# METHODS OF REDUCING THE RISK OF CARDIOVASCULAR EVENTS IN A SUBJECT WITH ATRIAL FIBRILLATION AND/OR ATRIAL FLUTTER

## PRIORITY CLAIM

**[0001]** This application claims priority to U.S. Provisional Application No. 62/934,121 filed on November 12, 2019, U.S. Provisional Application No. 62/934,637 filed November 13, 2019, U.S. Provisional Application No. 62/934,952 filed November 13, 2019, U.S. Provisional Application No. 62/934,879 filed November 13, 2019, U.S. Provisional Application 62/976,683 filed February 14, 2020, U.S. Provisional Application No. 62/948,058 filed December 13, 2019, the entire contents 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 describes methods of treating and preventing cardiovascular diseases and disorders.

**[0005]** In various examples, the present disclosure describes methods of treating and preventing cardiovascular diseases and disorders. In one aspect, the present disclosure refers to use of about 4 g of eicosapentaenoic acid (EPA),

or an atrial fibrillation flutter and/or atrial flutter therapeutic agent, in the manufacture of a medicament for treating atrial fibrillation and/or atrial flutter, or for one or more cardiovascular events other than atrial fibrillation and/or atrial flutter, in a patient, wherein: (a) the patient has been determined to have a triglyceride level of at least 150 mg/dl and a history of atrial fibrillation and/or atrial flutter by: having obtained information which indicates that the patient has the triglyceride level of at least 150 mg/dl and has previously had symptoms of atrial fibrillation and/or atrial flutter and/or was previously diagnosed with atrial fibrillation and/or atrial flutter; and/or having monitored the subject for the triglyceride level of at least 150 mg/dl and for symptoms of atrial fibrillation and/or atrial flutter; and (b) if the patient had previously had symptoms of atrial fibrillation and/or atrial flutter, had previously been diagnosed with atrial fibrillation and/or atrial flutter, and/or had symptoms of atrial fibrillation and/or atrial flutter when monitored, then (i) having determined whether a risk that the patient will experience symptoms of atrial fibrillation and/or atrial flutter if the patient had been administered about 4 g of eicosapentaenoic acid (EPA) per day is greater than reducing a risk of one or more cardiovascular events in the patient, wherein the risk that the patient will experience symptoms of atrial fibrillation and/or flutter is determined based on the patient's history of atrial fibrillation and/or atrial flutter determined in step (a); or (ii) having determined whether reducing a risk of one or more cardiovascular events if the patient had been administered about 4 g of EPA per day is greater than the risk that the patient will experience symptoms of atrial fibrillation and/or atrial flutter; and (c) if the risk is greater that the patient in (i) will experience symptoms of atrial fibrillation and/or atrial flutter, an atrial fibrillation and/or atrial flutter therapeutic agent is to be administered to the patient instead of about 4 g of EPA per day; and (d) if the risk is greater that the patient in (ii) will have a reduced risk of one or more cardiovascular events, about 4 g of EPA per day is to be administered to the patient. In another aspect, the present disclosure refers to use of about 4 g of EPA, or atrial fibrillation and/or atrial flutter therapeutic agent, in the manufacture of a medicament for treating atrial fibrillation and/or atrial flutter, or for a cardiovascular event other than atrial fibrillation and/or atrial flutter, in a subject wherein: (a) it had been determined whether the subject has a triglyceride level of at least 150 mg/dl and a history of atrial fibrillation and/or atrial flutter by: (i) having obtained information which indicates that the subject has the triglyceride level of at least 150 mg/dl and has previously had symptoms of atrial fibrillation and/or atrial flutter and/or was previously diagnosed with atrial fibrillation and/or atrial flutter; and/or (ii) having monitored the subject for the triglyceride level of at least 150 mg/dl and symptoms of atrial fibrillation and/or atrial flutter; and (b) if the subject had previously had symptoms of atrial fibrillation and/or atrial flutter, had previously been diagnosed with atrial

