TITLE

METHODS OF REDUCING THE RISK OF A CARDIOVASCULAR EVENT IN A SUBJECT ON STATIN THERAPY

PRIORITY CLAIM

[0001] This application claims priority to U.S. provisional patent application serial no. 61/666,447, 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.

[0003] Lovaza®, a lipid regulating agent, is indicated as an adjunct to diet to reduce triglyceride levels in adult patients with very high triglyceride levels. Unfortunately, Lovaza® can significantly increase LDL-C and/or non-HDL-C levels in some patients. A need exists for improved treatments for cardiovascular diseases and disorders.

SUMMARY

[0004] In various embodiments, the present invention provides methods of reducing the risk of a cardiovascular event in a subject on statin therapy. Thus, in a first aspect, the present invention refers to the eicosapentaenoic acid ethyl ester in the manufacture of a pharmaceutical composition for reducing a risk of a cardiovascular event in a subject on statin therapy, wherein the subject has a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL, optionally wherein said subject has established cardiovascular disease or has a high risk of developing cardiovascular disease; and wherein about 1 g to about 4 g of eicosapentaenoic acid ethyl ester is to be administered to the subject per day. In one ~~embodiment~~example, the method comprises administering to the subject a pharmaceutical composition comprising about

1 g to about 4 g of eicosapentaenoic acid ethyl ester or a derivative thereof. In another ~~embodiment~~example, the subject has a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL. In another ~~embodiment~~example, the composition contains not more than 10%, by weight, docosahexaenoic acid or derivative thereof, substantially no docosahexaenoic acid or derivative thereof, or no docosahexaenoic acid or derivative thereof. In another ~~embodiment~~example, eicosapentaenoic acid ethyl ester comprises at least 96%, by weight, of all fatty acids present in the composition; 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.

[0005] In another ~~embodiment~~example, the ~~invention~~disclosure provides a method of treating hypertriglyceridemia 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.

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.

What is claimed is:

1. Use of eicosapentaenoic acid ethyl ester in the manufacture of a pharmaceutical composition for ~~A method of~~ reducing a risk of a cardiovascular event in a subject on statin therapy, ~~the method comprising:~~ wherein the subject

~~(a) identifying a subject on statin therapy and having~~ has a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL, optionally wherein said subject has established cardiovascular disease or has a high risk of developing cardiovascular disease; and wherein

~~(b) administering to the subject a pharmaceutical composition comprising~~ about 1 g to about 4 g of eicosapentaenoic acid ethyl ester is to be administered to the subject per day.

2. The ~~method~~ use of claim 1 wherein the composition is to be administered to the subject in 1 to 4 dosage units per day.

3. The ~~method~~ use of claim 1 wherein the eicosapentaenoic acid ethyl ester comprises at least about 96 wt.% of all omega-3 fatty acids in the pharmaceutical composition.

4. The ~~method~~ use of claim 1, wherein the established cardiovascular disease is determined by the presence of any one of: documented coronary artery disease, documented cerebrovascular disease, documented carotid disease, documented peripheral arterial disease, or combinations thereof.

~~5. The method of claim 1 further comprising a step of measuring the subject's baseline lipid profile prior to administering the pharmaceutical composition to the subject.~~

~~6.~~5. The ~~method~~ use of claim 1 wherein the subject has one or more of: a baseline non-HDL-C value of about 200 mg/dL to about 300 mg/dL; a baseline total cholesterol value of about 250 mg/dL to about 300 mg/dL; a baseline VLDL-C value of about 140 mg/dL to about 200 mg/dL; a baseline HDL-C value of about 10 to about 30 mg/dL; and/or a baseline LDL-C value of about 40 to about 100 mg/dL.

~~7.~~6. The ~~method~~ use of claim 1 wherein the statin therapy comprises ~~administering~~ administration to the subject a statin and optionally ezetimibe.

~~8.~~7. The use~~method~~ of claim 1 wherein the subject: (a) has not been administered 200 mg or more per day of niacin and/or fibrates for at least 28 days before ~~step (a)~~administration of the pharmaceutical composition; (b) has not been administered omega-3 fatty acid prescription for a period of time beginning 28 days prior to administration of the pharmaceutical composition~~step (a)~~; (c) has not ingested dietary supplements comprising omega-3 fatty acids for a period of time beginning 28 days prior to administration of the pharmaceutical composition~~step (a)~~.

~~9.~~8. The use~~method~~ of ~~any of~~ claim ~~8~~7, wherein the period of time ends no earlier than about 6 months after a first administration of the pharmaceutical composition ~~in step (b)~~.

