infarction, heart failure, aneurysms (*e.g.* aortic aneurysm), peripheral artery disease, heart damage (*e.g.*, heart enlargement or hypertrophy) and other cardiovascular related diseases, disorders and/or conditions. In addition, hypertension has been shown to be an important risk factor for cardiovascular morbidity and mortality accounting for, or contributing to, 62% of all strokes and 49% of all cases of heart disease.

Despite the number of anti-hypertensive drugs available for treating hypertension, more than two-thirds of subjects are not controlled with one anti-hypertensive agent and require two or more anti-hypertensive agents selected from different drug classes. This further reduces the number of subjects with controlled blood pressure as compliance and side-effects increase with increasing medication.

Accordingly, there is a need in the art for alternative therapies and combination therapies for subjects having an angiotensinogen-associated disease.

Summary of the Invention

In one aspect, the present invention provides a double-stranded ribonucleic acid (RNAi) agent for inhibiting expression of angiotensinogen (AGT) in a cell, wherein said double-stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from nucleotides 2081-2104 of the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotides at the corresponding position of the nucleotide sequence of SEQ ID NO:2, and

wherein the antisense strand is substantially complementary to the sense strand,

wherein "substantially complementary" refers to not more than 5, 4, 3 or 2 mismatched base pairs upon hybridization.

In another aspect, the present invention provides a composition comprising a modified antisense polynucleotide agent, wherein said agent is capable of inhibiting the expression of AGT in a cell, and comprises a sequence complementary to the sequence of SEQ ID NO: 499, wherein the polynucleotide is 14 to 30 nucleotides in length.

In yet another aspect, the present invention provides a pharmaceutical composition comprising the double-stranded RNAi agent disclosed herein, or the composition comprising a modified antisense polynucleotide agent disclosed herein.

In yet another aspect, the present invention provides a double-stranded RNAi agent disclosed herein, or the composition comprising a modified antisense polynucleotide agent disclosed herein, or the pharmaceutical composition disclosed herein for use in a method of treating a subject having a angiotensinogen (AGT)-associated disorder.

In yet another aspect, the present invention provides a double-stranded ribonucleic acid (RNAi) agent for use in a method of treating a subject having a angiotensinogen (AGT)-associated disorder,

wherein said double-stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from nucleotides 2081-2104 of the nucleotide sequence of SEQ ID NO:1, and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotides at the corresponding position of the nucleotide sequence of SEQ ID NO:2,

wherein substantially all of the nucleotides of said antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus,

wherein substantially all of the nucleotides of said sense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus,

wherein said sense strand is conjugated to one or more GalNAc derivatives attached through a branched bivalent or trivalent linker at the 3'-terminus, thereby treating the subject, and

wherein said agent is to be administered subcutaneously,

wherein "substantially all" refers to not more than 5, 4, 3, 2 or 1 unmodified nucleotides.

In yet another aspect, the present invention provides use of a double-stranded RNAi agent disclosed herein, or the composition comprising a modified antisense polynucleotide agent disclosed herein, or the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating a subject having a angiotensinogen (AGT)-associated disorder.

In yet another aspect, the present invention provides use of a double-stranded ribonucleic acid (RNAi) agent in the manufacture of a medicament for treating a subject having a angiotensinogen (AGT)-associated disorder, wherein said double-stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from nucleotides 2081-2104 of the nucleotide sequence of SEQ ID NO:1, and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotides at the corresponding position of the nucleotide sequence of SEQ ID NO:2,

wherein substantially all of the nucleotides of said antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus,

wherein substantially all of the nucleotides of said sense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus,

wherein said sense strand is conjugated to one or more GalNAc derivatives attached through a branched bivalent or trivalent linker at the 3'-terminus, thereby treating the subject, and

wherein said agent is to be administered subcutaneously,

wherein "substantially all" refers to not more than 5, 4, 3, 2 or 1 unmodified nucleotides

The present disclosure provides iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of an angiotensinogen (AGT) gene. The AGT gene may be within a cell, *e.g.,* a cell within a subject, such as a human.

The present disclosure also provides methods and therapies for treating a subject having a disorder that would benefit from inhibiting or reducing the expression of an AGT gene, *e.g.,* an angiotensinogen-associated disease, such as hypertension, using iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of an AGT gene for inhibiting the expression of an AGT gene.