fibrillation and/or atrial flutter, and/or symptoms of atrial fibrillation and/or atrial flutter had been determined during the monitoring, then atrial fibrillation and/or atrial flutter therapeutic agent is to be administered to the subject, and (c) if the subject had not previously had symptoms of atrial fibrillation and/or atrial flutter, had not been previously diagnosed with atrial fibrillation and/or atrial flutter, and/or symptoms of atrial fibrillation and/or atrial flutter had not been determined during the monitoring, then about 4 g of eicosapentaenoic acid (EPA) per day is to be administered the subject to reduce a risk for a cardiovascular event, wherein a risk of atrial fibrillation and/or atrial flutter for the subject in (a) is lower following administration of an atrial fibrillation and/or atrial flutter therapeutic agent than it would be if the subject in (a) were to be administered about 4 g of EPA per day. In yet another aspect, the present disclosure refers to use of about 4 g eicosapentaenoic acid (EPA) or a statin in the manufacture of a medicament for treating atrial fibrillation or atrial flutter, or cardiovascular events other than atrial fibrillation or atrial flutter, in a subject: wherein a subject has been identified whose measured triglyceride level is above 150 mg/dl and who has previously experienced symptoms of atrial fibrillation or atrial flutter; wherein individuals who had been identified as having triglyceride levels above 150 mg/dl and who had previously experienced atrial fibrillation or atrial flutter episodes are, upon treatment with 4 g eicosapentaenoic acid (EPA) per day, likely to experience both (1) increased frequency of atrial fibrillation or atrial flutter episodes, and (2) decreased frequency of cardiovascular events other than atrial fibrillation or atrial flutter; and are to be treated according to either (a) or (b) below: (a) wherein it had been determined that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so the subject is to be treated with 4 g EPA per day; or (b) wherein it had been determined that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is not worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so excluding the subject from treatment with EPA, and instead the subject is to be treated with a statin. In a further aspect, the present disclosure refers to use of 4 g eicosapentaenoic acid (EPA) and/or a statin in the manufacture of a medicament for treating atrial fibrillation or atrial flutter, or cardiovascular events other than atrial fibrillation or atrial flutter, in a subject: wherein a subject has been identified whose measured triglyceride level is above 150 mg/dl, who is being treated with a statin, and who has previously experienced symptoms of atrial fibrillation or atrial flutter; wherein individuals who had been identified as having triglyceride levels above 150 mg/dl, who had been treated with a statin, and who had previously experienced atrial fibrillation or atrial flutter episodes are, upon treatment with 4 g eicosapentaenoic acid

(EPA) per day, likely to experience both (1) increased frequency of atrial fibrillation or atrial flutter episodes, and (2) decreased frequency of cardiovascular events other than atrial fibrillation or atrial flutter; and are to be treated according to either (a) or (b) below: (a) wherein it had been determined that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so the subject is to be treated with 4 g EPA per day and a statin; or (b) wherein it had been determined that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is not worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so excluding the subject from treatment with EPA, and instead the subject is to continue being treated with a statin. In one aspect, the present disclosure refers to use of 4 g eicosapentaenoic acid (EPA) or a statin in the manufacture of a medicament for treating atrial fibrillation or atrial flutter, or cardiovascular events other than atrial fibrillation or atrial flutter, in a subject: Wherein a subject has been identified whose measured triglyceride level is above 150 mg/dl who is being treated with a statin, and who has a previous history of atrial fibrillation or atrial flutter; wherein individuals who had been determined to have triglyceride levels above 150 mg/dl, who are being treated with a statin, and who have a previous history of atrial fibrillation or atrial flutter are, upon treatment with 4 g eicosapentaenoic acid (EPA) per day, are likely to experience both (1) increased frequency of atrial fibrillation or atrial flutter episodes, and (2) cardiovascular benefits expected to result from the EPA treatment; and are to be treated according to either (a) or (b) below: (a) wherein it had been determined that the expected cardiovascular benefits are worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so the subject is to be treated with 4 g EPA per day; or (b) wherein it had been determined that the expected cardiovascular benefits are not worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so excluding the subject from treatment with EPA, and instead the subject is to be treated with a statin. In another aspect, the present disclosure refers to use of at least about 4 g of eicosapentaenoic acid (EPA) in the manufacture of a medicament for reducing a risk of a cardiovascular event in a subject having triglyceride levels of at least 150 mg/dl and less than 65 years of age, wherein the subject is to be administered at least 4 g of eicosapentaenoic acid (EPA) per day for a period of time effective to reduce the cardiovascular event, wherein the subject does not exhibit an increase in symptoms atrial fibrillation and/or atrial flutter.

