

SUMMARY

[0004a] In one aspect, the present disclosure refers to the use of a PCSK9 inhibitor therapy in the manufacture of a pharmaceutical for treating coronary atherosclerosis, wherein the use comprises that a second therapy is to be administered to a subject that is on a first therapy, wherein the first therapy comprises a non-PCSK9 LDL-C lowering therapy, wherein the second therapy comprises the PCSK9 inhibitor therapy, wherein both the first and second therapies are to be administered to the subject in an amount and time sufficient to reverse coronary atherosclerosis in the subject, and wherein the first therapy is not the same as the second therapy.

[0004b] In another aspect, the present disclosure refers to the use of an anti-PCSK9 neutralizing antibody in the manufacture of a pharmaceutical for treating coronary atherosclerosis, wherein the use comprises that the anti-PCSK9 neutralizing antibody is to be administered to a subject that has a LDL-C level of less than 70 mg/dL, in an amount sufficient and time sufficient to lower the LDL-C level to less than 60 mg/dL.

[0004c] In another aspect, the present disclosure refers to the use of an anti-PCSK9 neutralizing antibody in the manufacture of a pharmaceutical for decreasing percent atheroma volume (PAV) in a subject, wherein the use comprises that the anti-PCSK9 neutralizing antibody is to be administered to a subject that has received at least a moderate level of treatment by a statin, in an amount sufficient and time sufficient to lower the LDL-C level to less than 90 mg/dL, thereby decreasing a percent atheroma volume (PAV) in the subject.

[0004d] In another aspect, the present disclosure refers to the use of an anti-PCSK9 neutralizing antibody in the manufacture of a pharmaceutical for decreasing total atheroma volume (TAV) in a subject, wherein the use comprises that the anti-PCSK9 neutralizing antibody is to be administered to a subject that has received at least a moderate level of treatment by a statin, in an amount sufficient and time sufficient to lower the LDL-C level to less than 90 mg/dL, thereby decreasing a total atheroma volume in the subject.

[0004e] In another aspect, the present disclosure refers to the use of a low dose statin treatment in combination with an anti-PCSK9 neutralizing antibody in the manufacture of a pharmaceutical for treating coronary atherosclerosis, wherein the use comprises: a. that at least the low dose statin treatment is to be administered to a statin-intolerant subject; and b.

that the amount of an anti-PCSK9 neutralizing antibody is to be administered to the subject, thereby treating coronary atherosclerosis; wherein the low dose statin treatment and the anti-PCSK9 neutralizing antibody are to be administered together or separately.

[0004f] In yet another aspect, the present disclosure refers to the use of a monoclonal antibody to human PCSK9 in the manufacture of a pharmaceutical for reducing an amount of atherosclerotic plaque in a subject, wherein the use comprises that the monoclonal antibody to human PCSK9 is to be administered to the subject having atherosclerotic plaque, wherein the subject is receiving optimized statin therapy, thereby reducing the amount of atherosclerotic plaque in the subject.

[0004g] In yet another aspect, the present disclosure refers to the use of evolocumab in combination with a statin therapy in the manufacture of a pharmaceutical for producing greater LDL-C lowering and regression of coronary atherosclerosis at a dose that is well tolerated, wherein the use comprises: that at least a moderate intensity of the statin therapy is to be administered to a subject; that an adequate amount of evolocumab is to be administered to the subject such that the subject's LDL-C levels drop to no more than 40 mg/dL; and that the subject's LDL-C levels is to be maintained at no more than 40 mg/dL for at least one year; wherein evolocumab and the statin therapy are to be administered together or separately.

[0004h] In yet another aspect, the present disclosure refers to the use of a PCSK9 inhibitor in the manufacture of a pharmaceutical for treating coronary atherosclerosis, wherein the use comprises that the PCSK9 inhibitor is to be administered to a subject that has a LDL-C level of less than 70 mg/dL, in an amount sufficient and time sufficient to lower the LDL-C level to less than 60 mg/dL.

[0004i] In yet another aspect, the present disclosure refers to the use of a PCSK9 inhibitor in the manufacture of a pharmaceutical for decreasing percent atheroma volume (PAV) in a subject, wherein the use comprises that the PCSK9 inhibitor is to be administered to a subject that has received at least a moderate level of treatment by a non-PCSK9 LDL-C lowering agent, in an amount sufficient and time sufficient to lower the LDL-C level to less than 90 mg/dL, thereby decreasing a percent atheroma volume (PAV) in the subject.

