s) of one or more lipid(s), wherein (an) increased or decreased concentration(s) in said sample, when compared to a control sample, is (are) indicative of effectiveness of said treatment,
wherein the one or more lipid(s) whose increase(s) in concentration is (are) compared to the control is (are) selected from: Cer(d18:1/20:0), LacCer(d18:1/20:0), Cer(d18:1/24:1), LacCer(d18:1/24:1), PS O-18:2/16:0-alkenyl, PS O-16:1/18:2-alkyl, Total Cer, Total LacCer, GlcCer(d18:1/24:1), LacCer(d18:1/22:0) and Cer(d18:1/18:0);
and wherein the one or more lipid(s) whose decrease(s) in concentration is (are) compared to the control is (are) selected from: Total PC, PC 16:0/20:4, Cer(d18:0/24:0), Total LPC, CE 14:0, CE 20:3, CE 17:1, PC 16:0/20:3, LPC 18:1, PC 18:0/20:3, PC 18:0/18:1 and Cer(d18:0/22:0);

or

b. determining in a sample from said subject one or more lipid-lipid ratio(s), wherein (an) increased or decreased lipid-lipid ratio(s) in said sample, when compared to a control sample, is (are) indicative of effectiveness of said treatment,
wherein the one or more lipid-lipid ratio(s) whose increase(s) is (are) compared to the control is (are) selected from:
GlcCer(d18:1/26:1)/Total CE, Cer(d18:1/24:1)/Total PC, Cer(d18:1/24:1)/PC 16:0/20:4, Cer(d18:1/20:0)/PC 16:0/20:4, LacCer(d18:1/20:0)/PC 16:0/20:3, Total Cer/Total PC, Total LacCer/Total PC, LacCer(d18:1/20:0)/PC 18:1/18:2, PS O-16:0/18:2-alkenyl/Total PS O, , Cer(d18:1/18:0)/PC 16:0/20:4, LacCer(d18:1/20:0)/Total LPC and LacCer(d18:1/20:0)/PC 16:0/20:4;
and wherein the one or more lipid-lipid ratio(s) whose decrease(s) is (are) compared to the control is (are) selected from:
Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/22:0)/Cer(d18:1/24:1), DAG 16:0/18:1/Total DAG, Cer(d18:0/24:0)/Cer(d18:1/22:0), Cer(d18:0/24:0)/Total CE, Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/24:0)/Total Cer, Cer(d18:0/24:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/24:0)/LacCer(d18:1/24:0), Cer(d18:0/22:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/Cer(d18:1/22:0) and Cer(d18:0/22:0)/Cer(d18:1/20:0), Cer(d18:0/22:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/22:0)/PS O-16:1/18:2-alkyl, GlcCer(d18:1/26:0)/LacCer(d18:1/20:0), Total LPC/Total LacCer and GlcCer(d18:1/26:0)/LacCer(d18:1/22:0);
or

c. determining in a sample from said subject one or more lipid-clinical concentration ratio(s), wherein (an) increased or decreased lipid-clinical

concentration ratio(s) in said sample, when compared to a control sample, is (are) indicative of effectiveness of said treatment,
wherein the one or more lipid-clinical concentration ratio(s) whose increase(s) is (are) compared to the control is (are) selected from:
Cer(d18:1/20:0)/apolipoprotein A-I (mg/dL),
Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL),
LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Total Cer/apolipoprotein A-I (mg/dL), Total LacCer/apolipoprotein A-I (mg/dL), Cer(d18:1/18:0)/apolipoprotein A-I (mg/dL),
LacCer(d18:1/22:0)/apolipoprotein A-I (mg/dL),
LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL) and
Cer(d18:1/24:1)/apolipoprotein B (mg/dL);
and wherein the one or more lipid-clinical concentration ratio(s) whose decrease(s) is (are) compared to the control is (are) selected from:
Cer(d18:0/24:0)/apolipoprotein B (mg/dL), Cer(d18:0/24:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:0/24:0)/apolipoprotein B (mg/dL), PC 16:0/20:4/apolipoprotein B (mg/dL) and
Cer(d18:0/24:0)/apolipoprotein A-I (mg/dL).