**[0006]** In one example, there are disclosed methods for treating a patient comprising: determining or having determined whether the patient has a triglyceride level of at least 150 mg/dl and a history of atrial fibrillation and/or atrial flutter by: obtaining or having obtained information which indicates that the patient has the triglyceride level of at least 150 mg/dl and has previously had symptoms of atrial fibrillation and/or atrial flutter and/or was previously diagnosed with atrial fibrillation and/or atrial flutter; and/or monitoring or having monitored the subject for the triglyceride level of at least 150 mg/dl and for symptoms of atrial fibrillation and/or atrial flutter; and (a) if the patient has previously had symptoms of atrial fibrillation and/or atrial flutter, was previously diagnosed with atrial fibrillation and/or atrial flutter, and/or had symptoms of atrial fibrillation and/or atrial flutter when monitored, then (i) determining whether a risk that the patient will experience symptoms of atrial fibrillation and/or atrial flutter if the patient were administered about 4 g of eicosapentaenoic acid (EPA) per day is greater than reducing a risk of one or more cardiovascular events in the patient; or (ii) determining whether reducing a risk of one or more cardiovascular events if the patient were administered about 4 g of EPA per day is greater than a risk that the patient will experience symptoms of atrial fibrillation and/or atrial flutter; and (b) if the risk is greater that the patient in (i) will experience symptoms of atrial fibrillation and/or atrial flutter, administering an atrial fibrillation flutter and/or atrial flutter therapeutic agent to the patient instead of about 4 g of EPA per day; and (c) if the risk is greater that the patient in (ii) will have a reduced risk of one or more cardiovascular events, administering about 4 g of EPA per day to the patient.

**[0007]** In some examples, the subject in (c) is likely to experience both (1) increased frequency of atrial fibrillation and/or atrial flutter symptoms, and (2) decreased frequency of cardiovascular events if administered about 4 g of EPA per day. In some examples, the subject is being treated with a statin and regardless if the subject is in (a) or (b), continuing to treat the subject with the statin.

**[0008]** In another example, there are described methods for treating a subject comprising: determining or having determined whether the subject has a triglyceride level of at least 150 mg/dl and a history of atrial fibrillation and/or atrial flutter by: (i) obtaining or having obtained information which indicates that the subject has the triglyceride level of at least 150 mg/dl and has previously had symptoms of atrial fibrillation and/or atrial flutter and/or was previously diagnosed with atrial fibrillation and/or

atrial flutter; and/or (ii) monitoring or having monitored the subject for the triglyceride level of at least 150 mg/dl and symptoms of atrial fibrillation and/or atrial flutter; and (a) if the subject has previously had symptoms of atrial fibrillation and/or atrial flutter, was previously diagnosed with atrial fibrillation and/or atrial flutter, and/or symptoms of atrial fibrillation and/or atrial flutter were determined during the monitoring, then administering atrial fibrillation and/or atrial flutter therapeutic agent to the subject, and (b) if the subject has not previously had symptoms of atrial fibrillation and/or atrial flutter, was not previously diagnosed with atrial fibrillation and/or atrial flutter, and/or symptoms of atrial fibrillation and/or atrial flutter were not determined during the monitoring, then administering about 4 g of eicosapentaenoic acid (EPA) per day to the subject to reduce a risk for a cardiovascular event, wherein a risk of atrial fibrillation and/or atrial flutter for the subject in (a) is lower following administration of an atrial fibrillation flutter and/or atrial flutter therapeutic agent than it would be if the subject in (a) were administered about 4 g of EPA per day.

**[0009]** In some examples, the subject in (a) is likely to experience both (1) increased frequency of atrial fibrillation and/or atrial flutter symptoms, and (2) decreased frequency of cardiovascular events if administered about 4 g of EPA per day. In some examples, the subject is being treated with a statin and regardless if the subject is in (a) or (b), continuing to treat the subject with the statin.

**[0010]** In another example, there are disclosed methods of treatment comprising: identifying a subject whose measured triglyceride level is above 150 mg/dl and who has previously experienced symptoms of atrial fibrillation or atrial flutter; determining that individuals who have triglyceride levels above 150 mg/dl and who have previously experienced atrial fibrillation or atrial flutter episodes are, upon treatment with 4 g eicosapentaenoic acid (EPA) per day, likely to experience both (1) increased frequency of atrial fibrillation or atrial flutter episodes, and (2) decreased frequency of cardiovascular events other than atrial fibrillation or atrial flutter; and selecting a treatment according to either (a) or (b): (a) determining that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so treating the subject with 4 g EPA per day; or (b) determining that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is not worth a risk of

increased frequency of atrial fibrillation or atrial flutter in the subject, and so excluding the subject from treatment with EPA, and instead treating the subject with a statin.

