(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 January 2014 (03.01.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/004993 A2

(51) International Patent Classification:
A61K 31/232 (2006.01)

(21) International Application Number:
PCT/US2013/048516

(22) International Filing Date:
28 June 2013 (28.06.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/666,433 29 June 2012 (29.06.2012) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2014/004993 A2

(54) Title: METHODS OF REDUCING LDL-P

(57) Abstract: In various embodiments, the present invention provides methods of treating and/or preventing cardiovascular-related disease and, in particular, a method of reducing LDL-P comprising administering to a subject in need thereof a pharmaceutical composition comprising eicosapentaenoic acid or a derivative thereof.

TITLE

METHODS OF REDUCING LDL-P

PRIORITY CLAIM

[0001] This application claims priority to U.S. provisional patent application serial no. 61/666,433, filed June 29, 2012, the entire contents of which are incorporated herein by reference.

BACKGROUND

[0002] Cardiovascular disease is one of the leading causes of death in the United States and most European countries. It is estimated that over 70 million people in the United States alone suffer from a cardiovascular disease or disorder including but not limited to high blood pressure, coronary heart disease, dyslipidemia, congestive heart failure and stroke. Low density lipoprotein particles (LDL particles) carry cholesterol through the bloodstream; higher concentrations of LDL particles generally correlate with increased arterial plaque levels, and thus with cardiovascular events such as heart attacks and stroke. A need exists for improved treatments for reducing LDL particle concentration in subjects having or at risk of developing cardiovascular disease.

SUMMARY

[0003] In various embodiments, the present invention provides methods of treating and/or preventing cardiovascular-related diseases and, in particular, a method of reducing low density lipoprotein particle concentration (also referred to as LDL particle concentration, LDL particle number, or LDL-P) comprising determining a baseline LDL-P level associated with the subject and thereafter administering to a subject in need thereof eicosapentaenoic acid or a derivative thereof.

[0004] In one embodiment, a pharmaceutical composition useful in accordance with the invention comprises, consists of or consists essentially of at least 95% by weight ethyl eicosapentaenoate (EPA-E), about 0.2% to about 0.5% by weight ethyl octadecatetraenoate (ODTA-E), about 0.05% to about 0.25% by weight ethyl

nonaecapentaenoate (NDPA-E), about 0.2% to about 0.45% by weight ethyl arachidonate (AA-E), about 0.3% to about 0.5% by weight ethyl eicosatetraenoate (ETA-E), and about 0.05% to about 0.32% ethyl heneicosapentaenoate (HPA-E). In another embodiment, the composition is present in a capsule shell. In another embodiment, the composition contains substantially no amount or no amount of docosahexaenoic acid (DHA) or derivative thereof such as ethyl-DHA (DHA-E).

[0005] In another embodiment, the invention provides a method of preventing an increase in LDL-P comprising administering a composition as described herein to a subject in need thereof one to about four times per day.

[0006] These and other embodiments of the present invention will be disclosed in further detail herein below.

DETAILED DESCRIPTION

[0007] While the present invention is capable of being embodied in various forms, the description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the invention, and is not intended to limit the invention to the specific embodiments illustrated. Headings are provided for convenience only and are not to be construed to limit the invention in any manner. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

[0008] The use of numerical values in the various quantitative values specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about." Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values recited as well as any ranges that can be formed by such values. Also disclosed herein are any and all ratios (and ranges of any such ratios) that can be formed by dividing a disclosed numeric value into any other disclosed numeric value. Accordingly, the skilled person will appreciate that many such ratios, ranges, and ranges of ratios can be unambiguously derived from the numerical values presented herein and in all instances

such ratios, ranges, and ranges of ratios represent various embodiments of the present invention.

[0009] In one embodiment, the invention provides a method for treatment and/or prevention of a cardiovascular-related disease. The term "cardiovascular-related disease" herein refers to any disease or disorder of the heart or blood vessels (*i.e.* arteries and veins) or any symptom thereof. Non-limiting examples of cardiovascular-related disease and disorders include hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia, coronary heart disease, vascular disease, stroke, atherosclerosis, arrhythmia, hypertension, myocardial infarction, and other cardiovascular events.

[0010] The term "treatment" in relation a given disease or disorder, includes, but is not limited to, inhibiting the disease or disorder, for example, arresting the development of the disease or disorder; relieving the disease or disorder, for example, causing regression of the disease or disorder; or relieving a condition caused by or resulting from the disease or disorder, for example, relieving, preventing or treating symptoms of the disease or disorder. The term "prevention" in relation to a given disease or disorder means: preventing the onset of disease development if none had occurred, preventing the disease or disorder from occurring in a subject that may be predisposed to the disorder or disease but has not yet been diagnosed as having the disorder or disease, and/or preventing further disease/disorder development if already present.