3. A method of choosing an appropriate treatment of CVD and/or one or more of its complications, such as AMI or CVD death, in a subject, comprising
   a. determining in a sample from said subject the concentration(s) of one or more lipid(s), wherein (an) increased or decreased concentration(s) in said sample, when compared to a control sample, is (are) indicative of said subject being in need of treatment or a change in, or supplementation of, an already administered treatment,
   wherein the one or more lipid(s) whose increase(s) in concentration is (are) compared to the control is (are) selected from:
   Cer(d18:1/20:0), LacCer(d18:1/20:0), Cer(d18:1/24:1),
   LacCer(d18:1/24:1), PS O-18:2/16:0-alkenyl, PS O-16:1/18:2-alkyl,

Total Cer, Total LacCer, GlcCer(d18:1/24:1), LacCer(d18:1/22:0) and Cer(d18:1/18:0);

and wherein the one or more lipid(s) whose decrease(s) in concentration is (are) compared to the control is (are) selected from:

Total PC, PC 16:0/20:4, Cer(d18:0/24:0), Total LPC, CE 14:0, CE 20:3, CE 17:1, PC 16:0/20:3, LPC 18:1, PC 18:0/20:3, PC 18:0/18:1 and Cer(d18:0/22:0);

or

b. determining in a sample from said subject one or more lipid-lipid ratio(s), wherein (an) increased or decreased lipid-lipid ratio(s) in said sample, when compared to a control sample, is (are) indicative of said subject being in need of treatment or a change in, or supplementation of, an already administered treatment,

wherein the one or more lipid-lipid ratio(s) whose increase(s) is (are) compared to the control is (are) selected from:

GlcCer(d18:1/26:1)/Total CE, Cer(d18:1/24:1)/Total PC, Cer(d18:1/24:1)/PC 16:0/20:4, Cer(d18:1/20:0)/PC 16:0/20:4, LacCer(d18:1/20:0)/PC 16:0/20:3, Total Cer/Total PC, Total LacCer/Total PC, LacCer(d18:1/20:0)/PC 18:1/18:2, PS O-16:0/18:2-alkenyl/Total PS O, Cer(d18:1/18:0)/PC 16:0/20:4, LacCer(d18:1/20:0)/Total LPC and LacCer(d18:1/20:0)/PC 16:0/20:4;

and wherein the one or more lipid-lipid ratio(s) whose decrease(s) is (are) compared to the control is (are) selected from:

Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/22:0)/Cer(d18:1/24:1), DAG 16:0/18:1/Total DAG, Cer(d18:0/24:0)/Cer(d18:1/22:0), Cer(d18:0/24:0)/Total CE, Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/24:0)/Total Cer, Cer(d18:0/24:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/24:0)/LacCer(d18:1/24:0), Cer(d18:0/22:0)/Cer(d18:1/18:0),

Cer(d18:0/24:0)/Cer(d18:1/22:0) and Cer(d18:0/22:0)/Cer(d18:1/20:0), Cer(d18:0/22:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/22:0)/PS O-16:1/18:2-alkyl, GlcCer(d18:1/26:0)/LacCer(d18:1/20:0), Total LPC/Total LacCer and GlcCer(d18:1/26:0)/LacCer(d18:1/22:0);
or

c. determining in a sample from said subject one or more lipid-clinical concentration ratio(s), wherein (an) increased or decreased lipid-clinical concentration ratio(s) in said sample, when compared to a control sample, is (are) indicative of said subject being in need of treatment or a change in, or supplementation of, an already administered treatment, wherein the one or more lipid-clinical concentration ratio(s) whose increase(s) is (are) compared to the control is (are) selected from: Cer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Total Cer/apolipoprotein A-I (mg/dL), Total LacCer/apolipoprotein A-I (mg/dL), Cer(d18:1/18:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/22:0)/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL) and Cer(d18:1/24:1)/apolipoprotein B (mg/dL);
and wherein the one or more lipid-clinical concentration ratio(s) whose decrease(s) is (are) compared to the control is (are) selected from: Cer(d18:0/24:0)/apolipoprotein B (mg/dL), Cer(d18:0/24:0)/total cholesterol (EDTA) (mg/dL), Cer(d18:0/24:0)/apolipoprotein B (mg/dL), PC 16:0/20:4/apolipoprotein B (mg/dL) and Cer(d18:0/24:0)/apolipoprotein A-I (mg/dL).

