METHODS OF REDUCING THE RISK OF CARDIOVASCULAR EVENTS IN A SUBJECT

PRIORITY CLAIM

[0001] This application claims priority to U.S. Provisional Application No. 62/735,670 filed on September 24, 2018, U.S. Provisional Application No. 62/735,680 filed on September 24, 2018, U.S. Provisional Application No. 62/758,387 filed on November 9, 2019, U.S. Provisional Application No. 62/813,888 filed on March 5, 2019, and U.S. Provisional Application No. 62/818,514 filed on March 14, 2019, the entire contents of each of which are incorporated herein by reference and relied upon.

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 examples, the present disclosure provides methods of treating and preventing cardiovascular diseases and disorders. In one aspect, the present disclosure refers to the use of eicosapentaenoic acid ethyl ester (E-EPA) in the manufacture of a medicament for reducing a risk of myocardial infarction, stroke, cardiovascular death, unstable angina, coronary revascularization procedures and/or unstable angina requiring hospitalization in a subject in need thereof, wherein: the subject has elevated triglyceride levels of greater than or equal to 150 mg/dL and (1) established cardiovascular disease,

or (2) diabetes and at least ~~2~~ 1 additional risk factor~~s~~ for cardiovascular disease selected from: (a) is a male age 55 or older or a female age 65 or older; (b) is a cigarette smoker or was a cigarette smoker who stopped less than 3 months prior; (c) has hypertension; (d) has an HDL-C level of ≤ 40 mg/dL for men or ≤ 50 mg/dL for women; (e) has an hsCRP level of > 3.0 mg/L; (f) has renal dysfunction; (g) has retinopathy; (h) has microalbuminuria; (i) has macroalbuminuria; and/or (j) has an ankle-brachial index (ABI) of < 0.9 without symptoms of intermittent claudication, the medicament is formulated for daily administration to provide about 4 g of E-EPA to the subject per day, and wherein, the subject is to be administered a high intensity statin regimen comprising about 40 mg to about 80 mg per day of atorvastatin or about 20 mg to about 40 mg per day of rosuvastatin. In another ~~aspect~~example, the present disclosure refers to the use of eicosapentaenoic acid ethyl ester (E-EPA) in the manufacture of a medicament for reducing a second or further cardiovascular event in a subject in need thereof, wherein: the subject has diabetes and at least one additional risk factor for cardiovascular disease, and the medicament is formulated for daily administration to provide about 4 g of E-EPA to the subject per day. In yet another ~~aspect~~example, the present disclosure refers to the use of eicosapentaenoic acid ethyl ester (E-EPA) in the manufacture of a medicament for reducing a third or further cardiovascular event in a subject in need thereof, wherein: the subject has established cardiovascular disease and has had a cardiovascular event, and the medicament is formulated for daily administration to provide about 4 g of E-EPA to the subject per day.

BRIEF DESCRIPTION OF THE DRAWINGS

[0005] Figure 1 is a schematic of the study design according to an embodiment of the present disclosure.

CLAIMS

1. Use of eicosapentaenoic acid ethyl ester (E-EPA) in the manufacture of a medicament for reducing a risk of myocardial infarction, stroke, cardiovascular death, unstable angina, coronary revascularization procedures and/or unstable angina requiring hospitalization in a subject in need thereof, wherein:

the subject has elevated triglyceride levels of greater than or equal to 150 mg/dL and (1) established cardiovascular disease, or (2) diabetes and at least 1~~2~~ additional risk factor~~s~~ for cardiovascular disease selected from: (a) is a male age 55 or older or a female age 65 or older; (b) is a cigarette smoker or was a cigarette smoker who stopped less than 3 months prior; (c) has hypertension; (d) has an HDL-C level of ≤ 40 mg/dL for men or ≤ 50 mg/dL for women; (e) has an hsCRP level of > 3.0 mg/L; (f) has renal dysfunction; (g) has retinopathy; (h) has microalbuminuria; (i) has macroalbuminuria; and/or (j) has an ankle-brachial index (ABI) of < 0.9 without symptoms of intermittent claudication,

the medicament is formulated for daily administration to provide about 4 g of E-EPA to the subject per day, and wherein,

the subject is to be administered a high intensity statin regimen comprising ~~about~~ 40 mg to ~~about~~ 80 mg per day of atorvastatin or ~~about~~ 20 mg to ~~about~~ 40 mg per day of rosuvastatin.