[0011] In one embodiment, the invention provides a method for reducing LDL-P in a subject. The term "reducing LDL-P" as used herein refers to (a) a decrease in LDL-P level in a subject compared to a baseline LDL-P level in the subject, (b) a decrease in LDL-P level in a subject compared to an LDL-P level associated with a subject group (*e.g.,* mean or median level), and/or (c) preventing an increase in an LDL-P level in a subject when one may be expected based on an increase in an LDL-P level associated with a subject group (*e.g.,* mean or median level). In one embodiment, the invention provides a method of reducing LDL-P in a subject in need thereof comprising determining a baseline LDL-P level associated with the subject and thereafter administering to the subject about 1 g to about 4 g of ethyl eicosapentaenoate per day. In some embodiments, the ethyl eicosapentaenoate

comprises at least about 80%, at least about 90%, at least about 95%, or at least about 96%, by weight, of all fatty acids administered to the subject. In some embodiments docosahexaenoic acid and its derivatives comprises no more than about 10%, no more than about 5%, no more than about 4%, no more than about 3%, no more than about 2%, or no more than about 1%, by weight, of all fatty acids administered to the subject. In some embodiments, the subject is administered substantially no docosahexaenoic acid or derivative thereof, or no docosahexaenoic acid or derivative thereof. In some embodiments, the ethyl eicosapentaenoate is administered to the subject 1 to 4 times per day.

[0012] In some embodiments, the subject is on concomitant lipid-altering therapy. In some embodiments, the subject is not on concomitant lipid-altering therapy. In another embodiment, the ethyl eicosapentaenoate is administered in a composition comprising no more than about 10%, no more than about 5%, no more than about 4%, no more than about 3%, no more than about 2%, or no more than about 1%, by weight, of docoseahexaenoic acid or its esters. In some embodiments, the composition comprises the composition contains not more than 4%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; and/or the composition contains about 0.1% to about 0.6% of at least one fatty acid other than eicosapentaenoic acid ethyl ester and docosahexaenoic acid (or derivative thereof).

[0013] In one embodiment, the present invention provides a method of blood lipid therapy comprising administering to a subject or subject group in need thereof a pharmaceutical composition as described herein. In another embodiment, the subject or subject group has an elevated LDL-P level. In some embodiments, the elevated LDL-P level is at least about 1,000 nmol/L, at least about 1,300 nmol/L, at least about 1,600 nmol/L, or at least about 2,000 nmol/L. In some embodiments, the elevated LDL-P level is expressed as a Multi-Ethnic Study of Atherosclerosis ("MESA") percentile associated with the subject or subject group. In some embodiments, the subject or subject group is in the 20th to 50th MESA percentile, the 50th to 80th MESA percentile, the 80th to 95th MESA percentile, or in the >95th MESA percentile.

[0014] In another embodiment, the subject or subject group being treated has a baseline LDL-P level (or median baseline LDL-P level in the case of a subject group),

fed or fasting, of at least about 1,000 nmol/L, at least about 1,100 nmol/L, at least about 1,200 nmol/L, at least about 1,300 nmol/L, at least about 1,400 nmol/L, at least about 1,500 nmol/L, at least about 1,600 nmol/L, at least about 1,700 nmol/L, at least about 1,800 nmol/L, at least about 1,900 nmol/L, or at least about 2,000 nmol/L.

[0015] In some embodiments, the elevated LDL-P level is expressed as a Framingham Offspring Study ("FOS") percentile associated with the subject or subject group. In some embodiments, the subject or subject group is in the 20th to 30th FOS percentile, the 30th to 40th FOS percentile, the 40th to 50th FOS percentile, the 50th to 60th FOS percentile, the 60th to 70th FOS percentile, the 70th to 80th FOS percentile, the 80th to 90th FOS percentile, the 90th to 95th FOS percentile, or the >95th FOS percentile. In some embodiments, the subject or subject group being treated has a baseline LDL-P level (or median baseline LDL-P level in the case of a subject group), fed or fasting, of at least about 1,100 nmol/L, at least about 1,220 nmol/L, at least about 1,330 nmol/L, at least about 1,440 nmol/L, at least about 1,540 nmol/L, at least about 1,670 nmol/L, at least about 1,820 nmol/L, at least about 2,020 nmol/L, or at least about 2,210 nmol/L.

[0016] LDL-P levels in a subject or a subject group may be determined by any suitable method known to those skilled in the art. In some embodiments, LDL-P level is determined directly by, for example, NMR. In some embodiments, an LDL-P level is determined indirectly by, for example, estimating an LDL-P level by determining one or more of: (a) a total cholesterol to HDL-C ratio of at least about 3; and/or (b) a LDL-C level of at least about 70 mg/dL, a non-HDL-C level of at least about 100 mg/dL and a triglyceride level of at least about 150 mg/dL.

[0017] In one embodiment, the subject or subject group being treated in accordance with methods of the invention has previously been treated with Lovaza® and has experienced an increase in, or no decrease in, LDL-P levels. In one such embodiment, Lovaza® therapy is discontinued and replaced by a method of the present invention.

[0018] In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a fasting baseline absolute plasma level of free EPA (or mean thereof in the case of a subject group) not greater than

about 0.70 nmol/ml, not greater than about 0.65 nmol/ml, not greater than about 0.60 nmol/ml, not greater than about 0.55 nmol/ml, not greater than about 0.50 nmol/ml, not greater than about 0.45 nmol/ml, or not greater than about 0.40 nmol/ml. In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a baseline fasting plasma level (or mean thereof) of free EPA, expressed as a percentage of total free fatty acid, of not more than about 3%, not more than about 2.5%, not more than about 2%, not more than about 1.5%, not more than about 1%, not more than about 0.75%, not more than about 0.5%, not more than about 0.25%, not more than about 0.2% or not more than about 0.15%. In one such embodiment, free plasma EPA and/or total fatty acid levels are determined prior to initiating therapy.