4. The method of any one of claims 1 to 3, wherein determining the lipid concentration(s), the lipid-lipid ratio(s) or the lipid-clinical concentration ratio(s), respectively, is done using an assay.

5. The method of any one of claims 2 to 4, wherein said treatment is a lipid modifying treatment.

6. The method of any one of the preceding claims, wherein

a. the lipid whose increase in concentration is compared to the control is selected from:
Cer(d18:1/20:0), LacCer(d18:1/20:0), Cer(d18:1/24:1), LacCer(d18:1/24:1), LacCer(d18:1/22:0) and Cer(d18:1/18:0);

b. the lipid whose decrease in concentration is compared to the control is selected from:
PC 16:0/20:4 and Cer(d18:0/24:0);

c. the lipid-lipid ratio whose increase is compared to the control is selected from:
Cer(d18:1/24:1)/PC 16:0/20:4, LacCer(d18:1/20:0)/PC 16:0/20:3, PS O-16:0/18:2-alkenyl/Total PS O and Cer(d18:1/18:0)/PC 16:0/20:4;

d. the lipid-lipid ratio whose decrease is compared to the control is selected from:
GlcCer(d18:1/26:0)/LacCer(d18:1/20:0), DAG 16:0/18:1/Total DAG, Cer(d18:0/24:0)/Total Cer, Total LPC/Total LacCer, GlcCer(d18:1/26:0)/LacCer(d18:1/22:0), Cer(d18:0/24:0)/Cer(d18:1/24:1), Cer(d18:0/24:0)/Cer(d18:1/18:0), Cer(d18:0/24:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/24:0)/Cer(d18:1/22:0), Cer(d18:0/22:0)/PS O-16:0/18:2-alkenyl, Cer(d18:0/22:0)/PS O-16:1/18:2-alkyl and Cer(d18:0/24:0)/LacCer(d18:1/24:0);

e. the lipid-clinical concentration ratio whose increase is compared to the control is selected from:
Cer(d18:1/20:0)/apolipoprotein A-I (mg/dL),
Cer(d18:1/24:1)/apolipoprotein A-I (mg/dL),
LacCer(d18:1/20:0)/apolipoprotein A-I (mg/dL), Total LacCer/apolipoprotein A-I (mg/dL), LacCer(d18:1/20:0)/HDL cholesterol (EDTA) (mg/dL) and Cer(d18:1/18:0)/apolipoprotein A-I (mg/dL).

7. The method of any one of the preceding claims, comprising determining at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, or at least 8 lipid concentrations, lipid-lipid ratios or lipid-clinical concentration ratios, respectively, or combinations thereof.

8. The method of any one of the preceding claims, wherein
   a. said CVD is characterized by coronary artery disease, peripheral artery disease, a stroke and/or CVD death; and/or
   b. said CVD is atherosclerosis-induced; and/or
   c. said subject has atherosclerosis; or
   d. said subject does not have atherosclerosis.

9. The method of any one of the preceding claims, wherein
   a. the method further comprises determining the serum level of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), Apolipoprotein B (ApoB) and/or Apolipoprotein C-III (ApoC-III) in said sample; and/or
   b. the subject does not have elevated serum levels of one or more of total cholesterol, low-density lipoprotein cholesterol (LDL-C), Apolipoprotein C-III (ApoC-III) or Apolipoprotein B (ApoB), or a decreased serum level of HDL-cholesterol (HDL-C).

10. The method of any one of the preceding claims, wherein said subject

a. is being or has been treated with one or more statins and/or any other HMG-CoA reductase inhibitor; or

b. has not yet undergone statin therapy or therapy with any other HMG-CoA reductase inhibitor.

