CLAIMS

What is claimed is:

1. A method of increasing HDL levels or improving the ratio of TG to HDL by
   (a) selecting an animal in need therof, and
   (b) administering a compound targeting ApoCIII to the animal,
whereby HDL levels are increased or the ratio of TG to HDL is improved.

2. A method of preventing, delaying or ameliorating a cardiovascular disease, disorder, condition or symptom thereof or onset of a cardiovascular disease, disorder, condition or symptom thereof in an animal comprising
   (a) selecting an animal in need thereof, and
   (b) administering a compound targeting ApoCIII to the animal,
thereby increasing HDL levels in the animal, wherein the cardiovascular disease, disorder, condition or symptom or the onset of the cardiovascular disease, disorder, condition, or symptom thereof, is prevented, delayed or ameliorated.

3. A method of reducing the risk of a cardiovascular disease, disorder, condition or symptom in an animal comprising
   (a) selecting an animal in need thereof, and
   (b) administering a compound targeting ApoCIII to the animal,
thereby raising HDL levels in the animal, wherein the risk of a cardiovascular disease, disorder, condition, or symptom thereof, is reduced.

4. A method of decreasing CETP levels by administering a compound targeting ApoCIII to an animal, wherein CETP levels are decreased.

5. A method of increasing ApoA1, PON1, fat clearance, chylomicron triglyceride clearance, postprandial triglyceride clearance and/or HDL comprising
   (a) selecting an animal in need thereof, and
   (b) administering a compound targeting ApoCIII to the animal,

wherein ApoA1, PON1, fat clearance, chylomicron triglyceride clearance, postprandial triglyceride clearance and/or HDL is increased.

6. A method of preventing, delaying or ameliorating pancreatitis comprising
(a) selecting an animal with, or at risk of, pancreatitis, and
(b) administering a compound targeting ApoCIII to the animal,
wherein the pancreatitis is prevented, delayed or ameliorated.

7. A method of preventing, delaying or ameliorating pancreatitis comprising
(a) selecting an animal with, or at risk of, pancreatiis, and
(b) administering a compound targeting ApoCIII to the animal,
thereby increasing chylomicron clearance, wherein the pancreatitis is prevented, delayed or ameliorated.

8. A compound targeting ApoCIII, for use in increasing HDL levels or improving the ratio of TG to HDL by
(a) selecting an animal in need therof, and
(b) administering a compound targeting ApoCIII to an animal,
whereby HDL levels are increased or the ratio of TG to HDL is improved.

9. A compound targeting ApoCIII, for use in preventing, delaying or ameliorating a cardiovascular disease, disorder, condition or symptom thereof or onset of a cardiovascular disease, disorder, condition or symptom thereof in an animal comprising
(a) selecting an animal in need thereof, and
(b) administering a compound targeting ApoCIII to the animal,
thereby increasing HDL levels in the animal, wherein the cardiovascular disease, disorder, condition or symptom or the onset of the cardiovascular disease, disorder, condition, or symptom thereof, is prevented, delayed or ameliorated.

10. A compound targeting ApoCIII, for use in reducing the risk of a cardiovascular disease, disorder, condition or symptom in an animal comprising
(a) selecting an animal in need thereof, and

(b) administering a compound targeting ApoCIII to the animal,

thereby raising HDL levels in the animal, wherein the risk of a cardiovascular disease, disorder, condition, or symptom thereof, is reduced.

11. A compound targeting ApoCIII, for use in decreasing CETP levels by administering a compound targeting ApoCIII to an animal, wherein CETP levels are decreased.

12. A compound targeting ApoCIII, for use in increasing ApoA1, PON1, fat clearance, chylomicron triglyceride clearance, postprandial triglyceride clearance and/or HDL comprising

(a) selecting an animal in need thereof, and

(b) administering a compound targeting ApoCIII to the animal,

wherein ApoA1, PON1, fat clearance, chylomicron triglyceride clearance, postprandial triglyceride clearance and/or HDL is increased.

13. A compound targeting ApoCIII, for use in preventing, delaying or ameliorating pancreatitis comprising

(a) selecting an animal with, or at risk of, pancreatiis, and

(b) administering a compound targeting ApoCIII to the animal,

wherein the pancreatitis is prevented, delayed or ameliorated.

14. A compound targeting ApoCIII, for use in preventing, delaying or ameliorating pancreatitis comprising

(a) selecting an animal with, or at risk of, pancreatitis, and

(b) administering a compound targeting ApoCIII to the animal,

thereby increasing chylomicron clearance, wherein the pancreatitis is prevented, delayed or ameliorated.