[0019] In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a fasting baseline absolute plasma level of total fatty acid (or mean thereof) not greater than about 250 nmol/ml, not greater than about 200 nmol/ml, not greater than about 150 nmol/ml, not greater than about 100 nmol/ml, or not greater than about 50 nmol/ml.

[0020] In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a fasting baseline plasma, serum or red blood cell membrane EPA level not greater than about 70 μg/ml, not greater than about 60 μg/ml, not greater than about 50 μg/ml, not greater than about 40 μg/ml, not greater than about 30 μg/ml, or not greater than about 25 μg/ml.

[0021] In another embodiment, methods of the present invention comprise a step of measuring the subject's (or subject group's mean) baseline lipid profile prior to initiating therapy. In another embodiment, methods of the invention comprise the step of identifying a subject or subject group having one or more of the following: baseline non-HDL-C value of about 200 mg/dL to about 400 mg/dL, for example at least about 210 mg/dL, at least about 220 mg/dL, at least about 230 mg/dL, at least about 240 mg/dL, at least about 250 mg/dL, at least about 260 mg/dL, at least about 270 mg/dL, at least about 280 mg/dL, at least about 290 mg/dL, or at least about 300 mg/dL; baseline total cholesterol value of about 250 mg/dL to about 400 mg/dL, for example at least about 260 mg/dL, at least about 270 mg/dL, at least about 280 mg/dL or at

least about 290 mg/dL; baseline VLDL-C value of about 140 mg/dL to about 200 mg/dL, for example at least about 150 mg/dL, at least about 160 mg/dL, at least about 170 mg/dL, at least about 180 mg/dL or at least about 190 mg/dL; baseline HDL-C value of about 10 to about 60 mg/dL, for example not more than about 40 mg/ dl, not more than about 35 mg/dL, not more than about 30 mg/dL, not more than about 25 mg/dL, not more than about 20 mg/dL, or not more than about 15 mg/dL; baseline LDL-C value of about 50 to about 300 mg/dL, for example not less than about 100 mg/dL, not less than about 90 mg/dL, not less than about 80 mg/dL, not less than about 70 mg/dL, not less than about 60 mg/dL or not less than about 50 mg/dL; and/or baseline LDL-P value of at least about 1,000 nmol/L, at least about 1,300 nmol/L, at least about 1,600 nmol/L, or at least about 2,000 nmol/L.

[0022] In a related embodiment, upon treatment in accordance with the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits one or more of the following outcomes:

[0023] (a) reduced triglyceride levels compared to baseline;

[0024] (b) reduced Apo B levels compared to baseline;

[0025] (c) increased HDL-C levels compared to baseline;

[0026] (d) no increase in LDL-C levels compared to baseline;

[0027] (e) a reduction in LDL-C levels compared to baseline;

[0028] (f) a reduction in non-HDL-C levels compared to baseline;

[0029] (g) a reduction in VLDL levels compared to baseline;

[0030] (h) an increase in apo A-I levels compared to baseline;

[0031] (i) an increase in apo A-I/apo B ratio compared to baseline;

[0032] (j) a reduction in lipoprotein A levels compared to baseline;

[0033] (k) a reduction in LDL particle number (LDL-P) compared to baseline;

[0034] (l) an increase in LDL size compared to baseline;

[0035] (m) a reduction in remnant-like particle cholesterol compared to baseline;

[0036] (n) a reduction in oxidized LDL compared to baseline;

[0037] (o) no change or a reduction in fasting plasma glucose (FPG) compared to baseline;

[0038] (p) a reduction in hemoglobin A_{1c} (HbA_{1c}) compared to baseline;

[0039] (q) a reduction in homeostasis model insulin resistance compared to baseline;

[0040] (r) a reduction in lipoprotein associated phospholipase A2 compared to baseline;

[0041] (s) a reduction in intracellular adhesion molecule-1 compared to baseline;

[0042] (t) a reduction in interleukin-6 compared to baseline;

[0043] (u) a reduction in plasminogen activator inhibitor-1 compared to baseline;

[0044] (v) a reduction in high sensitivity C-reactive protein (hsCRP) compared to baseline;

[0045] (w) an increase in serum or plasma EPA compared to baseline;

[0046] (x) an increase in red blood cell (RBC) membrane EPA compared to baseline; and/or

[0047] (y) a reduction or increase in one or more of serum phospholipid and/or red blood cell content of docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), arachidonic acid (AA), palmitic acid (PA), staeridonic acid (SA) or oleic acid (OA) compared to baseline.

[0048] In one embodiment, upon administering a composition of the invention to a subject, the subject exhibits a decrease in triglyceride levels, an increase in the concentrations of EPA and DPA (n-3) in red blood cells, and an increase of the ratio of EPA:arachidonic acid in red blood cells. In a related embodiment the subject exhibits substantially no increase or no increase in RBC DHA.

[0049] In one embodiment, methods of the present invention comprise measuring baseline levels of one or more markers set forth in (a) – (y) above prior to dosing the subject or subject group. In another embodiment, the methods comprise administering a composition as disclosed herein to the subject after baseline levels of one or more markers set forth in (a) – (y) are determined, and subsequently taking an additional measurement of said one or more markers.