11. The method of any one of the preceding claims, wherein the lipid concentration(s), the lipid-lipid ratio(s) or the lipid-clinical concentration ratio(s) is (are) determined by using mass spectrometry, nuclear magnetic resonance spectroscopy, fluorescence spectroscopy or dual polarisation interferometry, a high performance separation method such as HPLC or UPLC, an immunoassay such as an ELISA and/or with a binding moiety capable of specifically binding the analyte.

12. The method of any one of the preceding claims, wherein the method is for determining a risk of said patient to develop CVD complications including death and myocardial infarction (MI).

13. A drug for use for preventing or treating CVD complications, such as AMI or CVD death, in a subject in need thereof, wherein the drug is capable of modulating one or more of the lipid concentration(s), lipid-lipid ratio(s) or lipid-clinical concentration ratio(s) according to any one of claims 1 to 3 or 6(a),(b),(c),(d), or (e).

14. The drug according to claim 13, wherein the drug is to be administered at such a dose that said one or more lipid concentration(s), lipid-lipid ratio(s) or lipid-clinical concentration ratio(s) does (do) not significantly change when compared to a control sample.

15. A method for treating or preventing CVD complications, such as AMI or CVD death, in a subject in need thereof comprising administering a therapeutically effective dose of a drug capable of modulating one or more of the lipid concentration(s), lipid-lipid ratio(s) or lipid-clinical concentration ratio(s) according to any one of claims 1 to 3 or 6(a),(b),(c),(d), or (e), wherein the dose is such that said one or more lipid concentration(s), lipid-lipid ratio(s) or lipid-clinical concentration ratio(s) in a sample from said subject does (do) not significantly change when compared to a control sample.

16. The drug of claim 13 or 14 or the method of claim 15, wherein the drug is a statin or any other HMG-CoA reductase inhibitor; niacin (nicotinic acid); a cholesterol absorption inhibitor, such as ezetimibe or SCH-48461; a cholesteryl ester transfer protein (CETP) inhibitor, such as torcetrapib, anacetrapib or JTT-705; a bile acids sequestrant such as colesevelam, cholestyramine and colestipol; a fibrate, such as fenofibrate, gemfibrozil, clofibrate, and bezafibrate; or a phytosterol.

17. The method of claim 10, or the drug or the method of claim 16, wherein the statin is selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, fluvastatin XL, lovastatin, pitavastatin, pravastatin, rosuvastatin and/or simvastatin.

18. A lipid as defined in any one of claims 1 to 3 or for use in preventing or treating a subject at risk to develop CVD complications, such as AMI or CVD death, wherein the said lipid is to be taken as a dietary supplement or a medicament.

19. A modulator for use for modulating a lipid concentration, lipid-lipid ratio or lipid-clinical concentration ratio according to any one of claims 1-3 or 6(a),(b),(c),(d), or (e) in a subject at risk to develop CVD complications, such as AMI or CVD death.

20. The modulator of claim 19, wherein the modulator is a small molecule, an antisense RNA, a small interfering RNA (siRNA), or a natural or modified lipid.

21. An antibody against any one of the lipids defined in claims 1 to 3 or 6 for use in
    a. predicting one or more CVD complications, such as AMI or CVD death, in a subject; or
    b. preventing or treating one or more CVD complications, such as AMI or CVD death, in a subject.