**[0011]** In some examples, there are described methods of treatment comprising: identifying a subject whose measured triglyceride level is above 150 mg/dl, who is being treated with a statin, and who has previously experienced symptoms of atrial fibrillation or atrial flutter; determining that individuals who have triglyceride levels above 150 mg/dl, who are being treated with a statin, and who have previously experienced atrial fibrillation or atrial flutter episodes are, upon treatment with 4 g eicosapentaenoic acid (EPA) per day, likely to experience both (1) increased frequency of atrial fibrillation or atrial flutter episodes, and (2) decreased frequency of cardiovascular events other than atrial fibrillation or atrial flutter; and selecting a treatment according to either (a) or (b): (a) determining that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so treating the subject with 4 g EPA per day and a statin; or (b) determining that decreasing a subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is not worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so excluding the subject from treatment with EPA, and instead continuing to treat the subject with a statin.

**[0012]** In yet another example, there are described methods of treatment comprising: identifying a subject whose measured triglyceride level is above 150 mg/dl who is being treated with a statin, and who has a previous history of atrial fibrillation or atrial flutter; determining that individuals who have triglyceride levels above 150 mg/dl, who are being treated with a statin, and who have a previous history of atrial fibrillation or atrial flutter are, upon treatment with 4 g eicosapentaenoic acid (EPA) per day, likely to experience both (1) increased frequency of atrial fibrillation or atrial flutter episodes, and (2) cardiovascular benefits expected to result from the EPA treatment; and selecting a treatment according to either (a) or (b) below: (a) determining that the expected cardiovascular benefits are worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so treating the subject with 4 g EPA per day; or (b) determining that the expected cardiovascular benefits are not worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so excluding the subject from treatment with EPA, and instead treating the subject with a statin.

**[0013]** In another examples, there are described methods of reducing a risk of a cardiovascular event in a subject having triglyceride levels of at least about 150 mg/dl, the method comprising administering to the subject at least about 4 g of eicosapentaenoic acid (EPA) per day for a period of time effective to reduce the cardiovascular event, wherein the subject develops atrial fibrillation and/or atrial flutter during the period of time effective to reduce the risk of the cardiovascular event.

**[0014]** In some examples, there are described methods of reducing a risk of a cardiovascular event in a subject having triglyceride levels of at least about 150 mg/dl and less than 65 years of age, the method comprising administering to the subject at least about 4 g of eicosapentaenoic acid (EPA) per day for a period of time effective to reduce the cardiovascular event, wherein the subject does not exhibit an increase in symptoms atrial fibrillation and/or atrial flutter.

**[0015]** In some examples, the atrial fibrillation flutter and/or atrial flutter therapeutic agent is one or more of warfarin, beta blocker, calcium channel blocker. In some examples, the warfarin is administered at a dose of about 25 mg per day.

**[0016]** In some examples, reducing the risk for the cardiovascular event for the subject further comprises determining that one or more cardiovascular benefits are expected to occur. In some examples, the cardiovascular event does not include atrial fibrillation and/or atrial flutter.

**[0017]** In some examples, the subject did does have a history of atrial fibrillation and/or flutter prior to administration of the 4 g of EPA. In some examples, the subject has established cardiovascular disease. In some examples, 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. In some examples, the subject does not have an established cardiovascular disease but at least two risk factors for cardiovascular disease.

**[0018]** In some examples, the EPA is administered to the subject in 1 to 4 dosage units per day. In some examples, the subject is administered the EPA for at least about 4 months, at least about 1 year, at least about 2 years, at least about 3 years, at least about 4 years, or at least about 5 years.

**[0019]** In some examples, 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

CLAIMS

1. Use of about 4 g of eicosapentaenoic acid (EPA), or an atrial fibrillation flutter and/or atrial flutter therapeutic agent, in the manufacture of a medicament for treating atrial fibrillation and/or atrial flutter, or for one or more cardiovascular events other than atrial fibrillation and/or atrial flutter, in a patient, wherein:

(a) the patient has been determined to have a triglyceride level of at least 150 mg/dl and a history of atrial fibrillation and/or atrial flutter by:

having obtained information which indicates that the patient has the triglyceride level of at least 150 mg/dl and has previously had symptoms of atrial fibrillation and/or atrial flutter and/or was previously diagnosed with atrial fibrillation and/or atrial flutter; and/or

having monitored the subject for the triglyceride level of at least 150 mg/dl and for symptoms of atrial fibrillation and/or atrial flutter; and