[0050] In another embodiment, upon treatment with a composition of the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits any 2 or more of, any 3 or more of, any 4 or more of, any 5 or more of, any 6 or more of, any 7 or more of, any 8 or more of, any 9 or more of, any 10 or more of, any 11 or more of, any 12 or more of, any 13 or more of, any 14 or more of, any 15 or more of, any 16 or more of, any 17 or more of, any 18 or more of, any 19 or more of, any 20 or more of, any 21 or more of, any 22 or more of, any 23 or more of, any 24 or more of, or all 25 of outcomes (a) – (y) described immediately above.

[0051] In another embodiment, upon treatment with a composition of the present invention, the subject or subject group exhibits one or more of the following outcomes:

[0052] (a) a reduction in triglyceride level of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

[0053] (b) a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in non-HDL-C levels or a reduction in non-HDL-C levels of at least about 1%, at least about 3%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

[0054] (c) substantially no change in HDL-C levels, no change in HDL-C levels, or an increase in HDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

[0055] (d) a less than 60% increase, a less than 50% increase, a less than 40% increase, a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in LDL-C levels or a reduction in LDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

[0056] (e) a decrease in Apo B levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

[0057] (f) a reduction in VLDL levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

[0058] (g) an increase in apo A-I levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least

about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

[0059] (h) an increase in apo A-I/apo B ratio of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

[0060] (i) a reduction in lipoprotein (a) levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

[0061] (j) a reduction in mean LDL particle number (LDL-P) of at least about 5%, at least about 10%, at least about 15%, at least about 19%, at least about 20%, at least about 25%, at least about 30%, at least about 31%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

[0062] (k) an increase in mean LDL particle size of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

[0063] (l) a reduction in remnant-like particle cholesterol of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

[0064] (m) a reduction in oxidized LDL of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

[0065] (n) substantially no change, no significant change, or a reduction (e.g. in the case of a diabetic subject) in fasting plasma glucose (FPG) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

[0066] (o) substantially no change, no significant change or a reduction in hemoglobin A_{1c} (HbA_{1c}) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50% (actual % change or median % change) compared to baseline;

[0067] (p) a reduction in homeostasis model index insulin resistance of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

[0068] (q) a reduction in lipoprotein associated phospholipase A2 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

[0069] (r) a reduction in intracellular adhesion molecule-1 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

[0070] (s) a reduction in interleukin-6 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

[0071] (t) a reduction in plasminogen activator inhibitor-1 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

[0072] (u) a reduction in high sensitivity C-reactive protein (hsCRP) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

[0073] (v) an increase in serum, plasma and/or RBC EPA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 100%, at least about 200% or at least about 400% (actual % change or median % change) compared to baseline;

[0074] (w) an increase in serum phospholipid and/or red blood cell membrane EPA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, r at least about 50%, at least about 100%, at least about 200%, or at least about 400% (actual % change or median % change) compared to baseline;

[0075] (x) a reduction or increase in one or more of serum phospholipid and/or red blood cell DHA, DPA, AA, PA and/or OA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) compared to baseline; and/or

[0076] (y) a reduction in total cholesterol of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about

55% or at least about 75% (actual % change or median % change) compared to baseline.

[0077] In one embodiment, methods of the present invention comprise measuring baseline levels of one or more markers set forth in (a) – (y) prior to dosing the subject or subject group. In another embodiment, the methods comprise administering a composition as disclosed herein to the subject after baseline levels of one or more markers set forth in (a) – (y) are determined, and subsequently taking a second measurement of the one or more markers as measured at baseline for comparison thereto.

[0078] In another embodiment, upon treatment with a composition of the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits any 2 or more of, any 3 or more of, any 4 or more of, any 5 or more of, any 6 or more of, any 7 or more of, any 8 or more of, any 9 or more of, any 10 or more of, any 11 or more of, any 12 or more of, any 13 or more of, any 14 or more of, any 15 or more of, any 16 or more of, any 17 or more of, any 18 or more of, any 19 or more of, any 20 or more of, any 21 or more of, any 22 or more of, any 23 or more of, any 24 or more of, or all 25 of outcomes (a) – (y) described immediately above.

[0079] Parameters (a) – (y) can be measured in accordance with any clinically acceptable methodology. For example, triglycerides, total cholesterol, HDL-C and fasting blood sugar can be sample from serum and analyzed using standard photometry techniques. VLDL-TG, LDL-C and VLDL-C can be calculated or determined using serum lipoprotein fractionation by preparative ultracentrifugation and subsequent quantitative analysis by refractometry or by analytic ultracentrifugal methodology. Apo A1, Apo B and hsCRP can be determined from serum using standard nephelometry techniques. Lipoprotein (a) can be determined from serum using standard turbidimetric immunoassay techniques. LDL particle number (LDL-P)and particle size can be determined using nuclear magnetic resonance (NMR)

spectrometry. Remnants lipoproteins and LDL-phospholipase A2 can be determined from EDTA plasma or serum and serum, respectively, using enzymatic immunoseparation techniques. Oxidized LDL, intercellular adhesion molecule-1 and interleukin-6 levels can be determined from serum using standard enzyme immunoassay techniques. These techniques are described in detail in standard textbooks, for example Tietz Fundamentals of Clinical Chemistry, 6th Ed. (Burtis, Ashwood and Borter Eds.), WB Saunders Company.