[0004j] In yet another aspect, the present disclosure refers to the use of a PCSK9 inhibitor in the manufacture of a pharmaceutical for decreasing total atheroma volume (TAV) in a subject, wherein the use comprises that the PCSK9 inhibitor is to be administered to a subject that has received at least a moderate level of treatment by a non-PCSK9 LDL-C lowering agent, in an amount sufficient and time sufficient to lower the LDL-C level to less than 90 mg/dL, thereby decreasing a total atheroma volume in the subject.

[0004k] In yet another aspect, the present disclosure refers to the use of a non-PCSK9 LDL-C lowering therapy in combination with a PCSK9 inhibitor in the manufacture of pharmaceutical for reducing disease progression, wherein the use comprises that at least a moderate intensity of the non-PCSK9 LDL-C lowering therapy is to be administered to a subject with a LDL-C level of no more than 60 mg/dL; and that the PCSK9 inhibitor is to be administered at a level sufficient to decrease the LDL-C level of the subject to 30 mg/dL, thereby reducing disease progression; wherein the non-PCSK9 LDL-C lowering therapy and the PCSK9 inhibitor are to be administered together or separately.

[0004l] In yet another aspect, the present disclosure refers to the use of a PCSK9 inhibitor therapy in combination with a non-PCSK9 LDL-C lowering therapy in the manufacture of a pharmaceutical for producing greater LDL-C lowering and regression of coronary atherosclerosis at a dose that is well tolerated, wherein the use comprises: that at least a moderate intensity of the non-PCSK9 LDL-C lowering therapy is to be administered to a subject; that an adequate amount of the PCSK9 inhibitor is to be administered to the subject such that the subject's LDL-C levels drop to no more than 40 mg/dL; and that the subject's LDL-C levels is to be maintained at no more than 40 mg/dL for at least one year; wherein the PCSK9 inhibitor therapy and the non-PCSK9 LDL-C lowering therapy are to be administered together or separately.

[0004m] In yet another aspect, the present disclosure refers to the use of a PCSK9 inhibitor in the manufacture of a pharmaceutical for reducing a risk of a cardiovascular event, wherein the use comprises that a second therapy is to be administered to a subject that is on a first therapy, wherein the first therapy comprises a non-PCSK9 LDL-C lowering therapy, wherein the second therapy comprises the PCSK9 inhibitor, wherein both the first and second therapies are to be administered to the subject in an amount and time sufficient to reduce a risk of a cardiovascular event in the subject, and wherein the first

therapy is not the same as the second therapy, and wherein the risk is a) a composite for cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization or b) a composite for cardiovascular death, myocardial infarction, or stroke.

[0004n] In yet another aspect, the present disclosure refers to the use of a PCSK9 inhibitor in the manufacture of a pharmaceutical for reducing a risk of a cardiovascular event, wherein the use comprises that a second therapy is to be administered to a subject that is on a first therapy, wherein the first therapy comprises a non-PCSK9 LDL-C lowering therapy, wherein the second therapy comprises the PCSK9 inhibitor, wherein both the first and second therapies are to be administered to the subject in an amount and time sufficient to reduce a risk of a cardiovascular event in the subject, and wherein the first therapy is not the same as the second therapy, and wherein the risk is the composite of fatal MI and/or non-fatal MI and fatal and/or non-fatal coronary revascularization.

[0004o] In yet another aspect, the present disclosure refers to the use of a non-statin LDL-C lowering agent in combination with a statin in the manufacture of a pharmaceutical for reducing a risk of a major adverse limb event ("MALE"), wherein the use comprises: that the non-statin LDL-C lowering agent is to be administered to a subject; and that the statin is to be administered to the subject, wherein the subject has peripheral artery disease ("PAD"); wherein the non-statin LDL-C lowering agent and the statin are to be administered together or separately.

[0004p] In yet another aspect, the present disclosure refers to the use of a non-statin LDL-C lowering agent in combination with a statin in the manufacture of a pharmaceutical for reducing a risk of a major cardiovascular adverse event ("MACE"), wherein the use comprises: that the non-statin LDL-C lowering agent is to be administered to a subject; and that the statin is to be administered to the subject, wherein the subject has PAD; wherein the non-statin LDL-C lowering agent and the statin are to be administered together or separately.

[0004q] In yet another aspect, the present disclosure refers to the use of a non-PCSK9 LDL-C lowering therapy in combination with a PCSK9 inhibitor in the manufacture of a pharmaceutical for reducing a risk of a cardiovascular event, wherein the use comprises:

that a first therapy is to be provided to a subject, wherein the first therapy comprises the non-PCSK9 LDL-C lowering therapy; and that a second therapy is to be provided to the subject, wherein the second therapy comprises the PCSK9 inhibitor, wherein both the first and second therapies are to be administered to the subject, and wherein the subject has a Lp(a) level of 11.8 mg/dL to 50; wherein the non-PCSK9 LDL-C lowering therapy and the PCSK9 inhibitor are to be administered together or separately.