(b) if the patient had previously had symptoms of atrial fibrillation and/or atrial flutter, had previously been diagnosed with atrial fibrillation and/or atrial flutter, and/or had symptoms of atrial fibrillation and/or atrial flutter when monitored, then

(i) having determined whether a risk that the patient will experience symptoms of atrial fibrillation and/or atrial flutter if the patient had been administered about 4 g of eicosapentaenoic acid (EPA) per day is greater than reducing a risk of one or more cardiovascular events in the patient, wherein the risk that the patient will experience symptoms of atrial fibrillation and/or flutter is determined based on the patient's history of atrial fibrillation and/or atrial flutter determined in step (a); or

(ii) having determined whether reducing a risk of one or more cardiovascular events if the patient had been administered about 4 g of EPA per day is greater than the risk that the patient will experience symptoms of atrial fibrillation and/or atrial flutter; and

(c) if the risk is greater that the patient in (i) will experience symptoms of atrial fibrillation and/or atrial flutter, an atrial fibrillation and/or atrial flutter therapeutic agent is to be administered to the patient instead of about 4 g of EPA per day; and

(d) if the risk is greater that the patient in (ii) will have a reduced risk of one or more cardiovascular events, about 4 g of EPA per day is to be administered to the patient.

2. The use of claim 1, wherein the subject in (d) is likely to experience both (1) increased frequency of atrial fibrillation and/or atrial flutter symptoms, and (2) decreased frequency of cardiovascular events if the subject is to be administered about 4 g of EPA per day.

3. The use of claim 1, wherein the subject had been treated with a statin and regardless if the subject is in (c) or (d), the subject continues to be treated with the statin.

4. Use of about 4 g of EPA, or atrial fibrillation and/or atrial flutter therapeutic agent, in the manufacture of a medicament for treating atrial fibrillation and/or atrial flutter, or for a cardiovascular event other than atrial fibrillation and/or atrial flutter, in a subject wherein:

(a) it had been determined whether the subject has a triglyceride level of at least 150 mg/dl and a history of atrial fibrillation and/or atrial flutter by:

(i) having obtained information which indicates that the subject has the triglyceride level of at least 150 mg/dl and has previously had symptoms of atrial fibrillation and/or atrial flutter and/or was previously diagnosed with atrial fibrillation and/or atrial flutter; and/or

(ii) having monitored the subject for the triglyceride level of at least 150 mg/dl and symptoms of atrial fibrillation and/or atrial flutter; and

(b) if the subject had previously had symptoms of atrial fibrillation and/or atrial flutter, had previously been diagnosed with atrial fibrillation and/or atrial flutter, and/or symptoms of

atrial fibrillation and/or atrial flutter had been determined during the monitoring, then atrial fibrillation and/or atrial flutter therapeutic agent is to be administered to the subject, and

(c) if the subject had not previously had symptoms of atrial fibrillation and/or atrial flutter, had not been previously diagnosed with atrial fibrillation and/or atrial flutter, and/or symptoms of atrial fibrillation and/or atrial flutter had not been determined during the monitoring, then about 4 g of eicosapentaenoic acid (EPA) per day is to be administered the subject to reduce a risk for a cardiovascular event,

wherein a risk of atrial fibrillation and/or atrial flutter for the subject in (a) is lower following administration of an atrial fibrillation and/or atrial flutter therapeutic agent than it would be if the subject in (a) were to be administered about 4 g of EPA per day.

5. The use of claim 4, wherein the subject in (a) is likely to experience both (1) increased frequency of atrial fibrillation and/or atrial flutter symptoms, and (2) decreased frequency of cardiovascular events if about 4 g of EPA per day is to be administered.

6. The use of claim 4, wherein the subject had been treated with a statin and regardless if the subject is in (a) or (b), the subject continues to be treated with the statin.

7. The use of any one of claims 1 to 6, wherein the atrial fibrillation and/or atrial flutter therapeutic agent is one or more of warfarin, beta blocker, calcium channel blocker.

8. The use of claim 7, wherein the warfarin is to be administered at a dose of about 25 mg per day.

9. The use of any one of claims 1 to 8, wherein reducing the risk for the cardiovascular event for the subject further comprises determining that one or more cardiovascular benefits are expected to occur.