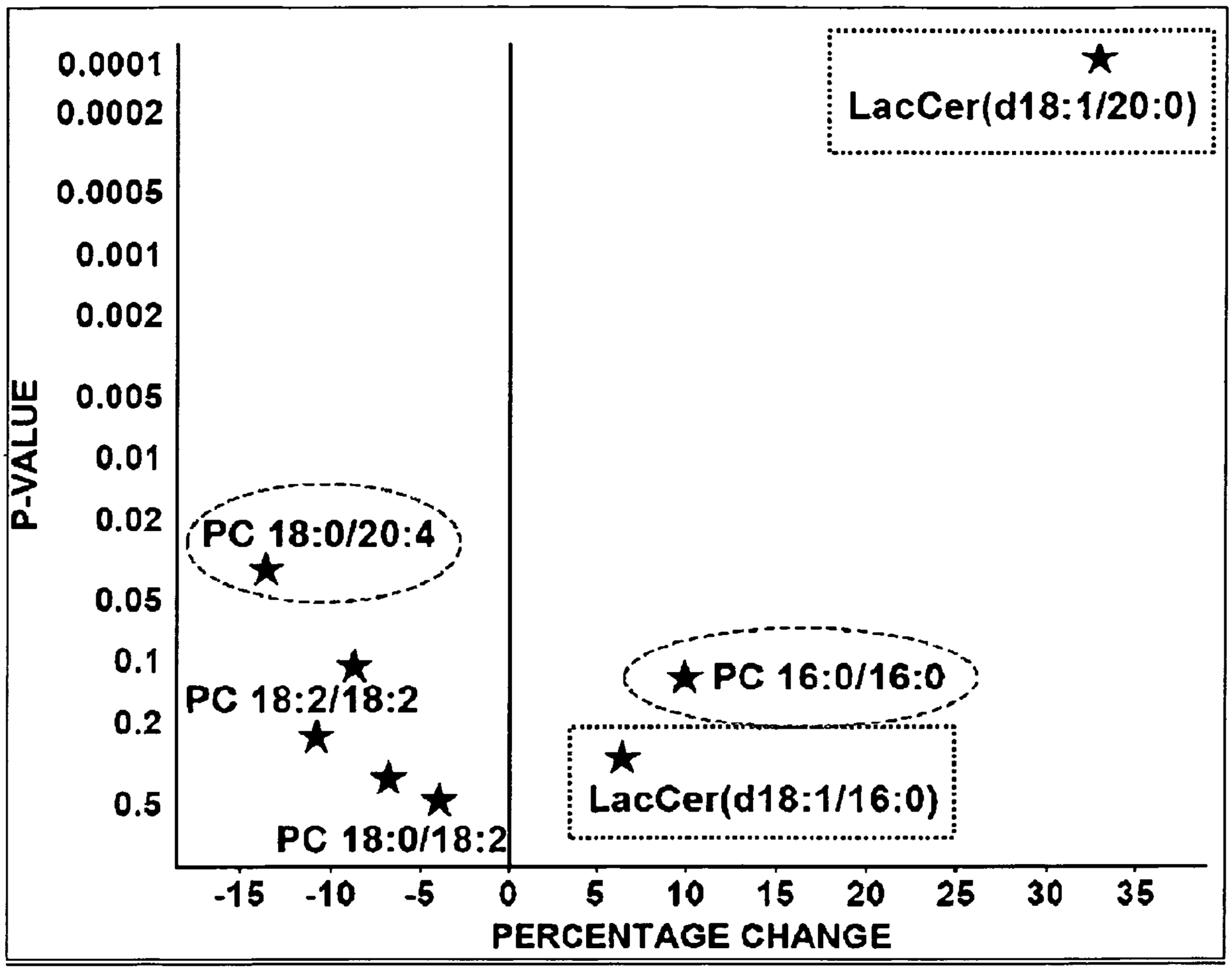
22. The method, drug, lipid or antibody of any one of the preceding claims, wherein the subject is at risk to develop or has suffered from one or more CVD complications such as acute myocardial infarction and/or cardiovascular death.