[0004r] In yet another aspect, the present disclosure refers to the use of a non-PCSK9 LDL-C lowering therapy in combination with a PCSK9 inhibitor in the manufacture of a pharmaceutical for reducing a risk of a major vascular event in a subject, wherein the use comprises: 1) that a first therapy is to be provided to a subject that has at least one of: (a) a recent MI, (b) multiple prior MIs, or (c) multivessel disease, wherein the first therapy comprises the non-PCSK9 LDL-C lowering therapy; and 2) that a second therapy is to be provided to the subject, wherein the second therapy comprises the PCSK9 inhibitor, thereby reducing a risk that the subject will have a major vascular event; wherein the non-PCSK9 LDL-C lowering therapy and the PCSK9 inhibitor are to be administered together or separately.

[0004s] In yet another aspect, the present disclosure refers to the use of a PCSK9 inhibitor in the manufacture of a pharmaceutical for reducing a risk of a cardiovascular event, wherein the use comprises that the PCSK9 inhibitor is to be administered to a subject that has a LDL-C level of greater than 70 mg/dL in an amount sufficient and time sufficient to lower the LDL-C level to less than 40 mg/dL.

[0005] In some examples, a method of treating coronary atherosclerosis is provided. The method comprises a) identifying a subject that is on a first therapy, wherein the first therapy comprises a non-PCSK9 LDL-C lowering therapy, and b) administering a second therapy to the subject. The second therapy comprises a PCSK9 inhibitor therapy. Both the first and second therapies are administered to the subject in an amount and time sufficient to reverse coronary atherosclerosis in the subject, and the first therapy is not the same as the second therapy.

[0006] In some examples, the first therapy is selected from at least one of: a statin, including but not limited to atorvastatin (LIPITOR®), cerivastatin, fluvastatin (LESCOL), lovastatin (MEVACOR, ALTOPREV), mevastatin, pitavastatin, pravastatin

(PRAVACHOL), rosuvastatin, rosuvastatin calcium (CRESTOR) and simvastatin (ZOCOR); ADVICOR (lovastatin + niacin), CADUET (atorvastatin + amlodipine); a selective cholesterol absorption inhibitor, including but not limited to ezetimibe (ZETIA); a Lipid Lowering Therapy (LLT) including but not limited to fibrates or fibric acid derivatives, including but not limited to gemfibrozil (LOPID), fenofibrate (ANTARA, LOFIBRA, TRICOR, TRIGLIDE) and clofibrate (ATROMID-S); a Resin including but not limited to cholestyramine (QUESTRAN, QUESTRAN LIGHT, PREVALITE, LOCHOLEST, LOCHOLEST LIGHT), cholestipol (CHOLESTID) and cholesevelan HCl (WELCHOL) and/or a combination thereof, including but not limited to VYTORIN (simvastatin + ezetimibe).

[0007] In some examples, a method of treating coronary atherosclerosis is provided. The method comprises a) identifying a subject that has a LDL-C level of less than 70 mg/dL, and b) administering an anti-PCSK9 neutralizing antibody to the subject, in an amount sufficient and time sufficient to lower the LDL-C level to less than 60 mg/dL.

[0008] In some examples, a method of decreasing percent atheroma volume (PAV) in a subject is provided. The method comprises a) identifying a subject that has received at least a moderate level of treatment by a statin, and b) administering an anti-PCSK9 neutralizing antibody to the subject in an amount sufficient and time sufficient to lower the LDL-C level to less than 100, e.g., less than 90 mg/dL, thereby decreasing a percent atheroma volume (PAV) in the subject.

[0009] In some examples, a method of decreasing total atheroma volume (TAV) in a subject is provided. The method comprises a) identifying a subject that has received at least a moderate level of treatment by a statin, and b) administering an anti-PCSK9 neutralizing antibody to the subject in an amount sufficient and time sufficient to lower the LDL-C level to less than 100, e.g., less than 90 mg/dL, thereby decreasing a total atheroma volume in the subject.

[0010] In some examples, a method of treating coronary atherosclerosis is provided. The method comprises a) administering an optimum statin treatment to a subject, wherein the subject has coronary atherosclerosis, and b) administering an amount of an anti-PCSK9 neutralizing antibody to the subject at the same time.

[0011] In some examples, a method of treating coronary atherosclerosis is provided. The method comprises a) identifying a statin-intolerant subject, b) administering at least a low dose statin treatment to the statin-intolerant subject, and c) administering an amount of an anti-PCSK9 neutralizing antibody to the subject, thereby treating coronary atherosclerosis.

