WHAT IS CLAIMED IS:

1. A method of treating a subject at increased risk of major adverse cardiovascular event (MACE) comprising:

selecting for treatment a subject at increased risk of MACE; and

administering to said subject an amount of naltrexone, or a pharmaceutically acceptable salt thereof and bupropion, or a pharmaceutically acceptable salt thereof, effective to reduce said increased risk.

2. The method of claim 1, wherein the subject has one or more of the following characteristics at the time of treatment: Type II diabetes; existing cardiovascular disease or a high likelihood of cardiovascular disease; congestive heart failure; family history of cardiovascular disease; current smoker; genetically predisposed to cardiovascular diseases; has or has had cardiac arrhythmia; has or has had atrial fibrillation, ventricular fibrillation, or tachyarrhythmia; does not have sinus tachycardia; has unstable angina; has hypertension; has had a stroke or is at increased risk of stroke; has an aneurysm; or has elevated triglycerides, elevated LDL, and/or low HDL.

3. The method of claim 2, wherein the subject has type 2 diabetes or a confirmed diagnosis of cardiovascular disease.

4. The method of claim 2, wherein the subject has either a confirmed diagnosis of cardiovascular disease or a high likelihood of cardiovascular disease, and wherein said subject has at least one of: a history of documented myocardial infarction > 3 months prior to said identifying; a history of coronary revascularization; a history of carotid or peripheral revascularization; angina with ischemic changes; ECG changes on a graded exercise test; positive cardiac imaging study; ankle brachial index <0.9 within 2 years prior to said identifying; or >50% stenosis of a coronary artery, carotid artery, or lower extremity artery within 2 years prior to treatment.

5. The method of claim 2, wherein the subject has type 2 diabetes and no more than one of: hypertension at >145/95 mm Hg, dyslipidemia requiring pharmacotherapy, documented low HDL within 12 months prior, or is a current tobacco user.

6. The method of claim 2, wherein the subject has a history of atrial fibrillation.

7. A method for preventing or delaying the onset of a major adverse cardiovascular event comprising:

selecting for treatment a subject who is not currently at increased risk of MACE; and

administering to said subject an amount of naltrexone, or a pharmaceutically acceptable salt thereof and bupropion, or a pharmaceutically acceptable salt thereof.

8. The method of any one of claims 1 to 7, wherein the subject is obese or overweight.

9. The method of any one of claims 1 to 7, wherein the subject is not obese or overweight.

10. The method of any one of claims 1 to 9, wherein the subject is concurrently taking a medication for management of one or more of conditions selected from a cardiovascular condition, diabetes, hypertension, dyslipidemia or a blood glucose condition.

11. The method of claim 10, wherein said medication is selected from Table 1 or 2.

12. The method of any one of claims 1 to 11, wherein the subject is concurrently taking a medication for management of depression.

13. The method of claim 12, wherein said medication is an antidepressant compound selected from a selective serotonin reuptake inhibitor, a serotonin-norepinephrine reuptake inhibitor, a serotonin antagonist and reuptake inhibitor, a TAAR1 agonist, a tricyclic antidepressant, a tetracyclic antidepressant, or a monoamine oxidase inhibitor.

14. The method of claim 12 or 13, wherein said medication is selected from Table 3.

15. The method of any one of claims 1 to 13, wherein the subject is not concurrently taking a statin.

16. A method of treating a subject for overweight or obesity, comprising:

selecting for treatment an overweight or obese subject at increased risk of a major adverse cardiovascular event; and

treating the subject for overweight or obesity by administering to the subject an amount of naltrexone, or a pharmaceutically acceptable salt thereof and bupropion, or a pharmaceutically acceptable salt thereof.

17. The method of claim 16, wherein said subject has one or more of the characteristics at the time of treatment selected from the subpopulations described in Table 8, wherein the point estimate of the hazard ratio for the subpopulation is selected from less than about 0.85, less than about 0.8, less than about 0.75, less than about 0.70, less than about 0.65, less than about 0.60, less than about 0.55, less than about 0.50, less than about 0.45, less than about 0.40, less than about 0.35, less than about 0.30, less than 0.25, less than 0.20, less than 0.15, or less than 0.10.