10. Use of about 4 g eicosapentaenoic acid (EPA) or a statin in the manufacture of a medicament for treating atrial fibrillation or atrial flutter, or cardiovascular events other than atrial fibrillation or atrial flutter, in a subject:

wherein a subject has been identified whose measured triglyceride level is above 150 mg/dl and who has previously experienced symptoms of atrial fibrillation or atrial flutter;

wherein individuals who had been identified as having triglyceride levels above 150 mg/dl and who had previously experienced atrial fibrillation or atrial flutter episodes are, upon treatment with 4 g eicosapentaenoic acid (EPA) per day, likely to experience both (1) increased frequency of atrial fibrillation or atrial flutter episodes, and (2) decreased frequency of cardiovascular events other than atrial fibrillation or atrial flutter; and

are to be treated according to either (a) or (b) below:

(a) wherein it had been determined that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so the subject is to be treated with 4 g EPA per day; or

(b) wherein it had been determined that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is not worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so excluding the subject from treatment with EPA, and instead the subject is to be treated with a statin.

11. Use of 4 g eicosapentaenoic acid (EPA) and/or a statin in the manufacture of a medicament for treating atrial fibrillation or atrial flutter, or cardiovascular events other than atrial fibrillation or atrial flutter, in a subject:

wherein a subject has been identified whose measured triglyceride level is above 150 mg/dl, who is being treated with a statin, and who has previously experienced symptoms of atrial fibrillation or atrial flutter;

wherein individuals who had been identified as having triglyceride levels above 150 mg/dl, who had been treated with a statin, and who had previously experienced atrial fibrillation or atrial flutter episodes are, upon treatment with 4 g eicosapentaenoic acid (EPA) per day, likely to experience both (1) increased frequency of atrial fibrillation or atrial flutter episodes, and (2) decreased frequency of cardiovascular events other than atrial fibrillation or atrial flutter; and

are to be treated according to either (a) or (b) below:

(a) wherein it had been determined that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so the subject is to be treated with 4 g EPA per day and a statin; or

(b) wherein it had been determined that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is not worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so excluding the subject from treatment with EPA, and instead the subject is to continue being treated with a statin.

12. Use of 4 g eicosapentaenoic acid (EPA) or a statin in the manufacture of a medicament for treating atrial fibrillation or atrial flutter, or cardiovascular events other than atrial fibrillation or atrial flutter, in a subject:

Wherein a subject has been identified whose measured triglyceride level is above 150 mg/dl who is being treated with a statin, and who has a previous history of atrial fibrillation or atrial flutter;

wherein individuals who had been determined to have triglyceride levels above 150 mg/dl, who are being treated with a statin, and who have a previous history of atrial fibrillation or atrial flutter are, upon treatment with 4 g eicosapentaenoic acid (EPA) per day, are likely

to experience both (1) increased frequency of atrial fibrillation or atrial flutter episodes, and (2) cardiovascular benefits expected to result from the EPA treatment; and

are to be treated according to either (a) or (b) below:

(a) wherein it had been determined that the expected cardiovascular benefits are worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so the subject is to be treated with 4 g EPA per day; or

(b) wherein it had been determined that the expected cardiovascular benefits are not worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so excluding the subject from treatment with EPA, and instead the subject is to be treated with a statin.

13. Use of at least about 4 g of eicosapentaenoic acid (EPA) in the manufacture of a medicament for reducing a risk of a cardiovascular event in a subject having triglyceride levels of at least 150 mg/dl and less than 65 years of age, wherein the subject is to be administered at least 4 g of eicosapentaenoic acid (EPA) per day for a period of time effective to reduce the cardiovascular event, wherein the subject does not exhibit an increase in symptoms atrial fibrillation and/or atrial flutter.

14. The use of any one of claims 1 to 13, wherein the subject has established cardiovascular disease.

15. The use of claim 14, 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.

16. The use of any one of claims 1 to 15, wherein the subject does not have an established cardiovascular disease but at least two risk factors for cardiovascular disease.

17. The use of any one of claims 1 to 16, wherein the EPA is to be administered to the subject in 1 to 4 dosage units per day.

18. The use of any one of claims 1 to 17, 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.

19. The use of any one of claims 1 to 18, wherein the subject is to be administered the EPA for at least 4 months, at least 1 year, at least 2 years, at least 3 years, at least 4 years, or at least 5 years.