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 one aspect, the present disclosure refers to the use of eicosapentaenoic acid, docosahexaenoic acid and docosapentaenoic acid in the manufacture of a medicament for reducing a risk of cardiovascular death and/or unstable angina in a subject on statin therapy, wherein 2 g of the medicament comprises eicosapentaenoic acid, docosahexaenoic acid and docosapentaenoic acid, wherein the medicament comprises eicosapentaenoic acid in an amount of at least 95 wt.% of all omega-3 fatty acids present, and is to be administered to the subject per day for a period of at least 2 years, wherein the subject has a fasting baseline triglyceride level of 135 mg/dL to 500 mg/dL. In another aspect, the present disclosure refers to the use of eicosapentaenoic acid, docosahexaenoic acid, and docosapentaenoic acid in the manufacture of a

medicament for reducing a risk of cardiovascular death and/or unstable angina in a subject on statin therapy with established cardiovascular disease, wherein 4 g of the medicament comprises eicosapentaenoic acid, docosahexaenoic acid, and docosapentaenoic acid, wherein the medicament comprises eicosapentaenoic acid in an amount of at least 95 wt.% of all omega-3 fatty acids present, and is to be administered to the subject per day for a period of at least 2 years, wherein the subject has a fasting baseline triglyceride level of 135 mg/dL to 500 mg/dL. In yet another aspect, the present disclosure refers to the use of eicosapentaenoic acid, docosahexaenoic acid, and docosapentaenoic acid in the manufacture of a medicament for reducing a risk of coronary revascularization in a subject on statin therapy, wherein 2 g of the medicament comprises eicosapentaenoic acid, docosahexaenoic acid, and docosapentaenoic acid, wherein the medicament comprises eicosapentaenoic acid in an amount of at least 95 wt.% of all omega-3 fatty acids present, and is to be administered to the subject per day for a period of at least 2 years, wherein the subject has a fasting baseline triglyceride level of 135 mg/dL to 500 mg/dL. In a further aspect, the present disclosure refers to the use of eicosapentaenoic acid, docosahexaenoic acid and docosapentaenoic acid in the manufacture of a medicament for reducing a risk of coronary revascularization in a subject on statin therapy with established cardiovascular disease, wherein 4 g of the medicament comprises eicosapentaenoic acid, docosahexaenoic acid, and docosapentaenoic acid, and the eicosapentaenoic acid comprises at least 95 wt.% of all omega-3 fatty acids present, wherein the medicament is to be administered to the subject per day for a period of at least 2 years, wherein the subject has a fasting baseline triglyceride level of 135 mg/dL to 500 mg/dL. In yet another aspect, the present disclosure refers to the use of eicosapentaenoic acid in the manufacture of a medicament for reducing risk of a cardiovascular event in a subject on statin therapy with residual atherogenic dyslipidemia and clinically evident cardiovascular disease,wherein the medicament comprises about 4 g of eicosapentaenoic acid in triglyceride form, wherein the medicament is to be administered to the subject per day for a period of at least about 2 years, wherein said administration reduces risk of cardiovascular death, risk of unstable angina and/or need for coronary revascularization. In another aspect, the present disclosure refers to the use of eicosapentaenoic acid in the manufacture of a medicament for reducing risk of a cardiovascular event in a subject on statin therapy with residual atherogenic dyslipidemia and clinically evident cardiovascular disease, wherein the medicament comprises about 4 g of eicosapentaenoic acid in triglyceride form, wherein the medicament is to be administered to the subject per day for a period of at least about 2