~~10.~~9. The ~~method~~ use of claim ~~8~~7, wherein the period of time ends about 6 months, about 1 year, about 2 years, about 3 years, about 4 years, about 5 years, or more than about 5 years after the first administration of the pharmaceutical composition ~~in step (b)~~.

~~11.~~10. The use~~method~~ of claim 1 wherein the cardiovascular event is one or more of: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and unstable angina.

~~12.~~11. The use~~method~~ of claim 1 wherein the cardiovascular event is one or more of: cardiac arrhythmia; cardiac arrest; peripheral cardiovascular disease requiring intervention, angioplasty, bypass surgery or aneurysm repair; and death.

~~13.~~12. The use~~method~~ of claim 1 wherein the cardiovascular event is onset of new congestive heart failure.

~~14.~~13. The use~~method~~ of claim 1 wherein the subject is to be administered about 1 g to about 4 g of the pharmaceutical composition per day for about 4 months, about 1 year, about 2 years, about 3 years, about 4 years, or about 5 years ~~in step (b)~~.

~~15.~~14. The use~~method~~ of claim ~~14~~13 wherein, after ~~administering~~ administration of the pharmaceutical composition ~~in step (b)~~, the subject exhibits one or more of (a) reduced triglyceride levels compared to baseline; (b) reduced Apo B levels compared to baseline; (c) increased HDL-C levels compared to baseline; (d) no increase in LDL-C levels compared to baseline; (e) a reduction in LDL-C levels compared to baseline; (f) a reduction in non-HDL-C levels compared to baseline; (g) a

reduction in VLDL levels compared to baseline; (h) a reduction in total cholesterol levels compared to baseline; (i) a reduction in high sensitivity C-reactive protein (hs-CRP) levels compared to baseline; and/or (j) a reduction in high sensitivity troponin (hsTnT) levels compared to baseline.

~~16.~~15. The ~~method~~ use of claim ~~14~~13, wherein the subject exhibits one or more of: (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%, or at least about 55% as compared to baseline; (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%, or at least about 50% as compared to baseline; (c) 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%, or at least about 50% as compared to baseline; and/or (d) 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%, or at least about 55% as compared to baseline.

~~17.~~16. The ~~method~~ use of claim 1 further comprising ~~assigning~~ assignment of a plurality of control subjects to a control population,

wherein each control subject is on stable statin therapy, has a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL, and has established cardiovascular disease or a high risk of developing cardiovascular disease, and

wherein the control subjects are not administered the pharmaceutical composition comprising about 1 g to about 4 g of eicosapentaenoic acid ethyl ester per day.

~~18.~~17. The ~~method~~ use of claim ~~17~~16, wherein a first time interval beginning at an initial administration of the pharmaceutical composition to the subject ~~in step (b)~~ to a first cardiovascular event of the subject is greater than or substantially greater than a first control time interval beginning at initial administration of a placebo to the control subjects to a first cardiovascular event in the control subjects.

~~19.~~18. The ~~method~~ use of claim ~~18~~17, wherein the first cardiovascular event of the subject is a major cardiovascular event selected from the group consisting of: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and unstable angina caused by myocardial ischemia.

~~20.~~19. The ~~method~~ use of claim ~~18~~17 or ~~19~~18, wherein the first cardiovascular event of the control subjects is a major cardiovascular event selected from the group consisting of: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and unstable angina caused by myocardial ischemia.

~~21.~~20. The ~~method~~ use of claim ~~18~~17, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any of: death (from any cause), nonfatal myocardial infarction, or nonfatal stroke.

~~22.~~21. The ~~method~~ use of claim ~~18~~17, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any of: death from a cardiovascular cause, nonfatal myocardial infarction, coronary revascularization, unstable angina, peripheral cardiovascular disease, or cardiac arrhythmia requiring hospitalization.

~~23.~~22. The ~~method~~ use of claim ~~18~~17, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any of: death from a cardiovascular cause, nonfatal myocardial infarction, and coronary revascularization, unstable angina.

~~24.~~23. The ~~method~~ use of claim ~~18~~17, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any of: death from a cardiovascular cause and nonfatal myocardial infarction.

~~25.~~24. The use~~method~~ of claim ~~18~~17, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any of: death (from any cause).

~~26.~~25. The use~~method~~ of claim ~~18~~17, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any of: fatal myocardial infarction and nonfatal myocardial infarction.