[0012] In some examples, a method of providing regression of coronary atherosclerosis is provided, the method comprises providing a subject that is on an optimized level of a statin, and administering to the subject an anti-PCSK9 neutralizing antibody, at a level adequate to regress coronary atherosclerosis, wherein regression is any change in PAV or TAV less than zero.

[0013] In some examples, a method of decreasing a LDL-C level in a subject beneath 80 mg/dL is provided. The method comprises administering an anti-PCSK9 neutralizing antibody to a subject. The subject has coronary atherosclerotic disease. The subject is on an optimized statin therapy for at least one year, and a LDL-C level in the subject decreases to an average value that is beneath 80 mg/dL for the at least one year.

[0014] In some examples, a method of reducing a relative risk of a cardiovascular event by at least 10% is provided. The method comprises administering a PCSK9 neutralizing antibody to a subject that is on at least a moderate intensity of a statin, in an amount sufficient to lower a LDL-C level of the subject by about 20 mg/dL.

[0015] In some examples, a method of reducing an amount of atherosclerotic plaque in a subject is provided. The method comprises administering to a subject having atherosclerotic plaque a monoclonal antibody to human PCSK9. The subject is also receiving optimized statin therapy, and the combination therapy thereby reduces the amount of atherosclerotic plaque in the subject.

[0016] In some examples, a method of reducing disease progression is provided. The method comprises identifying a subject with a LDL-C level of no more than 60 mg/dL, administering at least a moderate intensity of a statin therapy to the subject, and administering evolocumab at a level sufficient to decrease the LDL-C level of the subject to 30 mg/dL, thereby reducing disease progression.

[0017] In some examples, a method of combining evolocumab and a statin therapy to produce greater LDL-C lowering and regression of coronary atherosclerosis at a

dose that is well tolerated is provided. The method comprises administering at least a moderate intensity of a statin therapy to a subject, administering an adequate amount of evolocumab to the subject such that the subject's LDL-C levels drop to no more than 40 mg/dL, and maintaining the subject's LDL-C levels at no more than 40 mg/dL for at least one year.

[0018] In some examples, a method of treating coronary atherosclerosis is provided. The method comprises a) identifying a subject that has a LDL-C level of less than 70 mg/dL, and b) administering a PCSK9 inhibitor to the subject, in an amount sufficient and time sufficient to lower the LDL-C level to less than 60 mg/dL.

[0019] In some examples, a method of decreasing percent atheroma volume (PAV) in a subject is provided. The method comprises a) identifying a subject that has received at least a moderate level of treatment by a non-PCSK9 LDL-C lowering agent, and b) administering a PCSK9 inhibitor to the subject in an amount sufficient and time sufficient to lower the LDL-C level to less than 100 mg/dL, e.g., less than 90 mg/dL, thereby decreasing a percent atheroma volume (PAV) in the subject.

[0020] In some examples, a method of decreasing total atheroma volume (TAV) in a subject is provided. The method comprises a) identifying a subject that has received at least a moderate level of treatment by a non-PCSK9 LDL-C lowering agent and b) administering a PCSK9 inhibitor to the subject in an amount sufficient and time sufficient to lower the LDL-C level to less than 100 mg/dL, e.g., less than 90 mg/dL, thereby decreasing a total atheroma volume in the subject.

[0021] In some examples, a method of treating coronary atherosclerosis is provided. The method comprises a) administering an optimum non-PCSK9 LDL-C lowering therapy to a subject, wherein the subject has coronary atherosclerosis, and b) administering an amount of a PCSK9 inhibitor to the subject at the same time.

[0022] In some examples, a method of treating coronary atherosclerosis is provided. The method comprises a) identifying a statin-intolerant subject, b) administering a low intensity statin treatment or no statin treatment to the statin-intolerant subject, and c) administering an amount of a PCSK9 inhibitor to the subject, thereby treating coronary atherosclerosis.

[0023] In some examples, a method of providing regression of coronary atherosclerosis is provided. The method comprises providing a subject that is on an optimized level of a non-PCSK9 LDL-C lowering agent and administering to the subject a PCSK9 inhibitor, at a level adequate to regress coronary atherosclerosis. Regression is any change in PAV or TAV less than zero.

[0024] In some examples, a method of decreasing a LDL-C level in a subject beneath 80 mg/dL is provided. The method comprises administering a PCSK9 inhibitor to a subject. The subject has coronary atherosclerotic disease. The subject is on an optimized non-PCSK9 LDL-C lowering therapy for at least one year. A LDL-C level in the subject decreases to an average value that is beneath 80 mg/dL for the at least one year.

