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

[0003a] In one aspect, the present invention refers to a use of eicosapentaenoic acid ethyl ester in the manufacture of a medicament for reducing a risk of cardiovascular death, myocardial infarction, stroke, coronary revascularization, and/or unstable angina in a subject on stable statin therapy, wherein: (a) the subject has been identified as having dyslipidemia, as being on stable statin therapy and as having a fasting baseline triglyceride level of 135 mg/dL to 500 mg/dL, optionally wherein said subject has established cardiovascular disease or has a high risk of developing cardiovascular disease; and (b) the medicament is for daily administration in an amount to provide 4g of the eicosapentaenoic acid ethyl ester per day.

[0004] In various examples, described herein are methods of reducing the risk of a cardiovascular event in a subject on statin therapy. In one 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 example, the subject has a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL. In another 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 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 example, the 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.

[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.

What is claimed is:

1. Use of eicosapentaenoic acid ethyl ester in the manufacture of a medicament for reducing a risk of cardiovascular death, myocardial infarction, stroke, coronary revascularization, and/or unstable angina in a subject on stable statin therapy, wherein:

(a) the subject has been identified as having dyslipidemia, as being on stable statin therapy and as having a fasting baseline triglyceride level of 135 mg/dL to 500 mg/dL, optionally wherein said subject has established cardiovascular disease or has a high risk of developing cardiovascular disease; and

(b) the medicament is for daily administration in an amount to provide 4g of the eicosapentaenoic acid ethyl ester per day.

2. The use of claim 1, wherein the medicament is for administration to the subject in 1 to 4 dosage units per day.

3. The use of claim 1, wherein the eicosapentaenoic acid ethyl ester comprises at least 96 wt.% of all omega-3 fatty acids in the medicament.

4. The 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 use of claim 1, wherein the subject's baseline lipid profile is to be measured before administration of the medicament to the subject.

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

7. The use of claim 1, wherein the statin therapy comprises that, a statin and optionally ezetimibe is to be administered to the subject.

8. The use 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); (b) has not been administered omega-3 fatty acid prescription for a period of time beginning 28 days prior to step (a); (c) has not ingested dietary supplements comprising omega-3 fatty acids for a period of time beginning 28 days prior to step (a).

9. The use of claim 8, wherein the period of time ends no earlier than 6 months after a first administration of the medicament in step (b).

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

11. The use of claim 1, wherein the risk is cardiovascular death.

12. The use of claim 1, wherein the risk is coronary revascularization.

13. The use of claim 1, wherein the risk is unstable angina.

14. The use of claim 1, wherein the medicament is to be administered an amount of 4g per day for 4 months, 1 year, 2 years, 3 years, 4 years, or 5 years in step (b).

15. The use of claim 14, wherein the medicament is for one or more of (a) reducing triglyceride levels compared to baseline; (b) reducing Apo B levels compared to baseline; (c) increasing HDL-C levels compared to baseline; (d) not increasing LDL-C levels compared to baseline; (e) reducing LDL-C levels compared to baseline; (f) reducing non-HDL-C levels compared to baseline; (g) reducing VLDL levels compared to baseline; (h) reducing total cholesterol levels compared to baseline; (i) reducing high sensitivity C-reactive protein (hs-CRP) levels compared to baseline; and/or (j) reducing high sensitivity troponin (hsTnT) levels compared to baseline.

16. The use of claim 14, wherein the medicament is for one or more of: (a) reducing triglyceride levels by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, or at least 55% as compared to baseline; (b) increasing non-HDL-C

levels by less than 30%, less than 20% , less than 10%, less than 5%or no increase in non-HDL-C levels or reducing non-HDL-C levels by at least 1%, at least 3%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50% as compared to baseline; (c) increasing HDL-C levels by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50% as compared to baseline; and/or (d) increasing LDL-C levels by less than 30%, less than 20%, less than 10%, less than 5%or no increase in LDL-C levels or reducing LDL-C levels by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, or at least 55% as compared to baseline.

17. The use of claim 1, wherein the medicament is for providing a first time interval beginning at an initial administration of the medicament to the subject to a first cardiovascular event of the subject that is greater than or substantially greater than a first control time interval beginning at initial administration of a placebo to a plurality of control subjects to a first cardiovascular event in the control subjects, wherein:

each control subject is on stable statin therapy, has a fasting baseline triglyceride level of 135 mg/dL to 500 mg/dL, and has established cardiovascular disease or a high risk of developing cardiovascular disease, and the control subjects are not administered the medicament.

18. The use of claim 17, wherein the first cardiovascular event of the subject is cardiovascular death, myocardial infarction, stroke, coronary revascularization, and/or unstable angina caused by myocardial ischemia.

19. The use of claim 17 or 18, wherein the first cardiovascular event of the control subjects is cardiovascular death, myocardial infarction, stroke, coronary revascularization, and/or unstable angina caused by myocardial ischemia.

20. The use of claim 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 unstable angina.

21. The use of claim 17, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is death from a cardiovascular cause.

22. The use of claim 17, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is unstable angina.

23. The use of claim 17, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is coronary revascularization.

24. The use of claim 17, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is hospitalization for unstable angina.

25. The use of claim 24, wherein the unstable angina is caused by myocardial ischemia.

26. The use of claim 17, wherein the medicament is for providing a second time interval beginning at an initial administration of the medicament to the subject to a second cardiovascular event of the subject that 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.

27. The use of claim 26, 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, myocardial infarction, stroke, coronary revascularization, and unstable angina caused by myocardial ischemia.

28. The use of claim 17, wherein the subject has diabetes mellitus and the control subjects each have diabetes mellitus.

29. The use of claim 17, wherein the subject has metabolic syndrome and the control subjects each have metabolic syndrome.

30. The use of claim 17, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is carotid revascularization.

31. The use of claim 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.

32. The use of claim 17, wherein the medicament is for one or more of (a) reducing triglyceride levels compared to the control population; (b) reducing Apo B levels compared to the control population; (c) increasing HDL-C levels compared to the control population; (d) not increasing LDL-C levels compared to the control population; (e) reducing LDL-C levels compared to the control population; (f) reducing non-HDL-C levels compared to the control population; (g) reducing VLDL levels compared to the control population; (h) reducing total cholesterol levels compared to the control population; (i) reducing high sensitivity C-reactive protein (hs-CRP) levels compared to the control population; and/or (j) reducing high sensitivity troponin (hsTnT) levels compared to the control population.

33. The use of claim 14, wherein a first weight of the subject determined after administration of the medicament is less than a baseline weight of the subject determined before administration of the medicament.

34. The use of claim 14, wherein a first waist circumference of the subject determined after administration of the medicament is less than a baseline waist circumference of the subject determined before administration of the medicament.

35. The use of any one of claims 17, 18, 20-31, 33 and 34, 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.

36. The use of claim 26 or claim 27, 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.

37. The use of claim 17, wherein a plurality of subjects experience a first major cardiovascular event after an initial administration of the medicament 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.

38. The use of claim 37, wherein the first major cardiovascular event is any one of: cardiovascular death, myocardial infarction, stroke, coronary revascularization, and hospitalization for unstable angina.

39. The use of claim 38, wherein the unstable angina is determined to be caused by myocardial ischemia.

40. The use of claim 37, wherein the first and second incidence rates are determined for a time period beginning on the date of the initial administration and ending 4 months, 1 year, 2 years, 3 years, 4 years, or 5 years after the date of initial administration.

41. The use of claim 17, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is stroke.

42. The use of claim 17, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is myocardial infarction.