[0080] In one embodiment, subjects fast for up to 12 hours prior to blood sample collection, for example about 10 hours.

[0081] In another embodiment, the present invention provides a method of treating or preventing a cardiovascular event in a subject, wherein the subject is at or has achieved a guideline recommended LDL-C goal.

[0082] In another embodiment, the present invention provides a method of reducing an incidence of myocardial infarction (MI) and/or stroke in a subject. In a related embodiment, the subject has an LDL-C level that is within a normal range for the subject. In another embodiment, the subject has a triglyceride level that is within a normal range.

[0083] In another embodiment, the present invention provides a method of reducing an incidence of myocardial infarction (MI) and/or stroke in a subject group. In a related embodiment, the subjects in the subject group each have an LDL-C level that is within a normal range. In a related embodiment, the subjects in the subject group each have triglyceride level that is within a normal range.

[0084] In another embodiment, the present invention provides a method of reducing LDL-P level in a subject or subject group, wherein the subject is on concomitant statin therapy. In a related embodiment, the present invention provides a method of reducing LDL-P level in a subject or subject group comprising co-administering to the subject or subject group (a) one or more compositions as described herein and (b) a statin. In some embodiments, the subject is co-administered the statin in a dose that is less than the dose that would ordinarily be prescribed to the subject or subject group. In some embodiments, the subject is co-administered a sub-therapeutic dose of the statin. In

some embodiments, the statin is one or more of: amlodipine, atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, sitagliptin, and combinations thereof. In some embodiments, the method further comprises co-administration of ezetimibe. In some embodiments, the subject is co-administered a sub-therapeutic dose of ezetimibe.

[0085] The terms "co-administered," "concomitant administration," and "administered concomitantly" are used interchangeably herein and each refer to, for example, administration of two or more agents (e.g., EPA or a derivative thereof and a second active agent) at the same time, in the same dosage unit, one immediately after the other, within five minutes of each other, within ten minutes of each other, within fifteen minutes of each other, within thirty minutes of each other, within one hour of each other, within two hours of each other, within four hours of each other, within six hours of each other, within twelve hours of each other, within one day of each other, within one week of each other, within two weeks of each other, within one month of each other, within two months of each other, within six months of each other, within one year of each other, *etc.*

[0086] In another embodiment, the present invention provides a method of reducing LDL-P level in a subject or subject group, wherein the subject is on concomitant statin therapy. In a related embodiment, the present invention provides a method of reducing LDL-P level in a subject or subject group comprising co-administering to the subject or subject group (a) one or more compositions as described herein and (b) niacin (*e.g.,* extended release niacin). In some embodiments, the subject is co-administered the niacin in a dose that is less than the dose that would ordinarily be prescribed to the subject or subject group. In some embodiments, the subject is co-administered a sub-therapeutic dose of niacin.

[0087] In another embodiment, the present invention provides a method of treating or preventing primary hypercholesterolemia and/or mixed dyslipidemia (Fredrickson Types IIa and IIb) in a patient in need thereof, comprising administering to the patient one or more compositions as disclosed herein. In a related embodiment, the present invention provides a method of reducing triglyceride levels in a subject or subjects

when treatment with a statin or niacin extended-release monotherapy is considered inadequate (Frederickson type IV hyperlipidemia).

[0088] In another embodiment, the present invention provides a method of treating or preventing risk of recurrent nonfatal myocardial infarction in a patient with a history of myocardial infarction, comprising administering to the patient one or more compositions as disclosed herein.

[0089] In another embodiment, the present invention provides a method of slowing progression of or promoting regression of atherosclerotic disease in a patient in need thereof, comprising administering to a subject in need thereof one or more compositions as disclosed herein.

[0090] In another embodiment, the present invention provides a method of treating or preventing very high serum triglyceride levels (*e.g.* Types IV and V hyperlipidemia) in a patient in need thereof, comprising administering to the patient one or more compositions as disclosed herein.

[0091] In another embodiment, the present invention provides a method of treating subjects having very high serum triglyceride levels (*e.g.* greater than 1000 mg/dL or greater than 2000 mg/dL) and that are at risk of developing pancreatitis, comprising administering to the patient one or more compositions as disclosed herein.

[0092] In another embodiment, the present invention provides a method of treating subjects having a serum triglyceride level of at least about 135 mg/dL, at least 150 mg/dL, at least 200 mg/dL, 250 mg/dL, at least 300 mg/dL, at least 350 mg/dL, at least 400 mg/dL, at least 450 mg/dL, or at least 135 mg/dL and 500 mg/dL (*e.g.* no less than 135 mg/dL and no greater than 500 mg/dL), comprising administering to the patient one or more compositions as disclosed herein.