[0025] In some examples, a method of reducing an amount of atherosclerotic plaque in a subject is provided. The method comprises administering to a subject having atherosclerotic plaque a PCSK9 inhibitor. The subject is receiving optimized non-PCSK9 LDL-C lowering therapy, thereby reducing the amount of atherosclerotic plaque in the subject.

[0026] In some examples, a method of reducing disease progression is provided. The method comprises identifying a subject with a LDL-C level of no more than 60 mg/dL, administering at least a moderate intensity of a non-PCSK9 LDL-C lowering therapy to the subject, and administering a PCSK9 inhibitor at a level sufficient to decrease the LDL-C level of the subject to 30 mg/dL, thereby reducing disease progression.

[0027] In some examples, a method of combining a PCSK9 inhibitor therapy and a non-PCSK9 LDL-C lowering therapy to produce greater LDL-C lowering and regression of coronary atherosclerosis at a dose that is well tolerated is provided. The method comprises administering at least a moderate intensity of a non-PCSK9 LDL-C lowering therapy to a subject, administering an adequate amount of a PCSK9 inhibitor to the subject such that the subject's LDL-C levels drop to no more than 40 mg/dL, and maintaining the subject's LDL-C levels at no more than 40 mg/dL for at least one year.

[0028] In some examples, a method of treating a subject that is unable to tolerate a full therapeutic dose of a non-PCSK9 LDL-C lowering agent is provided. The method comprises identifying said subject and administering a PCSK9 inhibitor to the subject until a LDL cholesterol level of the subject decreases beneath 60 mg/dL.

[0029] In some examples, a method of treating a subject that is unable to tolerate a full therapeutic dose of a statin is provided. The method comprises identifying said subject and administering a PCSK9 inhibitor to the subject until a LDL cholesterol level of the subject decreases beneath 60 mg/dL.

[0030] In some examples, a method of treating coronary atherosclerosis is provided. The method comprises a) identifying a subject that has a LDL-C level of less than 70 mg/dL and b) administering a non-PCSK9 LDL-C lowering agent to the subject, in an amount sufficient and time sufficient to lower the LDL-C level to less than 60 mg/dL.

[0031] In some examples, a method of treating atherosclerotic cardiovascular disease is provided. The method comprises a) identifying a subject that is on a first therapy, wherein the first therapy comprises a non-PCSK9 LDL-C lowering therapy, and b) administering a second therapy to the subject. The second therapy comprises a PCSK9 inhibitor therapy, wherein both the first and second therapies are administered to the subject in an amount and time sufficient to reduce a risk of atherosclerotic cardiovascular disease in the subject. The first therapy is not the same as the second therapy. The risk is a) a composite for cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization or b) a composite for cardiovascular death, myocardial infarction, or stroke, or c) cardiovascular death, or d) fatal and/or non-fatal MI, or e) fatal and/or non-fatal stroke, or f) transient ischemic attack, or g) hospitalization for unstable angina, or h) elective, urgent, and/or emergent coronary revascularization.

[0032] In some examples, a method of reducing a risk of a cardiovascular event is provided. The method comprises a) identifying a subject that is on a first therapy, wherein the first therapy comprises a non-PCSK9 LDL-C lowering therapy, and b) administering a second therapy to the subject. The second therapy comprises a PCSK9 inhibitor, wherein both the first and second therapies are administered to the subject in an amount and time sufficient to reduce a risk of a cardiovascular event in the subject. The first therapy is not the same as the second therapy. The risk is a) a composite for cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization or b) a composite for cardiovascular death, myocardial infarction, or stroke, or c) cardiovascular death, or d) fatal and/or non-fatal MI, or e) fatal and/or non-fatal stroke, or f) transient

ischemic attack, or g) hospitalization for unstable angina, or h) elective, urgent, and/or emergent coronary revascularization.

[0033] In some examples, a method of reducing a risk of urgent coronary revascularization is provided. The method comprises a) identifying a subject that is on a first therapy, wherein the first therapy comprises a non-PCSK9 LDL-C lowering therapy, and b) administering a second therapy to the subject. The second therapy comprises a PCSK9 inhibitor therapy. Both the first and second therapies are administered to the subject in an amount and time sufficient to reduce the risk of atherosclerotic cardiovascular disease in the subject, and wherein the first therapy is not the same as the second therapy.

[0034] In some examples, a method of reducing a risk of a cardiovascular event is provided. The method comprises a) identifying a subject with cardiovascular disease, and b) administering a PCSK9 inhibitor to the subject in an amount and over time sufficient to reduce a risk of at least one of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or transient ischemic attack (TIA), coronary revascularization, or hospitalization for unstable angina.