years, wherein said administration reduces risk of cardiovascular death, need for coronary revascularization, risk of unstable angina, risk of stroke and/or risk of myocardial infarction. In another aspect, the present disclosure refers to the use of eicosapentaenoic acid and docosapentaenoic acid in the manufacture of a medicament for reducing risk of a cardiovascular event in a subject on statin therapy with residual atherogenic dyslipidemia and clinically evident cardiovascular disease, wherein about 2 g to about 4 g of the medicament comprises eicosapentaenoic acid and docosapentaenoic acid, wherein the medicament is to be administered to the subject per day for a period of at least about 2 years, wherein said administration reduces risk of cardiovascular death, risk of unstable angina and/or need for coronary revascularization. In a further aspect, the present disclosure refers to the use of eicosapentaenoic acid and docosapentaenoic acid in the manufacture of a medicament for reducing risk of a cardiovascular event in a subject on statin therapy with residual atherogenic dyslipidemia and clinically evident cardiovascular disease, wherein about 2 g to about 4 g of the medicament comprises eicosapentaenoic acid and docosapentaenoic acid, wherein the medicament is to be administered to the subject per day for a period of at least about 2 years, wherein said administration reduces risk of cardiovascular death, need for coronary revascularization, risk of unstable angina, risk of stroke and/or risk of myocardial infarction. In various examples, the present disclosure describes 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 invention 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, docosahexaenoic acid and docosapentaenoic acid in the manufacture of a medicament for reducing a risk of cardiovascular death and/or unstable angina in a subject on statin therapy, wherein 2 g of the medicament comprises eicosapentaenoic acid, docosahexaenoic acid and docosapentaenoic acid, wherein the medicament comprises eicosapentaenoic acid in an amount of at least 95 wt.% of all omega-3 fatty acids present, and is to be administered to the subject per day for a period of at least 2 years, wherein the subject has a fasting baseline triglyceride level of 135 mg/dL to 500 mg/dL.

2. Use of eicosapentaenoic acid, docosahexaenoic acid, and docosapentaenoic acid in the manufacture of a medicament for reducing a risk of cardiovascular death and/or unstable angina in a subject on statin therapy with established cardiovascular disease, wherein 4 g of the medicament comprises eicosapentaenoic acid, docosahexaenoic acid, and docosapentaenoic acid, wherein the medicament comprises eicosapentaenoic acid in an amount of at least 95 wt.% of all omega-3 fatty acids present, and is to be administered to the subject per day for a period of at least 2 years, wherein the subject has a fasting baseline triglyceride level of 135 mg/dL to 500 mg/dL.

3. Use of eicosapentaenoic acid, docosahexaenoic acid, and docosapentaenoic acid in the manufacture of a medicament for reducing a risk of coronary revascularization in a subject on statin therapy, wherein 2 g of the medicament comprises eicosapentaenoic acid, docosahexaenoic acid, and docosapentaenoic acid, wherein the medicament comprises eicosapentaenoic acid in an amount of at least 95 wt.% of all omega-3 fatty acids present, and is to be administered to the subject per day for a period of at least 2 years, wherein the subject has a fasting baseline triglyceride level of 135 mg/dL to 500 mg/dL.

4. Use of eicosapentaenoic acid, docosahexaenoic acid and docosapentaenoic acid in the manufacture of a medicament for reducing a risk of coronary revascularization in a subject on statin therapy with established cardiovascular disease, wherein 4 g of the medicament comprises eicosapentaenoic acid, docosahexaenoic acid, and docosapentaenoic acid, and the eicosapentaenoic acid comprises at least 95 wt.% of all

omega-3 fatty acids present, wherein the medicament is to be administered to the subject per day for a period of at least 2 years, wherein the subject has a fasting baseline triglyceride level of 135 mg/dL to 500 mg/dL.

5. Use of eicosapentaenoic acid in the manufacture of a medicament for reducing risk of a cardiovascular event in a subject on statin therapy with residual atherogenic dyslipidemia and clinically evident cardiovascular disease,wherein the medicament comprises about 4 g of eicosapentaenoic acid in triglyceride form, wherein the medicament is to be administered to the subject per day for a period of at least about 2 years, wherein said administration reduces risk of cardiovascular death, risk of unstable angina and/or need for coronary revascularization.

6. Use of eicosapentaenoic acid in the manufacture of a medicament for reducing risk of a cardiovascular event in a subject on statin therapy with residual atherogenic dyslipidemia and clinically evident cardiovascular disease, wherein the medicament comprises about 4 g of eicosapentaenoic acid in triglyceride form, wherein the medicament is to be administered to the subject per day for a period of at least about 2 years, wherein said administration reduces risk of cardiovascular death, need for coronary revascularization, risk of unstable angina, risk of stroke and/or risk of myocardial infarction.

7. Use of eicosapentaenoic acid and docosapentaenoic acid in the manufacture of a medicament for reducing risk of a cardiovascular event in a subject on statin therapy with residual atherogenic dyslipidemia and clinically evident cardiovascular disease, wherein about 2 g to about 4 g of the medicament comprises eicosapentaenoic acid and docosapentaenoic acid, wherein the medicament is to be administered to the subject per day for a period of at least about 2 years, wherein said administration reduces risk of cardiovascular death, risk of unstable angina and/or need for coronary revascularization.