[0093] In one embodiment, a composition of the invention is administered to a subject in an amount sufficient to provide a daily dose of eicosapentaenoic acid of about 1 mg to about 10,000 mg, 25 about 5000 mg, about 50 to about 3000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about

225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg, about 2500 mg, about 2525 mg, about 2550 mg, about 2575 mg, about 2600 mg, about 2625 mg, about 2650 mg, about 2675 mg, about 2700 mg, about 2725 mg, about 2750 mg, about 2775 mg, about 2800 mg, about 2825 mg, about 2850 mg, about 2875 mg, about 2900 mg, about 2925 mg, about 2950 mg, about 2975 mg, about 3000 mg, about 3025 mg, about 3050 mg, about 3075 mg, about 3100 mg, about 3125 mg, about 3150 mg, about 3175 mg, about 3200 mg, about 3225 mg, about 3250 mg, about 3275 mg, about 3300 mg, about 3325 mg, about 3350 mg, about 3375 mg, about 3400 mg, about 3425 mg, about 3450 mg, about 3475 mg, about 3500 mg, about 3525 mg, about 3550 mg, about 3575 mg, about 3600 mg, about 3625 mg, about 3650 mg, about 3675 mg, about 3700 mg, about 3725 mg, about 3750 mg, about 3775 mg, about 3800 mg, about 3825 mg, about 3850 mg, about 3875 mg, about 3900 mg, about 3925 mg, about 3950 mg, about 3975 mg, about 4000 mg, about 4025 mg, about 4050 mg, about 4075 mg, about 4100 mg, about 4125 mg, about 4150 mg, about 4175 mg, about 4200 mg, about 4225 mg, about 4250 mg, about 4275 mg, about 4300 mg, about 4325 mg, about 4350 mg, about 4375 mg, about 4400 mg, about 4425 mg, about 4450 mg, about 4475 mg, about 4500 mg, about 4525

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[0094] In another embodiment, any of the methods disclosed herein are used in treatment or prevention of a subject or subjects that consume a traditional Western diet. In one embodiment, the methods of the invention include a step of identifying a subject as a Western diet consumer or prudent diet consumer and then treating the subject if the subject is deemed a Western diet consumer. The term "Western diet" herein refers generally to a typical diet consisting of, by percentage of total calories, about 45% to about 50% carbohydrate, about 35% to about 40% fat, and about 10% to about 15% protein. A Western diet may alternately or additionally be characterized by relatively high intakes of red and processed meats, sweets, refined grains, and desserts, for example more than 50%, more than 60% or more or 70% of total calories come from these sources.

[0095] In one embodiment, a composition for use in methods of the invention comprises eicosapentaenoic acid, or a pharmaceutically acceptable ester, derivative, conjugate or salt thereof, or mixtures of any of the foregoing, collectively referred to herein as "EPA." The term "pharmaceutically acceptable" in the present context means that the substance in question does not produce unacceptable toxicity to the subject or interaction with other components of the composition.

[0096] In one embodiment, the EPA comprises all-cis eicosa-5,8,11,14,17-pentaenoic acid. In another embodiment, the EPA comprises an eicosapentaenoic acid ester. In another embodiment, the EPA comprises a $C_1 - C_5$ alkyl ester of eicosapentaenoic acid. In another embodiment, the EPA comprises eicosapentaenoic

acid ethyl ester, eicosapentaenoic acid methyl ester, eicosapentaenoic acid propyl ester, or eicosapentaenoic acid butyl ester. In another embodiment, the EPA comprises In one embodiment, the EPA comprises all-cis eicosa-5,8,11,14,17-pentaenoic acid ethyl ester.

[0097] In another embodiment, the EPA is in the form of ethyl-EPA, lithium EPA, mono-, di- or triglyceride EPA or any other ester or salt of EPA, or the free acid form of EPA. The EPA may also be in the form of a 2-substituted derivative or other derivative which slows down its rate of oxidation but does not otherwise change its biological action to any substantial degree.

[0098] In another embodiment, EPA is present in a composition useful in accordance with methods of the invention in an amount of about 50 mg to about 5000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg, about 2500 mg, about 2525 mg, about 2550 mg, about 2575 mg, about 2600 mg, about 2625 mg, about

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[0099] In another embodiment, a composition useful in accordance with the invention contains not more than about 10%, not more than about 9%, not more than about 8%, not more than about 7%, not more than about 6%, not more than about 5%, not more than about 4%, not more than about 3%, not more than about 2%, not more than about 1%, or not more than about 0.5%, by weight, docosahexaenoic acid (DHA), if any. In another embodiment, a composition of the invention contains substantially no docosahexaenoic acid. In still another embodiment, a composition useful in the present invention contains no docosahexaenoic acid and/or derivative thereof.

[0100] In another embodiment, EPA comprises at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%, by weight, of all fatty acids present in a composition that is useful in methods of the present invention.

[0101] In one embodiment, a composition of the invention comprises ultra-pure EPA. The term "ultra-pure" as used herein with respect to EPA refers to a composition comprising at least 95% by weight EPA (as the term "EPA" is defined and exemplified herein). Ultra-pure EPA comprises at least 96% by weight EPA, at least 97% by weight EPA, or at least 98% by weight EPA, wherein the EPA is any form of EPA as set forth herein.

[0102] In another embodiment, a composition useful in accordance with methods of the invention contains less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5% or less than 0.25%, by weight of the total composition or by weight of the total fatty acid content, of any fatty acid other than EPA. Illustrative examples of a "fatty acid other than EPA" include linolenic acid (LA), arachidonic acid (AA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), stearadonic acid (STA), eicosatrienoic acid (ETA) and/or docosapentaenoic acid (DPA). In another embodiment, a composition useful in accordance with methods of the invention contains about 0.1% to about 4%, about 0.5% to about 3%, or about 1% to about 2%, by weight, of total fatty acids other than EPA and/or DHA.