[0035] In some examples, a method of lowering LDL-C levels in a subject is provided. The method comprising administering: a) a first therapy to a subject, wherein the first therapy comprises a non-PCSK9 LDL-C lowering therapy, and b) administering a second therapy to the subject, wherein the second therapy comprises a PCSK9 inhibitor. Both the first and second therapies are administered to the subject for at least five years, and the first therapy is not the same as the second therapy, and wherein the subject's LDL-C level is maintained beneath 50 mg/dL.

[0036] In some examples, a method of reducing a risk of a cardiovascular event is provided. The method comprises a) identifying a subject that is on a first therapy, the first therapy comprises a non-PCSK9 LDL-C lowering therapy. The method further comprises b) administering a second therapy to the subject. The second therapy comprises a PCSK9 inhibitor. Both the first and second therapies are administered to the subject in an amount and time sufficient to reduce a risk of a cardiovascular event in the subject. The first therapy is not the same as the second therapy. The risk is at least one of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization.

[0037] In some examples, a method of treating a subject is provided. The method comprises identifying a subject with peripheral artery disease (“PAD”) and reducing a level of PCSK9 activity in the subject.

[0038] In some examples, a method of reducing a risk of an adverse limb event in a subject is provided, the method comprises reducing a level of PCSK9 activity in a subject, wherein the subject has PAD.

[0039] In some examples, a method of reducing a risk of a major cardiovascular adverse event (“MACE”) is provided. The method comprises administering a non-statin LDL-C lowering agent to a subject and administering a statin to the subject. The subject has PAD. In some examples, a method of reducing a risk of PAD and/or CAD and/or cerebrovascular disease is provided. The method comprises administering a non-statin LDL-C lowering agent to a subject and administering a statin to the subject.

[0040] In some examples, a method of reducing a risk of a major adverse limb event (“MALE”) is provided. The method comprises administering a non-statin LDL-C lowering agent to a subject and administering a statin to the subject. The subject has PAD.

[0041] In some examples, a method of reducing a risk of a cardiovascular event is provided. The method comprises providing a first therapy to a subject. The first therapy comprises a non-PCSK9 LDL-C lowering therapy. The method further comprises providing a second therapy to the subject. The second therapy comprises a PCSK9 inhibitor. The first and second therapies are administered to the subject, and wherein the subject has a Lp(a) level of 11.8 mg/dL to 50.

[0042] In some examples, a method of reducing a risk of a major vascular event in a subject is provided. The method comprises 1) identifying a subject that has at least one of: (a) a recent MI, (b) multiple prior MIs, or (c) multivessel disease. The method further comprises 2) providing a first therapy to a subject, wherein the first therapy comprises a non-PCSK9 LDL-C lowering therapy. The method further comprises 3) providing a second therapy to the subject, wherein the second therapy comprises a PCSK9 inhibitor, thereby reducing a risk that the subject will have a major vascular event.

In some examples, a method of treating coronary atherosclerosis is provided that comprises administering, to a subject who has a LDL-C level of greater than 70 mg/dL a PCSK9 inhibitor in an amount sufficient and over a time period sufficient to lower the LDL-C level

to less than 40 mg/dL. In some examples, a method of reducing a risk of a cardiovascular event is provided that comprises administering, to a subject who has a LDL-C level of greater than 70 mg/dL, a PCSK9 inhibitor in an amount sufficient and over a time period sufficient to lower the LDL-C level to less than 40 mg/dL.

BRIEF DESCRIPTION OF THE DRAWINGS

[0043] **Figure 1** depicts the disposition of the patients during the GLAGOV study.

[0044] **Figure 2** depicts the mean ($\pm$ standard error) percent change in LDL-C in patients treated with placebo (circles) and evolocumab (triangles) during the study.

[0045] **Figure 3** depicts the prespecified subgroup analysis of the primary end point, the change in percent atheroma volume (PAV) from baseline to 78-week follow-up. Results are expressed as least square mean $\pm$ standard error LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin kexin type 9; TAV, total atheroma volume.

[0046] **Figure 4A** depicts the change in percent atheroma volume (PAV, left panel) and percentage of patients demonstrating regression of PAV (right panel) in the placebo (white) and evolocumab (black) treatment groups, stratified according to baseline LDL-C.