18. The method of claim 16 or 17, wherein said subject has one or more of the characteristics at the time of treatment selected from: has had type 2 diabetes for less than 6 years; is a current smoker, optionally does not have type 2 diabetes: at risk of adverse cardiovascular outcomes but does not have type 2 diabetes; over 65 years old; male; non-Caucasian; has a BMI category of $\geq$35 kg/m^2 and less than 40 kg/m^2; does not have type 2

diabetes or is not on any antidiabetic medication selected from insulin, metformin, or thiazolidinediones; has renal impairment characterized by GFR≥ 90 mL/min; currently using one or more beta blocker agents; currently using one or more diuretics; currently not using a concomitant medication of one or more angiotensin II receptor blockers (ARB) or angiotensin-converting enzyme inhibitors (ACEi); currently using one or more calcium channel blockers; currently using one or more medications selected from GLP-1 receptor agonists, DPP-4 inhibitors, or sulfonylurea; currently using one or more serotonin reuptake inhibitors; does not have depression; or is not currently using any anti-depression medications.

19. The method of claim 16 or 17, wherein the subject has had type 2 diabetes for less than 6 years.

20. The method of claim 16 or 17, wherein the subject is a current smoker.

21. The method of any one of claims 1 to 20, wherein said administering reduces the risk of a major adverse cardiovascular event in said subject.

22. The method of any of claims 1 to 20, wherein the method increases the time until first incidence of one or more events selected from the group consisting of: MACE, Four-point Expanded MACE, Five-point Expanded MACE, CV death, nonfatal MI, stroke, fatal stroke, nonfatal stroke, Nonfatal HUSA (hospitalization due to unstable angina), coronary revascularization procedure, and/or all-cause mortality.

23. The method of any of claims 1 to 21, wherein the method reduces the predicted severity of an adverse cardiovascular event or decreases the predicted mortality from an adverse cardiovascular event, or decreases the progression of cardiovascular disease.

24. The method of any of claims 1 to 23, wherein the method increases the predicted life expectancy of the subject, the predicted time period between adverse cardiovascular events, or the effectiveness of a cardiovascular intervention in the subject.

25. The method of any one of claims 1 to 24, wherein said major adverse cardiovascular event is cardiovascular death, non-fatal myocardial infarction, cardiac arrhythmia, or non-fatal stroke.

26. The method of any one of claims 1 to 25, wherein said major adverse cardiovascular event is cardiovascular death.

27. The method of Claim 26, wherein said cardiovascular death comprises death resulted from fatal myocardial infarction and stroke.

28. The method of any one of claims 1 to 25, wherein said major adverse cardiovascular event is non-fatal stroke.

29. The method of any one of claims 1 to 25, wherein said major adverse cardiovascular event is non-fatal myocardial infarction.

30. The method of any one of claims 1 to 24, wherein said major adverse cardiovascular event comprises both fatal and non-fatal stroke.

31. The method of any one of claims 1 to 25, wherein said major adverse cardiovascular event comprises cardiac arrhythmia.

32. The method of any one of claims 1 to 24, wherein said major adverse cardiovascular event comprises both fatal and non-fatal myocardial infarction.

33. The method of any one of claims 1 to 25, wherein said major adverse cardiovascular event further comprises progression from unstable angina to myocardial infarction or death.

34. The method of any one of claims 1 to 33, wherein said administering results in weight loss of more than 5%, 4%, 3%, 2%, or 1% of said subject's body weight.

35. The method of any one of claims 1 to 33, wherein the reduction in risk of MACE is achieved and the subject has not lost more than 5%, 4%, 3%, 2%, or 1% of their body weight.

36. The method of any one of claims 1 to 35, wherein one or both of naltrexone and bupropion, or a pharmaceutically acceptable salt thereof, is administered in a sustained release formulation.

37. The method of any one of claims 1 to 36, wherein naltrexone or a pharmaceutically acceptable salt thereof is administered in a daily dosage of 4-50 mg.

38. The method of any one of claims 1 to 37, wherein bupropion or a pharmaceutically acceptable salt thereof is administered in a daily dosage of 50-400 mg.

39. The method of any one of claims 1 to 38, wherein said an amount of naltrexone and bupropion is a daily dose of 32 mg of sustained release naltrexone, and 360 mg of sustained release bupropion, or pharmaceutically acceptable salts thereof.

40. The method of claim 39, wherein said naltrexone and bupropion are administered in a single oral dosage form.

41. The method of any one of claims 1 to 40, wherein said subject is treated for at least 12 weeks, 20 weeks, 26 weeks or 52 weeks.

42. The method of any of claims 1 to 41, wherein the subject's vital signs do not change by more than 10%, or 5% during the course of treatment, wherein the vital sign is selected from the group of resting blood pressure, systolic blood pressure, diastolic blood pressure, and/or heart rate.