[0103] In another embodiment, a composition useful in accordance with the invention has one or more of the following features: (a) eicosapentaenoic acid ethyl ester represents at least about 96%, at least about 97%, or at least about 98%, by weight, of all fatty acids present in the composition; (b) the composition contains not more than about 4%, not more than about 3%, or not more than about 2%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; (c) the composition contains not more than about 0.6%, not more than about 0.5%, or not more than about 0.4% of any individual fatty acid other than eicosapentaenoic acid ethyl ester; (d) the composition has a refractive index (20 °C) of about 1 to about 2, about 1.2 to about 1.8 or about 1.4 to about 1.5; (e) the composition has a specific gravity (20 °C) of about 0.8 to about 1.0, about 0.85 to about 0.95 or about 0.9 to about 0.92; (e) the composition contains not more than about 20 ppm, not more than about 15 ppm or not more than about 10 ppm heavy metals, (f) the composition contains not more than about 5 ppm, not more than about 4 ppm, not more than about 3 ppm, or not more than

about 2 ppm arsenic, and/or (g) the composition has a peroxide value of not more than about 5 meq/kg, not more than about 4 meq/kg, not more than about 3 meq/kg, or not more than about 2 meq/kg.

[0104] In another embodiment, a composition useful in accordance with the invention comprises, consists of or consists essentially of at least 95% by weight ethyl eicosapentaenoate (EPA-E), about 0.2% to about 0.5% by weight ethyl octadecatetraenoate (ODTA-E), about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate (NDPA-E), about 0.2% to about 0.45% by weight ethyl arachidonate (AA-E), about 0.3% to about 0.5% by weight ethyl eicosatetraenoate (ETA-E), and about 0.05% to about 0.32% ethyl heneicosapentaenoate (HPA-E). In another embodiment, the composition is present in a capsule shell.

[0105] In another embodiment, compositions useful in accordance with the invention comprise, consist essential of, or consist of at least 95%, 96% or 97%, by weight, ethyl eicosapentaenoate, about 0.2% to about 0.5% by weight ethyl octadecatetraenoate, about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate, about 0.2% to about 0.45% by weight ethyl arachidonate, about 0.3% to about 0.5% by weight ethyl eicosatetraenoate, and about 0.05% to about 0.32% ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative thereof such as ethyl-DHA. In one embodiment the composition contains substantially no amount or no amount of DHA or derivative thereof such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (*e.g.* tocopherol) or other impurities in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, about 500 mg to about 1 g of the composition is provided in a capsule shell.

[0106] In another embodiment, compositions useful in accordance with the invention comprise, consist essential of, or consist of at least 96% by weight ethyl eicosapentaenoate, about 0.22% to about 0.4% by weight ethyl octadecatetraenoate, about 0.075% to about 0.20% by weight ethyl nonaecapentaenoate, about 0.25% to about 0.40% by weight ethyl arachidonate, about 0.3% to about 0.4% by weight ethyl

eicosatetraenoate and about 0.075% to about 0.25% ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative thereof such as ethyl-DHA. In one embodiment the composition contains substantially no amount or no amount of DHA or derivative thereof such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (*e.g.* tocopherol) or other impurities in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, the invention provides a dosage form comprising about 500 mg to about 1 g of the foregoing composition in a capsule shell. In one embodiment, the dosage form is a gel or liquid capsule and is packaged in blister packages of about 1 to about 20 capsules per sheet.

[0107] In another embodiment, compositions useful in accordance with the invention comprise, consist essential of, or consist of at least 96%, 97% or 98%, by weight, ethyl eicosapentaenoate, about 0.25% to about 0.38% by weight ethyl octadecatetraenoate, about 0.10% to about 0.15% by weight ethyl nonaecapentaenoate, about 0.25% to about 0.35% by weight ethyl arachidonate, about 0.31% to about 0.38% by weight ethyl eicosatetraenoate, and about 0.08% to about 0.20% ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative thereof such as ethyl-DHA. In one embodiment the composition contains substantially no amount or no amount of DHA or derivative thereof such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (*e.g.* tocopherol) or other impurities in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, the invention provides a dosage form comprising about 500 mg to about 1 g of the foregoing composition in a capsule shell.

[0108] In another embodiment, a composition as described herein is administered to a subject once or twice per day. In another embodiment, 1, 2, 3 or 4 capsules, each containing about 1 g of a composition as described herein, are administered to a

subject daily. In another embodiment, 1 or 2 capsules, each containing about 1 g of a composition as described herein, are administered to the subject in the morning, for example between about 5 am and about 11 am, and 1 or 2 capsules, each containing about 1 g of a composition as described herein, are administered to the subject in the evening, for example between about 5 pm and about 11 pm.

[0109] In one embodiment, a subject being treated in accordance with methods of the invention is not otherwise on lipid-altering therapy, for example statin, fibrate, niacin and/or ezetimibe therapy.