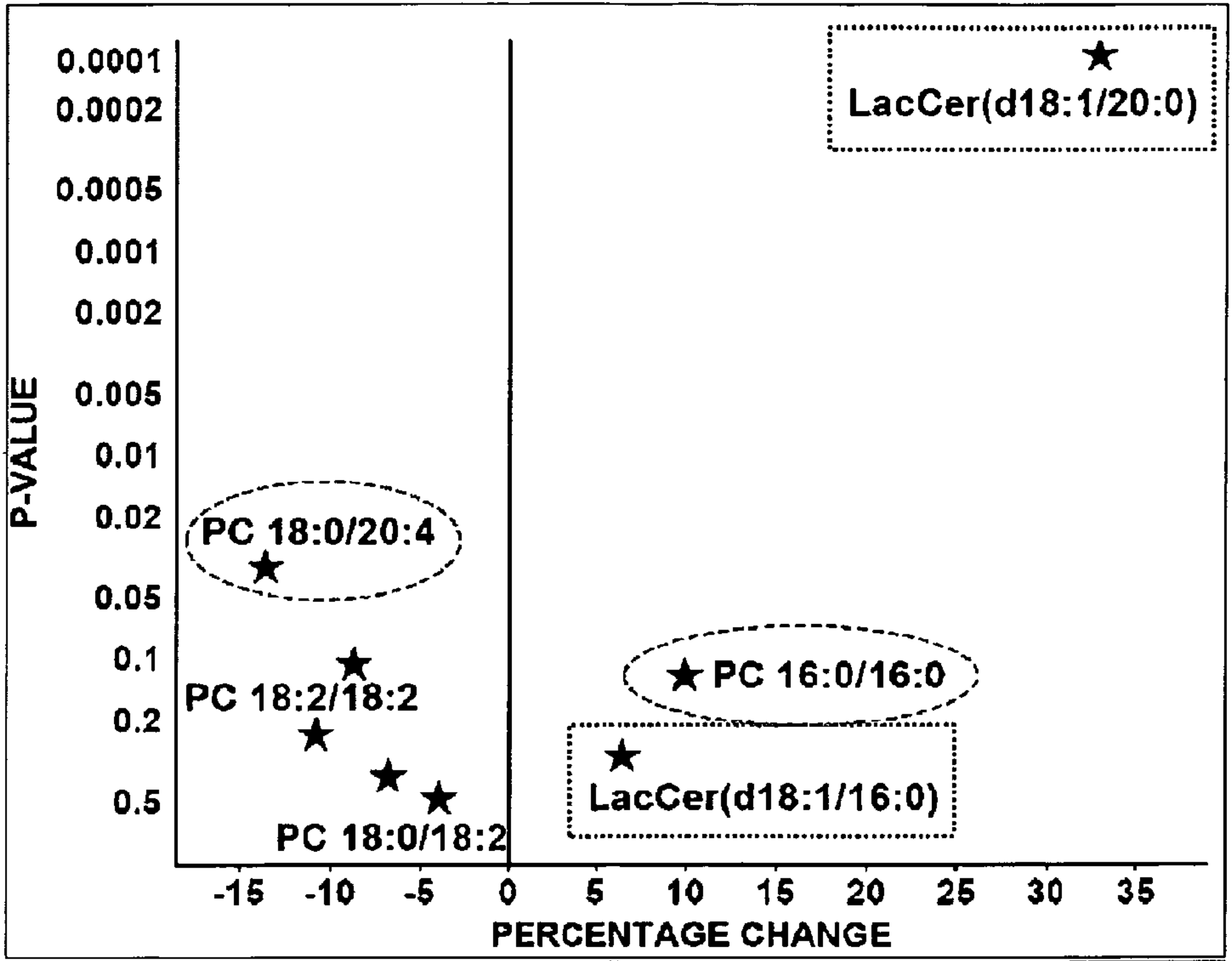
23. A kit for predicting CVD complications or for performing the methods or uses according to any one of the preceding claims, wherein the kit comprises a lipid standard chosen from the lipids defined in claims 1-3 and 6(a),(b),(c),(d), or (e), one or more control lipidomic markers, and/ or an antibody against any one of the lipids defined in claims 1-3 and 6(a),(b),(c),(d), or (e), and optionally reagents for performing said methods or uses.

24. Use of a kit as defined in claim 23 for predicting or detecting atherosclerosis or CVD, wherein the lipid concentration(s), lipid ratio(s) or lipid-clinical concentration ratio(s) thereof in a sample from a subject is (are) optionally determined by using mass spectrometry.

25. The method of any one of claims 1-12, 15-17 or the drug of claims 13, 14, 16, or 17, wherein the control sample is from (a) CAD patient(s) or a group of CAD patients that has/have remained free of any major CVD complications, wherein the sample is preferably a blood sample, or a serum sample.

26. The method of any one of claims 1-12, 15-17 or 24, or the drug of claims 13, 14, 16, 17 or 24, wherein the one or more CVD complication(s) are severe CVD complications, particularly CVD death.


P-VALUE
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PERCENTAGE CHANGE


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PERCENTAGE CHANGE