43. The method of any one of claims 1 to 41, wherein the subject was administered:

about 8 mg of said sustained release naltrexone or a pharmaceutically acceptable salt thereof and about 90 mg of said sustained release bupropion or a pharmaceutically acceptable salt thereof daily for a first week of treatment;

about 16 mg of said sustained release naltrexone or a pharmaceutically acceptable salt thereof and about 180 mg of said sustained release bupropion or a pharmaceutically acceptable salt thereof daily for a second week of treatment;

about 24 mg of said sustained release naltrexone or a pharmaceutically acceptable salt thereof and about 270 mg of said sustained release bupropion or a pharmaceutically acceptable salt thereof daily for a third week of treatment; and

about 32 mg of said sustained release naltrexone or a pharmaceutically acceptable salt thereof and about 360 mg of said sustained release bupropion or a pharmaceutically acceptable salt thereof daily for a fourth week of treatment and any subsequent weeks of treatment.

44. The method of any of the preceding claims, wherein the subject has had one or more of the following characteristics: (a) a myocardial infarction within 3 months prior treatment with the method; (b) a history of angina pectoris Grade III or Grade IV as per the Canadian Cardiovascular Society grading scheme; (c) a history of cerebrovascular disease; (d) a history of stroke; (e) a history of tachycardia other than sinus tachycardia; (f) a planned bariatric surgery, cardiac surgery, or coronary angioplasty; (g) a history of seizures, cranial trauma, or a condition that predisposes the subject to seizures; (h) a history of mania, current diagnosis of active psychosis, current diagnosis of active bulimia, or current diagnosis of anorexia nervosa; or (i) a condition with life expectancy less than 4 years.

45. The method of any of the preceding claims, wherein the naltrexone and bupropion is administered one, two, three, or four times a day.

46. Use of naltrexone and bupropion for the preparation of a medicament, wherein the medicament is for use in accordance with a method set forth in any one of the preceding claims.

WHAT IS CLAIMED IS:

1. Use of an amount of naltrexone, or a pharmaceutically acceptable salt thereof and bupropion, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a subject at increased risk of major adverse cardiovascular event (MACE);

wherein the amount of naltrexone, or a pharmaceutically acceptable salt thereof and bupropion, or a pharmaceutically acceptable salt thereof used in the manufacture of the medicament is effective to reduce said increased risk.

2. The use of claim 1, wherein the subject has one or more of the following characteristics at the time of treatment: Type 2 diabetes; existing cardiovascular disease or a high likelihood of cardiovascular disease; congestive heart failure; family history of cardiovascular disease; current smoker; genetically predisposed to cardiovascular diseases; has or has had cardiac arrhythmia; has or has had atrial fibrillation, ventricular fibrillation, or tachyarrhythmia; does not have sinus tachycardia; has unstable angina; has hypertension; has had a stroke or is at increased risk of stroke; has an aneurysm; or has elevated triglycerides, elevated LDL, and/or low HDL.

3. The use of claim 2, wherein the subject has type 2 diabetes or a confirmed diagnosis of cardiovascular disease.

4. The use of claim 2, wherein the subject has either a confirmed diagnosis of cardiovascular disease or a high likelihood of cardiovascular disease, and wherein said subject has at least one of: a history of documented myocardial infarction > 3 months prior to said identifying; a history of coronary revascularization; a history of carotid or peripheral revascularization; angina with ischemic changes; ECG changes on a graded exercise test; positive cardiac imaging study; ankle brachial index <0.9 within 2 years prior to said identifying; or >50% stenosis of a coronary artery, carotid artery, or lower extremity artery within 2 years prior to treatment.

5. The use of claim 2, wherein the subject has type 2 diabetes and no more than one of: hypertension at >145/95 mm Hg, dyslipidemia requiring pharmacotherapy, documented low HDL within 12 months prior, or is a current tobacco user.

6. The use of claim 2, wherein the subject has a history of atrial fibrillation.

7. Use of an amount of naltrexone, or a pharmaceutically acceptable salt thereof and bupropion, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a subject for preventing or delaying the onset of a major adverse cardiovascular event.

8. The use of any one of claims 1 to 7, wherein the subject is obese or overweight.

9. The use of any one of claims 1 to 7, wherein the subject is not obese or overweight.

10. Use of an amount of naltrexone, or a pharmaceutically acceptable salt thereof and bupropion, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a subject for overweight or obesity, wherein said overweight or obese subject is at increased risk of a major adverse cardiovascular event.

11. The use of claim 10, wherein said subject has one or more of the characteristics at the time of treatment selected from the subpopulations described in Table 8, wherein the point estimate of the hazard ratio for the subpopulation is selected from less than about 0.85, less than about 0.8, less than about 0.75, less than about 0.70, less than about 0.65, less than about 0.60, less than about 0.55, less than about 0.50, less than about 0.45, less than about 0.40, less than about 0.35, less than about 0.30, less than 0.25, less than 0.20, less than 0.15, or less than 0.10.

