TITLE

COMPOSITIONS AND METHODS FOR LOWERING TRIGLYCERIDES WITHOUT RAISING LDL-C LEVELS IN A SUBJECT ON CONCOMITANT STATIN THERAPY

BACKGROUND

[0001] 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, dislipidemia, congestive heart failure and stroke.

SUMMARY

[0001a] In one aspect, the present disclosure refers to use of ethyl eicosapentaenoate in the manufacture of a medicament for preventing myocardial infarction and/or stroke in a subject on stable statin therapy, wherein: (a) the subject has previously been identified as having dyslipidemia, as being on stable statin therapy and as having a fasting baseline triglyceride level of about 200 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 (b) the medicament is formulated to be administered daily to provide about 4 g of the ethyl eicosapentaenoate per day.

[0002] In various examples, the present disclosure provides pharmaceutical compositions and methods of using such compositions to treat and/or prevent cardiovascular-related diseases. In one example, the subject is on concomitant statin therapy. In another example, the subject on statin therapy has a baseline fasting serum triglyceride level of about 200 mg/dL to about 500 mg/dL.

[0003] In one example, the disclosure provides a method of lowering triglycerides in a subject on stable statin therapy having baseline fasting triglycerides of about 200 mg/dl to about 500 mg/dl, the method comprising administering to the subject a pharmaceutical composition comprising polyunsaturated fatty acids, for example about 1 g to about 4 g of EPA per day, wherein upon administering the composition to the subject daily for a period of 12 weeks the subject exhibits at least 5% lower fasting triglycerides than a control subject maintained on stable statin therapy (optionally with placebo matching the EPA) without concomitant EPA for a period of 12 weeks wherein the control subject also has baseline fasting triglycerides of about 200 mg/dl to about 500 mg/dl. In another example, upon administering the composition to the subject daily for a period of 12 weeks the subject exhibits no serum LDL-C increase, no statistically significant serum LDL-C increase, a serum LDL-C decrease, or the subject is statistically non-inferior to the control subjects (statin plus optional placebo) in regard to serum LDL-C elevation).

[0004] These and other embodiments of the present invention will be disclosed in further detail herein below.

CLAIMS

What is claimed is:

1. Use of ethyl eicosapentaenoate in the manufacture of a medicament for preventing myocardial infarction and/or stroke in a subject on stable statin therapy, wherein:

(a) the subject has previously been identified as having dyslipidemia, as being on stable statin therapy and as having a fasting baseline triglyceride level of about 200 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

(b) the medicament is formulated to be administered daily to provide about 4 g of the ethyl eicosapentaenoate per day.

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

3. The use of claim 1, wherein the ethyl eicosapentaenoate comprises at least about 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: clinical coronary heart disease (CHD) or clinical CHD risk equivalents with a 10-year risk greater than 20%, symptomatic carotid artery disease (CD), peripheral artery disease (PAD), abdominal aortic aneurism, diabetes mellitus type 1, diabetes mellitus type 2, or combinations thereof.

5. The use of claim 1, wherein in step (a) the subject’s baseline lipid profile has previously been measured.

6. The 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 400 mg/dL; a baseline total cholesterol value of about 250 mg/dL to about 400 mg/dL; a baseline VLDL-C value of about 140 mg/dL to about 200 mg/dL; a baseline HDL-C value of not more than about 30 mg/dL; and/or a baseline LDL-C value of not less than about 40 mg/dL.

7. The use of claim 1, wherein being on stable statin therapy in step (a) means that the subject has experienced no change in statin dose for at least 4 weeks prior to step (a).

8. The use of claim 1 wherein the subject has not experienced a lipid-altering treatment, other than statin therapy, for at least 6 weeks prior to step (a).

9. The use of claim 1, wherein the medicament is formulated to be administered daily for a period of about 1 to about 40 weeks.

10. The use of claim 8, wherein the medicament is formulated to be administered daily for a period of about 6 months.

11. The use of claim 1, wherein the method prevents myocardial infarction in the subject.

12. The use of claim 1 or claim 11, wherein the method prevents stroke in the subject.

13. The use of claim 1 wherein the medicament is formulated 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; and/or (i) reducing high sensitivity C-reactive protein (hs-CRP) levels compared to baseline.

14. The use of claim 1 wherein the medicament is formulated for one or more of: (a) reducing triglyceride level by at least about 5% as compared to baseline; (b) increasing non-HDL-C levels by less than 30% as compared to baseline; (c) increasing HDL-C levels by at least about 5% as compared to baseline; and/or (d) increasing LDL-C levels by less than 30% as compared to baseline.

15. The use of claim 1, wherein the medicament is formulated to prevent myocardial infarction and/or stroke in said subject compared with control subjects, wherein each said control subject is on stable statin therapy, has a fasting baseline triglyceride level of about 200 mg/dL to about 500 mg/dL, and has established cardiovascular disease or a high risk of developing cardiovascular disease.

16. The use of claim 15, wherein the method prevents myocardial infarction in the subject compared to a risk of myocardial infarction in the control subjects.

17. The use of claim 15, wherein the method prevents stroke in the subject compared to a risk of stroke in the control subjects.

18. The use of claim 15, wherein the method prevents myocardial infarction and stroke in the subject compared to a risk of myocardial infarction and stroke in the control subjects.

19. The use of claim 15, wherein the method prevents myocardial infarction or stroke in the subject compared to a risk of myocardial infarction or stroke in the control subjects.

20. The use of claim 15, wherein the subject has diabetes mellitus and the control subjects each have diabetes mellitus.

21. The use of claim 15, wherein the subject has metabolic syndrome and the control subjects each have metabolic syndrome.

22. The use of claim 15, wherein the medicament is formulated 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; and/or (i) reducing high sensitivity C-reactive protein (hs-CRP) levels compared to the control population.

23. The use of any one of claims 1 to 22, wherein the subject has established cardiovascular disease or has a high risk of developing cardiovascular disease.

24. The use of claim 7, wherein being on stable statin therapy in step (a) means that the subject is taking ezetimibe.