15. The method or use of any preceding claim, wherein the animal has, or is at risk for, hypertriglyceridemia.

16. The method or use of claim 15, wherein the animal has a triglyceride level between 100-200 mg/dL, 100-300 mg/dL, 100-400 mg/dL, 100-500 mg/dL, 200-500 mg/dL, 300-500 mg/dL

400-500 mg/dL, 500-1000 mg/dL, 600-1000 mg/dL, 700-1000 mg/dL, 800-1000 mg/dL, 900-1000 mg/dL, 500-1500 mg/dL, 1000-1500 mg/dL, 100-2000 mg/dL, 150-2000 mg/dL, 200-2000 mg/dL, 300-2000 mg/dL, 400-2000 mg/dL, 500-2000 mg/dL, 600-2000 mg/dL, 700-2000 mg/dL, 800-2000 mg/dL, 900-2000 mg/dL, 1000-2000 mg/dL, 1100-2000 mg/dL, 1200-2000 mg/dL, 1300-2000 mg/dL, 1400-2000 mg/dL, or 1500-2000 mg/dL.

17. The method or use of claim 15, wherein the hypertriglyceridemia is Fredrickson Type II, IV or V.

18. The method or use of any preceding claim, wherein the animal has a genetic defect leading to hypertriglyceridemia.

19. The method or use of claim 18, wherein the genetic defect is a heterozygous LPL deficiency or an ApoCIII polymorphism.

20. The method or use of any preceding claim, wherein the animal has a triglyceride level ≥ 500 mg/dL and a heterozygous LPL deficiency.

21. The method or use of claim 5, 7, 12 or 14, wherein the increased chylomicron clearance enhances clearance of postprandial triglycerides and/or decreases postprandial triglycerides.

22. The method or use of any preceding claim, wherein ApoCIII has a nucleic acid sequence as shown in SEQ ID NO: 1 or SEQ ID NO: 2.

23. The method or use of any preceding claim, wherein the compound targeting ApoCIII is a modified oligonucleotide.

24. The method or use of claim 23, wherein the modified oligonucleotide has a nucleobase sequence comprising at least 8 contiguous nucleobases of a nucleobase sequence of SEQ ID NO: 3.

25. The method or use of claim 23, wherein the nucleobase sequence of the modified oligonucleotide is 80% complementary to a nucleobase sequence of SEQ ID NO: 1 or SEQ ID NO: 2.

26. The method or use of claim 23, wherein the nucleobase sequence of the modified oligonucleotide is 90% complementary to a nucleobase sequence of SEQ ID NO: 1 or SEQ ID NO: 2.

27. The method or use of claim 23, wherein the nucleobase sequence of the modified oligonucleotide is 100% complementary to a nucleobase sequence of SEQ ID NO: 1 or SEQ ID NO: 2.

28. The method or use of any of claims 23-27, wherein the modified oligonucleotide consists of a single-stranded modified oligonucleotide.

29. The method or use of any of claims 23-28, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides.

30. The method or use of claim 29, wherein the modified oligonucleotide consists of 20 linked nucleosides.

31. The method or use of any of claims 23-30, wherein at least one internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.

32. The method or use of claim 31, wherein each modified internucleoside linkage of the modified oligonucleotide is a phosphorothioate internucleoside linkage.

33. The method or use of any of claims 23-32, wherein at least one nucleoside of the modified oligonucleotide comprises a modified sugar.

34. The method or use of claim 33, wherein at least one modified sugar is a bicyclic sugar.

35. The method or use of claim 33, wherein at least one modified sugar comprises a 2'-O-methyoxyethyl.

36. The method or use of any of claims 23-33, wherein at least one nucleoside of the modified oligonucleotide comprises a modified nucleobase.

37. The method or use of claim 36, wherein the modified nucleobase is a 5-methylcytosine.

38. The method or use of claim 23, wherein the modified oligonucleotide comprises:

(a) a gap segment consisting of linked deoxynucleosides;

(b) a 5' wing segment consisting of linked nucleosides;

(c) a 3' wing segment consisting linked nucleosides;

wherein the gap segment is positioned immediately adjacent to and between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar.

39. The method or use of claim 23, wherein the modified oligonucleotide comprises:

(a) a gap segment consisting of 8-12 linked deoxynucleosides;

(b) a 5' wing segment consisting of 1-5 linked nucleosides;

(c) a 3' wing segment consisting 1-5 linked nucleosides;

wherein the gap segment is positioned immediately adjacent to and between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methyoxyethyl sugar, wherein each cytosine is a 5'-methylcytosine, and wherein each internucleoside linkage is a phosphorothioate linkage.