12. The use of claim 10 or 11, wherein said subject has one or more of the characteristics at the time of treatment selected from: has had type 2 diabetes for less than 6 years; is a current smoker, optionally does not have type 2 diabetes; at risk of adverse cardiovascular outcomes but does not have type 2 diabetes; over 65 years old; male; non-Caucasian; has a BMI category of $\geq$35 kg/m^2 and less than 40 kg/m^2; does not have type 2 diabetes or is not on any antidiabetic medication selected from insulin, metformin, or thiazolidinediones; has renal impairment characterized by GFR $\geq$90 mL/min; currently using one or more beta blocker agents; currently using one or more diuretics; currently not using a concomitant medication of one or more angiotensin II receptor blockers (ARB) or angiotensin-converting enzyme inhibitors (ACEi); currently using one or more calcium channel blockers; currently using one or more medications selected from GLP-1 receptor agonists, DPP-4 inhibitors, or sulfonylurea; currently using one or more serotonin reuptake inhibitors; does not have depression; or is not currently using any anti-depression medications.

13. The use of claim 10 or 11, wherein the subject has had type 2 diabetes for less than 6 years.

14. The use of claim 10 or 11, wherein the subject is a current smoker.

15. The use of any one of claims 1 to 14, wherein said treatment reduces the risk of a major adverse cardiovascular event in said subject.

16. The use of any one of claims 1 to 14, wherein the treatment increases the time until first incidence of one or more events selected from the group consisting of: MACE, Four-point Expanded MACE, Five-point Expanded MACE, CV death, nonfatal MI, stroke, fatal stroke, nonfatal stroke, Nonfatal HUSA (hospitalization due to unstable angina), coronary revascularization procedure, and/or all-cause mortality.

17. The use of any of claims 1 to 15, wherein the treatment reduces the predicted severity of an adverse cardiovascular event or decreases the predicted mortality from an adverse cardiovascular event, or decreases the progression of cardiovascular disease.

18. The use of any of claims 1 to 17, wherein the treatment increases the predicted life expectancy of the subject, the predicted time period between adverse cardiovascular events, or the effectiveness of a cardiovascular intervention in the subject.

19. The use of any one of claims 1 to 18, wherein said major adverse cardiovascular event is selected from cardiovascular death, non-fatal myocardial infarction, cardiac arrhythmia, or non-fatal stroke.

20. The use of any one of claims 1 to 19, wherein said major adverse cardiovascular event is cardiovascular death.

21. The use of any one of claims 1 to 19, wherein said major adverse cardiovascular event further comprises progression from unstable angina to myocardial infarction or death.

22. The use of any one of claims 1 to 21, wherein said treatment results in weight loss of more than 5% of said subject's body weight.

23. The use of any one of claims 1 to 21, wherein the reduction in risk of MACE is achieved and the subject has not lost more than 5% of their body weight.

24. The use of any one of claims 1 to 23, wherein one or both of naltrexone and bupropion, or pharmaceutically acceptable salts thereof, in the medicament is to be administered in a sustained release formulation.

25. The use of any one of claims 1 to 24, wherein said amount of naltrexone and bupropion in the medicament is to be in the form of a daily dose of 32 mg of sustained release

naltrexone, and 360 mg of sustained release bupropion, or pharmaceutically acceptable salts thereof.

26. The use of claim 25, wherein the medicament comprising naltrexone and bupropion is to be administered in a single oral dosage form.

27. The use of any one of claims 1 to 26, wherein said subject is treated for at least 12 weeks, 20 weeks, 26 weeks or 52 weeks.

28. The use of any one of the preceding claims, wherein the subject has had one or more of the following characteristics: (a) a myocardial infarction within 3 months prior treatment with the use; (b) a history of angina pectoris Grade III or Grade IV as per the Canadian Cardiovascular Society grading scheme; (c) a history of cerebrovascular disease; (d) a history of stroke; (e) a history of tachycardia other than sinus tachycardia; (f) a planned bariatric surgery, cardiac surgery, or coronary angioplasty; (g) a history of seizures, cranial trauma, or a condition that predisposes the subject to seizures; (h) a history of mania, current diagnosis of active psychosis, current diagnosis of active bulimia, or current diagnosis of anorexia nervosa; or (i) a condition with life expectancy less than 4 years.

29. The use of any one of the preceding claims, wherein the medicament comprising naltrexone and bupropion is to be administered one, two, three, or four times a day.