8. Use of eicosapentaenoic acid and docosapentaenoic acid in the manufacture of a medicament for reducing risk of a cardiovascular event in a subject on statin therapy with residual atherogenic dyslipidemia and clinically evident cardiovascular disease, wherein about 2 g to about 4 g of the medicament comprises eicosapentaenoic acid and docosapentaenoic acid, wherein the medicament is to be administered to the subject per

day for a period of at least about 2 years, wherein said administration reduces risk of cardiovascular death, need for coronary revascularization, risk of unstable angina, risk of stroke and/or risk of myocardial infarction.

9. The use of claim 2 or 4, 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.

10. The use of any one of claims 1-8, wherein the medicament is to be administered to the subject in 1 to 4 dosage units per day.

11. The use of claim 1 or 3, wherein the medicament comprises at least 1100 mg of eicosapentaenoic acid and comprises docosapentaenoic acid in an amount up to 10% by weight of total fatty acids in the medicament.

12. The use of claim 2 or 4, wherein the medicament comprises 2200 mg of eicosapentaenoic acid and comprises docosapentaenoic acid in an amount up to 10% by weight of total fatty acids in the medicament.

13. The use of claim 5 or 6, wherein the eicosapentaenoic acid in triglyceride form comprises at least about 96 wt.% of all omega-3 fatty acids in the medicament.

14. The use of claim 7 or 8, wherein the eicosapentaenoic acid comprises at least about 90 wt. % or at least about 96 wt. % of all omega-3 fatty acids in the medicament, wherein the docosapentaenoic acid comprises less than 10 wt. %, less than 8 wt. %, or less than 5 wt. % of all omega-3 fatty acids in the medicament , and/or wherein the medicament further comprises less than 5% docosahexaenoic acid, by weight, of all omega-3 fatty acids in the medicament.

15. The use of any one of claims 1-8, further comprising the subject’s baseline lipid profile to be measured.

16. The use of any one of claims 1-8, 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.

17. The use of any one of claims 1-6, wherein the subject has: 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.

18. The use of any one of claims 1, 3, 5, 6, and 7, wherein the statin therapy comprises a statin and optionally ezetimibe to be administered to the subject.

19. The use of any one of claims 1, 3, 5, 6, 7, and 8, 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 administration of the medicament; (b) has not been administered omega-3 fatty acid prescription for a period of time beginning 28 days prior to administration of the medicament; or (c) has not ingested dietary supplements comprising omega-3 fatty acids for a period of time beginning 28 days prior to administration of the medicament.

20. The use of claim 19, wherein the period of time ends no earlier than about 6 months after a first administration of the medicament, or 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 medicament.

21. The use of any one of claims 1, 5, 6, 7, and 8, wherein the subject is to be administered 4 g of the medicament per day for at least 3 years.

22. The use of claim 1, wherein the subject is to be administered 4 g of the medicament per day for at least 4 years, or at least 5 years.

23. The use of claim 3, wherein the subject is to be administered 2 g of the medicament per day for at least 3 years, 4 years, or 5 years.

24. The use of claim 8, wherein the subject is to be administered about 3 g or about 4 g of the medicament per day for at least about 3 years.

25. The use of any one of claims 1, 2, and 5, wherein the administration further reduces the risk of myocardial infarction, the risk of stroke, or both, in the subject.

26. The use of claim 25, wherein the administration further reduces the risk of unstable angina in the subject.

27. The use of claim 1 or 2, wherein the administration further reduces the risk of coronary revascularization in the subject.

28. The use of claim 3 or 27, wherein the coronary revascularization is selected from elective coronary revascularization and emergent coronary revascularization.

29. The use of claim 3 or 4, wherein the administration further reduces the risk of myocardial infarction, stroke, unstable angina, cardiovascular death, or any combinations thereof in the subject.

30. The use of any one of claims 5-8, wherein the medicament is formulated to delay onset of a first said cardiovascular event of said subject compared with control subjects, wherein each said 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.

31. The use of claim 30, wherein the medicament is formulated to delay onset of a second said cardiovascular event of said subject compared with control subjects.

32. The use of claim 30, wherein the subject has diabetes mellitus and the control subjects each have diabetes mellitus.

33. The use of claim 30, wherein the subject has metabolic syndrome and the control subjects each have metabolic syndrome.