40. The method or use of claim 23, wherein the modified oligonucleotide comprises:

(a) a gap segment consisting of 10 linked deoxynucleosides;

(b) a 5' wing segment consisting of 5 linked nucleosides;

(c) a 3' wing segment consisting 5 linked nucleosides;

wherein the gap segment is positioned immediately adjacent to and between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a 2'-O-

methyoxyethyl sugar, wherein each cytosine is a 5'-methylcytosine, and wherein each internucleoside linkage is a phosphorothioate linkage.

41. The method or use of claims 38-40, wherein the modified oligonucleotide has a nucleobase sequence comprising at least 8 contiguous nucleobases of a nucleobase sequence of SEQ ID NO: 3.

42. A method of reducing the risk for a cardiovascular disease in an animal comprising administering to the animal a therapeutically effective amount of a compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein the modified oligonucleotide is complementary to an ApoCIII nucleic acid as shown in SEQ ID NO: 1 or SEQ ID NO: 2, and wherein the compound administered to the animal reduces the risk for a cardiovascular disease, by increasing HDL levels.

43. A method of reducing the risk for a cardiovascular disease or pancreatitis in an animal comprising administering to the animal a therapeutically effective amount of a compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, and having a nucleobase sequence comprising at least 8 contiguous nucleobases of SEQ ID NO: 3, and wherein the compound administered to the animal reduces the risk for a cardiovascular disease or pancreatitis, by increasing HDL levels and/or improving the ratio of TG to HDL.

44. A method of preventing, treating, ameliorating or reducing at least one symptom of a cardiovascular disease in an animal, comprising administering to the animal a therapeutically effective amount of a compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein the modified oligonucleotide is complementary to an ApoCIII nucleic acid, as shown in SEQ ID NO: 1 or SEQ ID NO: 2, and wherein the compound administered to the animal prevents, treats, ameliorates or reduces at least one symptom of the cardiovascular disease in the animal, by increasing HDL levels.

45. A method of preventing, treating, ameliorating or reducing at least one symptom of a cardiovascular disease in an animal, comprising administering to the animal a therapeutically effective amount of a compound comprising a modified oligonucleotide consisting of 12 to 30

linked nucleosides, and having a nucleobase sequence comprising at least 8 contiguous nucleobases of SEQ ID NO: 3, and wherein the compound administered to the animal prevents, treats, ameliorates or reduces at least one symptom of the cardiovascular disease in the animal, by increasing HDL levels in the animal.

46. A compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein the modified oligonucleotide is complementary to an ApoCIII nucleic acid as shown in SEQ ID NO: 1 or SEQ ID NO: 2, for use in reducing the risk for a cardiovascular disease in an animal, and wherein the compound reduces the risk for a cardiovascular disease by increasing HDL levels.

47. A compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, and having a nucleobase sequence comprising at least 8 contiguous nucleobases of SEQ ID NO: 3, for use in reducing the risk for a cardiovascular disease or pancreatitis in an animal, wherein the compound reduces the risk for a cardiovascular disease or pancreatitis by increasing HDL levels and/or improving the ratio of TG to HDL.

48. A compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein the modified oligonucleotide is complementary to an ApoCIII nucleic acid, as shown in SEQ ID NO: 1 or SEQ ID NO: 2, for use in preventing, treating, ameliorating or reducing at least one symptom of a cardiovascular disease in an animal, and wherein the compound prevents, treats, ameliorates or reduces at least one symptom of the cardiovascular disease in the animal by increasing HDL levels.

49. A compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, and having a nucleobase sequence comprising at least 8 contiguous nucleobases of SEQ ID NO: 3, for use in preventing, treating, ameliorating or reducing at least one symptom of a cardiovascular disease in an animal, wherein the compound prevents, treats, ameliorates or reduces at least one symptom of the cardiovascular disease in the animal by increasing HDL levels in the animal.

50. The method or use of any preceding claim, wherein the symptoms may be any one of, but not limited to, angina; chest pain; shortness of breath; palpitations; weakness; dizziness; nausea; sweating; tachycardia; bradycardia; arrhythmia; atrial fibrillation; swelling in the lower extremities; cyanosis; fatigue; fainting; numbness of the face; numbness of the limbs; claudication or cramping of muscles; bloating of the abdomen; or fever.

51. A method of raising HDL levels and/or improving the ratio of TG to HDL in an animal by administering to the animal a compound consisting of SEQ ID NO: 3 to raise the HDL levels and/or improving the ratio of TG to HDL in the animal.