WHAT IS CLAIMED IS:

1. Use of a PCSK9 inhibitor therapy in the manufacture of a pharmaceutical for treating coronary atherosclerosis, wherein the use comprises
that a second therapy is to be administered to a subject that is on a first therapy, wherein the first therapy comprises a non-PCSK9 LDL-C lowering therapy, wherein the second therapy comprises the PCSK9 inhibitor therapy, wherein both the first and second therapies are to be administered to the subject in an amount and time sufficient to reverse coronary atherosclerosis in the subject, and wherein the first therapy is not the same as the second therapy.
2. Use of an anti-PCSK9 neutralizing antibody in the manufacture of a pharmaceutical for treating coronary atherosclerosis, wherein the use comprises
that the anti-PCSK9 neutralizing antibody is to be administered to a subject that has a LDL-C level of less than 70 mg/dL, in an amount sufficient and time sufficient to lower the LDL-C level to less than 60 mg/dL.
3. Use of an anti-PCSK9 neutralizing antibody in the manufacture of a pharmaceutical for decreasing percent atheroma volume (PAV) in a subject, wherein the use comprises
that the anti-PCSK9 neutralizing antibody is to be administered to a subject that has received at least a moderate level of treatment by a statin, in an amount sufficient and time sufficient to lower the LDL-C level to less than 90 mg/dL, thereby decreasing a percent atheroma volume (PAV) in the subject.
4. Use of an anti-PCSK9 neutralizing antibody in the manufacture of a pharmaceutical for decreasing total atheroma volume (TAV) in a subject, wherein the use comprises
that the anti-PCSK9 neutralizing antibody is to be administered to a subject that has received at least a moderate level of treatment by a statin, in an amount sufficient and time sufficient to lower the LDL-C level to less than 90 mg/dL, thereby decreasing a total atheroma volume in the subject.

5. Use of a low dose statin treatment in combination with an anti-PCSK9 neutralizing antibody in the manufacture of a pharmaceutical for treating coronary atherosclerosis, wherein the use comprises:
 - a. that at least the low dose statin treatment is to be administered to a statin-intolerant subject; and
 - b. that the amount of an anti-PCSK9 neutralizing antibody is to be administered to the subject, thereby treating coronary atherosclerosis; wherein the low dose statin treatment and the anti-PCSK9 neutralizing antibody are to be administered together or separately.
6. Use of a monoclonal antibody to human PCSK9 in the manufacture of a pharmaceutical for reducing an amount of atherosclerotic plaque in a subject, wherein the use comprises that the monoclonal antibody to human PCSK9 is to be administered to the subject having atherosclerotic plaque, wherein the subject is receiving optimized statin therapy, thereby reducing the amount of atherosclerotic plaque in the subject.
7. Use of evolocumab in combination with a statin therapy in the manufacture of a pharmaceutical for producing greater LDL-C lowering and regression of coronary atherosclerosis at a dose that is well tolerated, wherein the use comprises:
 - that at least a moderate intensity of the statin therapy is to be administered to a subject;
 - that an adequate amount of evolocumab is to be administered to the subject such that the subject's LDL-C levels drop to no more than 40 mg/dL; and
 - that the subject's LDL-C levels is to be maintained at no more than 40 mg/dL for at least one year; wherein evolocumab and the statin therapy are to be administered together or separately.
8. Use of a PCSK9 inhibitor in the manufacture of a pharmaceutical for treating coronary atherosclerosis, wherein the use comprises
 - that the PCSK9 inhibitor is to be administered to a subject that has a LDL-C level of less than 70 mg/dL, in an amount sufficient and time sufficient to lower the LDL-C level to less than 60 mg/dL.

9. Use of a PCSK9 inhibitor in the manufacture of a pharmaceutical for decreasing percent atheroma volume (PAV) in a subject, wherein the use comprises

that the PCSK9 inhibitor is to be administered to a subject that has received at least a moderate level of treatment by a non-PCSK9 LDL-C lowering agent, in an amount sufficient and time sufficient to lower the LDL-C level to less than 90 mg/dL, thereby decreasing a percent atheroma volume (PAV) in the subject.
10. Use of a PCSK9 inhibitor in the manufacture of a pharmaceutical for decreasing total atheroma volume (TAV) in a subject, wherein the use comprises

that the PCSK9 inhibitor is to be administered to a subject that has received at least a moderate level of treatment by a non-PCSK9 LDL-C lowering agent, in an amount sufficient and time sufficient to lower the LDL-C level to less than 90 mg/dL, thereby decreasing a total atheroma volume in the subject.
11. Use of a non-PCSK9 LDL-C lowering therapy in combination with a PCSK9 inhibitor in the manufacture of pharmaceutical for reducing disease progression, wherein the use comprises

that at least a moderate intensity of the non-PCSK9 LDL-C lowering therapy is to be administered to a subject with a LDL-C level of no more than 60 mg/dL; and