[0110] In another embodiment, compositions useful in accordance with methods of the invention are orally deliverable. The terms "orally deliverable" or "oral administration" herein include any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject, whether or not the agent or composition is swallowed. Thus "oral administration" includes buccal and sublingual as well as esophageal administration. In one embodiment, the composition is present in a capsule, for example a soft gelatin capsule.

[0111] A composition for use in accordance with the invention can be formulated as one or more dosage units. The terms "dose unit" and "dosage unit" herein refer to a portion of a pharmaceutical composition that contains an amount of a therapeutic agent suitable for a single administration to provide a therapeutic effect. Such dosage units may be administered one to a plurality (*i.e.* 1 to about 10, 1 to 8, 1 to 6, 1 to 4 or 1 to 2) of times per day, or as many times as needed to elicit a therapeutic response.

[0112] In another embodiment, the invention provides use of any composition described herein for treating moderate to severe hypertriglyceridemia in a subject in need thereof, comprising: providing a subject having a fasting baseline triglyceride level of about 500 mg/dL to about 1500 mg/dL and administering to the subject a pharmaceutical composition as described herein. In one embodiment, the composition comprises about 1 g to about 4 g of eicosapentaenoic acid ethyl ester, wherein the composition contains substantially no docosahexaenoic acid.

[0113] In one embodiment, compositions of the invention, upon storage in a closed container maintained at room temperature, refrigerated (*e.g.* about 5 to about 5 -10 °C) temperature, or frozen for a period of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, exhibit at least about 90%, at least about 95%, at least about 97.5%, or at least about 99% of the active ingredient(s) originally present therein.

[0114] In one embodiment, the invention provides use of a composition as described herein in manufacture of a medicament for treatment of any of a cardiovascular-related disease. In another embodiment, the subject is diabetic.

[0115] In one embodiment, a composition as set forth herein is packaged together with instructions for using the composition to treat a cardiovascular disorder and/or reduce LDL-P.

What is claimed is:

1. A method of reducing LDL-P in a subject in need thereof, comprising:

determining a baseline LDL-P level associated with the subject; and

thereafter administering to the subject about 1 g to about 4 g of ethyl eicosapentaenoate per day.

2. The method of claim 1, further comprising a step of measuring a baseline lipid profile in the subject prior to administering the pharmaceutical composition to said subject.

3. The method of claim 2, wherein the subject has:

a baseline LDL-P of at least 1,000 nmol/L and optionally less than 1,300 nmol/L;

a baseline LDL-P of at least 1,300 nmol/L and optionally less than 1,600 nmol/L;

a baseline LDL-P of at least 1,600 nmol/L and optionally less than 2,000 nmol/L; or

a baseline LDL-P of at least 2,000 nmol/L.

4. The method of any one of claims 1 to 3, wherein after administration of the pharmaceutical composition, the subject experiences a reduction in LDL-P of at least about 5%, at least about 10%, at least about 15%, at least about 19%, at least about 20%, at least about 25%, at least about 30%, at least about 31%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline.

5. The method of any one of claims 1 to 4, wherein the subject is associated a first MESA percentile group before administration of the composition, and wherein the subject is associated with a second, lower MESA percentile group after administration.

6. The method of claim 5, wherein:

the first MESA percentile group is a >95th percentile group, and the second MESA percentile group is selected from the group consisting of: an 80th to 95th percentile group, a 50th to 80th percentile group, a 20th to 50th percentile group, or a <20th percentile group;

the first MESA percentile group is an 80th to 95th percentile group, and the second MESA percentile group is selected from the group consisting of: a 50th to 80th percentile group, a 20th to 50th percentile group, or a <20th percentile group;

the first MESA percentile group is a 50th to 80th percentile group, and the second MESA percentile group is selected from the group consisting of: a 20th to 50th percentile group, or a <20th percentile group; or

the first MESA percentile group is a 20th to 50th percentile group, and the second MESA percentile group is a <20th percentile group.

7. The method of any one of claims 1 to 6, wherein the subject is administered 2 g to about 4 g of ethyl eicosapentaenoate per day.

8. The method of claim 7, wherein the subject is administered about 2 g or about 4 g of ethyl eicosapentaenoic acid per day.

9. The method of any one of claims 1 to 8, wherein the ethyl eicosapentaenoate is administered to the subject 1 to 4 times per day.

10. The method of any one of claims 1 to 9, wherein the ethyl eicosapentaenoate comprises at least about 80%, at least about 90%, at least about 95%, or at least about 96%, by weight, of all fatty acids administered to the subject.

11. The method of any one of claims 1 to 10, wherein docosahexaenoic acid and its derivatives comprise no more than about 10%, no more than about 5%, no more than about 4%, or no more than about 3%, by weight, of all fatty acids administered to the subject.

12. The method of any one of claims 1 to 11, wherein the composition is present in a capsule.

13. The method of any one of claims 1 to 12, wherein the subject is not on concomitant lipid-altering therapy.

14. The method of any one of claims 1 to 13, wherein the subject is diabetic.

15. The method of any one of claims 1 to 14, wherein the pharmaceutical composition is packaged together with instructions for using the composition to lower LDL-P.

16. The method of any one of claims 1 to 15, wherein the subject is not on concomitant lipid-altering therapy.

17. The method of any one of claims 1 to 16, wherein the pharmaceutical composition is packaged in blister packages of about 1 to less than about 20 capsules per sheet.