52. A method of preventing, treating, ameliorating or reducing at least one symptom of a cardiovascular disease in an animal by administering to the animal a compound consisting of SEQ ID NO: 3 to prevent, treat, ameliorate or reduce at least one symptom of the cardiovascular disease in the animal, by increasing HDL levels and/or improving the ratio of TG to HDL in the animal.

53. A method of raising HDL levels and/or improving the ratio of TG to HDL in an animal by administering to the animal a modified oligonucleotide, having the sequence of SEQ ID NO: 3 wherein the modified oligonucleotide comprises:

(a) a gap segment consisting of 10 linked deoxynucleosides;

(b) a 5' wing segment consisting of 5 linked nucleosides;

(c) a 3' wing segment consisting 5 linked nucleosides;

wherein the gap segment is positioned immediately adjacent to and between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methyoxyethyl sugar, wherein each cytosine is a 5'-methylcytosine, and wherein each internucleoside linkage is a phosphorothioate linkage, wherein the modified oligonucleotide raises the HDL levels and/or improving the ratio of TG to HDL in the animal.

54. A method of preventing, treating, ameliorating or reducing at least one symptom of a cardiovascular disease in an animal by administering to the animal a modified oligonucleotide, having the sequence of SEQ ID NO: 3 wherein the modified oligonucleotide comprises:

(a) a gap segment consisting of 10 linked deoxynucleosides;

(b) a 5' wing segment consisting of 5 linked nucleosides;

(c) a 3' wing segment consisting 5 linked nucleosides;

wherein the gap segment is positioned immediately adjacent to and between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methyoxyethyl sugar, wherein each cytosine is a 5'-methylcytosine, and wherein each internucleoside linkage is a phosphorothioate linkage, wherein the modified oligonucleotide prevents, treats, ameliorates or reduces at least one symptom in the animal with the cardiovascular disease by raising the HDL levels and/or improving the ratio of TG to HDL in the animal.

55. A method of raising HDL levels and/or improving the ratio of TG to HDL in an animal by administering to the animal a compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein the modified oligonucleotide is complementary to an ApoCIII nucleic acid, as shown in SEQ ID NO: 1 or SEQ ID NO: 2, to raise the HDL levels and/or improving the ratio of TG to HDL in the animal.

56. A method of preventing, treating, ameliorating or reducing at least one symptom of a cardiovascular disease in an animal by administering to the animal a compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein the modified oligonucleotide is complementary to an ApoCIII nucleic acid, as shown in SEQ ID NO: 1 or SEQ ID NO: 2, to prevent, treat, ameliorate or reduce at least one symptom of the cardiovascular disease in the animal, by raising the HDL levels and/or improving the ratio of TG to HDL of the animal.

57. A method of decreasing CETP levels by administering to an animal a compound having a nucleobase sequence comprising at least 8 contiguous nucleobases of SEQ ID NO: 3, wherein CETP levels are decreased.

58. A method of increasing ApoA1, PON1, fat clearance, chylomicron triglyceride clearance or HDL by administering to an animal a compound having a nucleobase sequence comprising at least 8 contiguous nucleobases of SEQ ID NO: 3, wherein ApoA1, PON1, fat clearance, chylomicron triglyceride clearance or HDL is increased.

59. A method of decreasing CETP levels by administering to an animal a compound having a nucleobase sequence consisting of SEQ ID NO: 3, wherein CETP levels are decreased.

60. A method of increasing ApoA1, PON1, fat clearance, chylomicron triglyceride clearance or HDL by administering to an animal a compound consisting of at least 8 contiguous nucleobases of SEQ ID NO: 3, wherein ApoA1, PON1, fat clearance, chylomicron triglyceride clearance or HDL is increased.

61. A compound consisting of SEQ ID NO: 3, for use in raising HDL levels and/or improving the ratio of TG to HDL in an animal.

62. A compound consisting of SEQ ID NO: 3, for use in preventing, treating, ameliorating or reducing at least one symptom of a cardiovascular disease in an animal by increasing HDL levels and/or improving the ratio of TG to HDL in the animal.

63. A modified oligonucleotide, having the sequence of SEQ ID NO: 3 wherein the modified oligonucleotide comprises:

(a) a gap segment consisting of 10 linked deoxynucleosides;

(b) a 5' wing segment consisting of 5 linked nucleosides;

(c) a 3' wing segment consisting 5 linked nucleosides;

wherein the gap segment is positioned immediately adjacent to and between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methyoxyethyl sugar, wherein each cytosine is a 5'-methylcytosine, and wherein each internucleoside linkage is a phosphorothioate linkage, for use in raising HDL levels and/or improving the ratio of TG to HDL in an animal.