that the PCSK9 inhibitor is to be administered at a level sufficient to decrease the LDL-C level of the subject to 30 mg/dL, thereby reducing disease progression; wherein the non-PCSK9 LDL-C lowering therapy and the PCSK9 inhibitor are to be administered together or separately.
12. Use of a PCSK9 inhibitor therapy in combination with a non-PCSK9 LDL-C lowering therapy in the manufacture of a pharmaceutical for producing greater LDL-C lowering and regression of coronary atherosclerosis at a dose that is well tolerated, wherein the use comprises:

that at least a moderate intensity of the non-PCSK9 LDL-C lowering therapy is to be administered to a subject;

that an adequate amount of the PCSK9 inhibitor is to be administered to the subject such that the subject's LDL-C levels drop to no more than 40 mg/dL; and

that the subject's LDL-C levels is to be maintained at no more than 40 mg/dL for at least one year; wherein the PCSK9 inhibitor therapy and the non-PCSK9 LDL-C lowering therapy are to be administered together or separately.

13. Use of a PCSK9 inhibitor in the manufacture of a pharmaceutical for reducing a risk of a cardiovascular event, wherein the use comprises

that a second therapy is to be administered to a subject that is on a first therapy, wherein the first therapy comprises a non-PCSK9 LDL-C lowering therapy, wherein the second therapy comprises the PCSK9 inhibitor, wherein both the first and second therapies are to be administered to the subject in an amount and time sufficient to reduce a risk of a cardiovascular event in the subject, and wherein the first therapy is not the same as the second therapy, and wherein the risk is a) a composite for cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization or b) a composite for cardiovascular death, myocardial infarction, or stroke.

14. Use of a PCSK9 inhibitor in the manufacture of a pharmaceutical for reducing a risk of a cardiovascular event, wherein the use comprises

that a second therapy is to be administered to a subject that is on a first therapy, wherein the first therapy comprises a non-PCSK9 LDL-C lowering therapy, wherein the second therapy comprises the PCSK9 inhibitor, wherein both the first and second therapies are to be administered to the subject in an amount and time sufficient to reduce a risk of a cardiovascular event in the subject, and wherein the first therapy is not the same as the second therapy, and wherein the risk is the composite of fatal MI and/or non-fatal MI and fatal and/or non-fatal coronary revascularization.

15. Use of a non-statin LDL-C lowering agent in combination with a statin in the manufacture of a pharmaceutical for reducing a risk of a major adverse limb event ("MALE"), wherein the use comprises:

that the non-statin LDL-C lowering agent is to be administered to a subject;
and

that the statin is to be administered to the subject, wherein the subject has peripheral artery disease (“PAD”); wherein the non-statin LDL-C lowering agent and the statin are to be administered together or separately.

16. Use of a non-statin LDL-C lowering agent in combination with a statin in the manufacture of a pharmaceutical for reducing a risk of a major cardiovascular adverse event (“MACE”), wherein the use comprises:

that the non-statin LDL-C lowering agent is to be administered to a subject; and

that the statin is to be administered to the subject, wherein the subject has PAD; wherein the non-statin LDL-C lowering agent and the statin are to be administered together or separately.

17. Use of a non-PCSK9 LDL-C lowering therapy in combination with a PCSK9 inhibitor in the manufacture of a pharmaceutical for reducing a risk of a cardiovascular event, wherein the use comprises:

that a first therapy is to be provided to a subject, wherein the first therapy comprises the non-PCSK9 LDL-C lowering therapy; and

that a second therapy is to be provided to the subject, wherein the second therapy comprises the PCSK9 inhibitor, wherein both the first and second therapies are to be administered to the subject, and wherein the subject has a Lp(a) level of 11.8 mg/dL to 50; wherein the non-PCSK9 LDL-C lowering therapy and the PCSK9 inhibitor are to be administered together or separately.

18. Use of a non-PCSK9 LDL-C lowering therapy in combination with a PCSK9 inhibitor in the manufacture of a pharmaceutical for reducing a risk of a major vascular event in a subject, wherein the use comprises:

1) that a first therapy is to be provided to a subject that has at least one of: (a) a recent MI, (b) multiple prior MIs, or (c) multivessel disease, wherein the first therapy comprises the non-PCSK9 LDL-C lowering therapy; and

2) that a second therapy is to be provided to the subject, wherein the second therapy comprises the PCSK9 inhibitor,

thereby reducing a risk that the subject will have a major vascular event; wherein the non-PCSK9 LDL-C lowering therapy and the PCSK9 inhibitor are to be administered together or separately.

19. Use of a PCSK9 inhibitor in the manufacture of a pharmaceutical for reducing a risk of a cardiovascular event, wherein the use comprises that the PCSK9 inhibitor is to be administered to a subject that has a LDL-C level of greater than 70 mg/dL in an amount sufficient and time sufficient to lower the LDL-C level to less than 40 mg/dL.