~~27.~~26. The use~~method~~ of claim ~~26~~25, wherein nonfatal myocardial infarction includes silent myocardial infarction.

~~28.~~27. The use~~method~~ of claim ~~18~~17, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is coronary revascularization.

~~29.~~28. The use~~method~~ of claim ~~18~~17, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is hospitalization for unstable angina.

~~30.~~29. The use~~method~~ of claim ~~29~~28, wherein the unstable angina is caused by myocardial ischemia.

~~31.~~30. The use~~method~~ of claim ~~18~~17, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any one of: fatal stroke or nonfatal stroke.

~~32.~~31. The use~~method~~ of claim 1 or claim ~~18~~17, wherein a second time interval beginning at an initial administration of the pharmaceutical composition to the subject ~~in step (b)~~ to a second cardiovascular event of the subject is greater than or substantially greater than a second control time interval beginning at initial administration of a placebo to the control subjects to a second cardiovascular event in the control subjects.

~~33.~~32. The use~~method~~ of claim ~~32~~31, wherein the second cardiovascular event of the subject and the second cardiovascular event of the control subjects is a major cardiovascular event selected from the group consisting of: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and unstable angina caused by myocardial ischemia.

~~34.~~33. The use~~method~~ of claim ~~18~~17, wherein the subject has diabetes mellitus and the control subjects each have diabetes mellitus.

~~35.~~34. The use~~method~~ of claim ~~18~~17, wherein the subject has metabolic syndrome and the control subjects each have metabolic syndrome.

~~36.~~35. The use~~method~~ of claim ~~18~~17, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any one of: new coronary heart failure, new coronary heart failure leading to hospitalization, transient ischemic attack, amputation for coronary vascular disease, and carotid revascularization.

~~37.~~36. The use~~method~~ of claim ~~18~~17, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any one of: elective coronary revascularization and emergent coronary revascularization.

~~38.~~37. The use~~method~~ of claim ~~18~~17, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is an onset of diabetes.

~~39.~~38. The use~~method~~ of claim ~~18~~17, wherein, after an initial administration of the pharmaceutical composition ~~in step (b)~~, the subject exhibits one or more of (a) reduced triglyceride levels compared to the control population; (b) reduced Apo B levels compared to the control population; (c) increased HDL-C levels compared to the control population; (d) no increase in LDL-C levels compared to the control population; (e) a reduction in LDL-C levels compared to the control population; (f) a reduction in non-HDL-C levels compared to the control population; (g) a reduction in VLDL levels compared to the control population; (h) a reduction in total cholesterol levels compared to the control population; (i) a reduction in high sensitivity C-reactive protein (hs-CRP) levels compared to the control population; and/or (j) a reduction in high sensitivity troponin (hsTnT) levels compared to the control population.

~~40.~~39. The use~~method~~ of claim ~~18~~17, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is cardiac arrhythmia requiring hospitalization.

41.40. The usemethod of claim 1817, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is cardiac arrest.

42.41. The usemethod of claim 1413, wherein a first weight of the subject determined after step (b)administration of the pharmaceutical composition is less than a baseline weight of the subject determined before administration of the pharmaceutical compositionstep (b).

43.42. The usemethod of claim 1413, wherein a first waist circumference of the subject determined after administration of the pharmaceutical compositionstep (b) is less than a baseline waist circumference of the subject determined before administration of the pharmaceutical compositionstep (b).

44.43. The usemethod of any one of claims 18-17 to 38-37 or 40-39 to 4342, wherein the first control time interval is an average, a median, or a mean of a plurality of first control time intervals associated with each control subject.

45.44. The usemethod of claim 32-31 or claim 3332, wherein the second control time interval is an average, a median, or a mean of a plurality of second control time intervals associated with each control subject.

46.45. The usemethod of claim 1716, wherein a plurality of subjects experience a first major cardiovascular event after an initial administration of the pharmaceutical composition in step (b) at a first incidence rate, and wherein the control subjects experience a first major cardiovascular event after an initial administration of a placebo at a second incidence rate,

wherein the first incidence rate is less than the second incidence rate.

47.46. The usemethod of claim 4645, wherein the first major cardiovascular event is any one of: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina.

48.47. The usemethod of claim 4746, wherein the unstable angina is determined to be caused by myocardial ischemia.

~~49.~~48. The use~~method~~ of claim ~~46~~45, wherein the first and second incidence rates are determined for a time period beginning on the date of the initial administration and ending about 4 months, about 1 year, about 2 years, about 3 years, about 4 years, or about 5 years after the date of initial administration.