64. A modified oligonucleotide, having the sequence of SEQ ID NO: 3 wherein the modified oligonucleotide comprises:

(a) a gap segment consisting of 10 linked deoxynucleosides;

(b) a 5' wing segment consisting of 5 linked nucleosides;

(c) a 3' wing segment consisting 5 linked nucleosides;

wherein the gap segment is positioned immediately adjacent to and between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar, wherein each cytosine is a 5'-methylcytosine, and wherein each internucleoside linkage is a phosphorothioate linkage, for use in preventing, treating, ameliorating or reducing at least one symptom of a cardiovascular disease in an animal by raising the HDL levels and/or improving the ratio of TG to HDL in the animal.

65. A compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein the modified oligonucleotide is complementary to an ApoCIII nucleic acid, as shown in SEQ ID NO: 1 or SEQ ID NO: 2, for use in raising HDL levels and/or improving the ratio of TG to HDL in an animal.

66. A compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein the modified oligonucleotide is complementary to an ApoCIII nucleic acid, as shown in SEQ ID NO: 1 or SEQ ID NO: 2, for use in preventing, treating, ameliorating or reducing at least one symptom of a cardiovascular disease in an animal by raising the HDL levels and/or improving the ratio of TG to HDL of the animal.

67. A compound having a nucleobase sequence comprising at least 8 contiguous nucleobases of SEQ ID NO: 3, for use in decreasing CETP levels in an animal.

68. A compound having a nucleobase sequence comprising at least 8 contiguous nucleobases of SEQ ID NO: 3, for use in increasing ApoA1, PON1, fat clearance, chylomicron triglyceride clearance or HDL in an animal.

69. A compound having a nucleobase sequence consisting of SEQ ID NO: 3, for use in decreasing CETP levels in an animal.

70. A compound consisting of at least 8 contiguous nucleobases of SEQ ID NO: 3, for use in increasing ApoA1, PON1, fat clearance, chylomicron triglyceride clearance or HDL in an animal.

71. The method or use of any preceding claim, wherein the animal is human.

72. The method or use of any preceding claim, wherein the cardiovascular disease is aneurysm, angina, arrhythmia, atherosclerosis, cerebrovascular disease, coronary heart disease, hypertension, dyslipidemia, hyperlipidemia, hypertriglyceridemia or hypercholesterolemia.

73. The method or use of claim 72, wherein the dyslipidemia is chylomicronemia.

74. The method or use of claim 73, wherein the animal is at risk for pancreatitis.

75. The method or use of any preceding claim, wherein reducing ApoCIII levels prevents, treats or ameliorates pancreatitis.

76. The method or use of any preceding claim, wherein reducing ApoCIII levels enhance clearance of postprandial triglycerides.

77. The method or use of any preceding claim, wherein reducing ApoCIII levels lowers postprandial triglycerides.

78. The method or use of any preceding claim, wherein the compound is parenterally administered.

79. The method or use of claim 78, wherein the parenteral administration is subcutaneous administration.

80. The method or use of any preceding claim, further comprising a second agent.

81. The method or use of claim 80, wherein the second agent is selected from an ApoCIII lowering agent, cholesterol lowering agent, non-HDL lipid lowering agent, LDL lowering agent, TG lowering agent, cholesterol lowering agent, HDL raising agent, fish oil, niacin, fibrate, statin, DCCR (salt of diazoxide), glucose-lowering agent or anti-diabetic agents.

82. The method or use of claim 81, wherein the animal fails to respond to a maximally tolerated dose of the second agent.

83. The method or use of claim 80, wherein the second agent is administered concomitantly or sequentially with the compound.

84. The method or use of any preceding claim, wherein the compound is a salt form.

85. The method or use of any preceding claim, further comprising a pharmaceutically acceptable carrier or diluent.

CLAIMS

1. A method of increasing HDL levels or improving the ratio of TG to HDL by

(a) selecting an animal in need thereof;

(b) administering a compound targeting ApoCIII to the animal, whereby HDL levels are increased or the ratio of TG to HDL is improved;

(c) further comprising a second agent, wherein the second agent is selected from an ApoCIII lowering agent, cholesterol lowering agent, non-HDL lipid lowering agent, LDL lowering agent, TG lowering agent, cholesterol lowering agent, HDL raising agent, fish oil, niacin, fibrate, statin, DCCR (salt of diazoxide), glucose-lowering agent or anti-diabetic agents; and wherein the animal fails to respond to a maximally tolerated dose of the second agent.