2. The use according to claim 1, wherein risk of occurrence of one or more components of a 3-point composite endpoint composed of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke is reduced in the subject.

3. The use according to claim 2, wherein risk of occurrence of one or more components of the 3-point composite endpoint composed of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke is reduced by at least about 20% in the subject.

4. The use according to claim 1, wherein risk of occurrence of one or more components of a 5-point composite endpoint composed of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, coronary revascularization, or unstable angina requiring hospitalization is reduced in the subject.

5. The use according to claim 4, wherein risk of occurrence of one or more components of the 5-point composite endpoint composed of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, or unstable angina requiring hospitalization is reduced by at least about 20% in the subject.

6. The use according to claim 1, wherein the subject is less than about 65 years of age.

7. The use according to claim 1, wherein the subject has a high sensitivity reactive protein (hsCRP) level of 2 mg/L or less.

8. The use according to claim 1, wherein the subject has a fasting baseline triglyceride level of at least about 200 mg/dL and a fasting baseline high density lipoprotein-C (HDL-C) level of about 35 mg/dL or less.

9. The use according to claim 1, wherein the subject has a fasting baseline triglyceride level of ~~about~~ 135 mg/dL to ~~about~~ 500 mg/dL.

10. The use according to claim 1, wherein the medicament is to be administered for at least about 2 years.

~~11. Use of eicosapentaenoic acid ethyl ester (E-EPA) in the manufacture of a medicament for reducing a second or further cardiovascular event in a subject in need thereof, wherein:~~

~~the subject has diabetes and at least one additional risk factor for cardiovascular disease, and~~

~~the medicament is formulated for daily administration to provide about 4 g of E-EPA to the subject per day.~~

~~12. Use of eicosapentaenoic acid ethyl ester (E-EPA) in the manufacture of a medicament for reducing a third or further cardiovascular event in a subject in need thereof, wherein:~~

~~the subject has established cardiovascular disease and has had a cardiovascular event, and~~

~~the medicament is formulated for daily administration to provide about 4 g of E-EPA to the subject per day.~~

13. The use according to claim 11 or 12, wherein the cardiovascular event is selected from the group consisting of cardiovascular death, myocardial infarction, stroke, coronary revascularization, and unstable angina.

14. The use according to any one of claims 11-13, wherein the subject is on statin therapy.

15. The use according to any one of claims 11-14, wherein the subject has a baseline triglyceride level of at least 135 mg/dL.

16. The use according to any one of claims 11-15, wherein the E-EPA comprises at least about 90 wt. % of all omega-3 fatty acids in the medicament.

17. The use according to any one of claims 11-15, wherein the E-EPA comprises at least about 96 wt. % of all omega-3 fatty acids in the medicament.

18. The use according to claim 17, wherein about 1 g of the medicament is present in each of 4 capsules.

19. The use according to any one of claims 11 to 18, wherein the subject is to be administered the medicament for at least 2 years.

20. The use according to claim 11, wherein the at least one additional risk factor for cardiovascular disease is selected from the group consisting of (a) a male gender of at least 55 years of age or a female gender of at least 65 years of age, (b) smokes cigarettes or has stopped smoking cigarettes within three months before administration of the medicament, (c) blood pressure of at least 140 mmHg systolic or at least 90 mmHg diastolic, (d) on antihypertensive medication, (e) a male gender with HDL-cholesterol level 40 mg/dL or less or a female gender with HDL-cholesterol level 40 mg/dL or less, (f) has a hsCRP level of greater than 3 mg/L, (g) a creatine clearance between 30 mL/min and 60 mL/min, (h) has non-proliferative retinopathy, (i) pre-proliferative retinopathy, (j) proliferative retinopathy, (k) maculopathy, (l) advanced diabetic eye disease or a history of photocoagulation, (m) micro- or macro-albuminuria, and (n) a asymptomatic ankle-brachial index of less than 0.9.

21. The use according to claim 11, wherein the subject has at least two additional risk factors for cardiovascular disease.