Accordingly, disclosed are double-stranded ribonucleic acid (RNAi) agents for inhibiting expression of angiotensinogen (AGT), which comprise a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2, wherein substantially all of the nucleotides of the

sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, and wherein the sense strand is conjugated to a ligand attached at the 3'-terminus. In one example, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

Also disclosed are double-stranded ribonucleic acid (RNAi) agents for inhibiting expression of angiotensinogen (AGT), which comprise a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand

comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from nucleotides 2801-2101; 803-843; 834-859; 803-859; 803-875; 834-875; 847-875; 1247-1271; 1566-1624; 1570-1624; 1584-1624; 1584-1624; 1584-1621; 2035-2144; 2070-2144; 2070-2103; 2201-2223; 2227-2360; 2227-2304; 2290-2318; 2304-2350; 2304-2326; 2320-2342; 2333-2360; 2333-2358; 485-503; 517-535; 560-578; 635-653; 803-821; 814-832; 822-840; 825-843; 834-852; 837-855; 841-859; 855-873; 967-985; 1247-1265; 1248-1266; 1249-1267; 1251-1269; 1253-1271; 1566-1584; 1570-1588; 1572-1590; 1574-1592; 1584-1602; 1587-1605; 1591-1609; 1592-1610; 1595-1613; 1601-1619; 1602-1620; 1605-1623; 1729-1747; 1738-1756; 1739-1757; 1741-1769; 1767-1785; 1810-1828; 1827-1845; 1880-1989; 1892-1914; 1894-1914;1894-2012; 2035-2053; 2046-2064; 2057-2075; 2070-2088; 2072-2090; 2078-2096; 2078-2107; 2078-2011; 2080-2098; 2081-2099; 2081-2104; 2081-2011; 2082-2100; 2084-2102; 2084-2011; 2090-2108; 2100-2118; 2111-2129; 2124-2142; 2125-2143; 2167-2185; 2179-2197; 2201-2219; 2202-2220; 2203-2221; 2204-2222; 2227-2245; 2230-2248; 2234-2252; 2244-2264; 2255-2273; 2266-2284; 2268-2286; 2270-2288; 2279-2297; 2281-2299; 2283-2301; 2284-2302; 2285-2303; 2286-2304; 2288-2306; 2290-2308; 2291-2309; 2291-2311; 2291-2318; 2291-2315; 2292-2310; 2294-2312; 2296-2314; 2299-2317; 2304-2322; 2304-2329; 2306-2324; 2307-2325; 2309-2327; 2309-2329; 2309-2342; 2309-2350; 2309-2358; 2314-2332; 2316-2334; 2317-2335; 2320-2338; 2321-2339; 2323-2341; 2325-2343; 2326-2344; 2328-2346; 2329-2347; 2331-2349; 2333-2351; 2334-2352; 2335-2353; 2339-2357; 2340-2358; or 2341-2359 of the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotides at the corresponding position of the nucleotide sequence of SEQ ID NO:2 such that the antisense strand is substantially complementary to the at least 15 contiguous nucleotides in the sense strand. In certain examples, substantially all of the nucleotides of the sense strand are modified nucleotides. In other examples, substantially all of the nucleotides of the antisense strand are modified nucleotides. In yet other examples, substantially all of the nucleotides of both strands are modified nucleotides. In one example, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides. In one example, the sense strand is conjugated to a ligand attached at the 3'-terminus. In one example, the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from nucleotides 2801-2101 of the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotides at the corresponding position of the nucleotide sequence of SEQ ID NO:2 such that the antisense strand is substantially complementary to the at least 15 contiguous nucleotides in the sense strand.

Also disclosed are double-stranded ribonucleic acid (RNAi) agents for inhibiting expression of angiotensinogen (AGT), which comprise a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides from nucleotides 803-843; 834-859; 803-859; 1247-1271; 1566-1624; 1570-1624; 1584-1624; 1584-1624; 1584-1621; 2035-2144; 2070-2144; 2070-2103; 2201-2223; 2227-2360; 2227-2304; 2290-2318; 2304-2350; 2304-2326; 2320-2342; 2333-2360; 2333-2358; 485-503; 517-535; 560-578; 635-653; 803-821; 814-832; 822-840; 825-843; 834-852; 837-855; 841-859; 855-873; 967-985; 1247-1265; 1248-1266; 1249-1267; 1251-1269; 1253-1271; 1566-1584; 1570-1588; 1572-1590; 1574-1592; 1584-1602; 1587-1605; 1591-1609; 1592-1610; 1595-1613; 1601-1619; 1602-1620; 1605-1623; 1729-1747; 1738-1756; 1739-1757; 1741-1769; 1767-1785; 1810-1828; 1827-1845; 1880-1989; 1894-2012; 2035-2053; 2046-2064; 2057-2075; 2070-2088; 2072-2090; 2078-2096; 2080-2098; 2081-2099; 2082-2100; 2084-2102; 2090-2108; 2100-2118; 2111-2129; 2124-2142; 2125-2143; 2167-2185; 2179-2197; 2201-2219; 2202-2220; 2203-2221; 2204-2222; 2227-2245; 2230-2248; 2234-2252; 2244-2264; 2255-2273; 2266-2284; 2268-2286; 2270-2288; 2279-2297; 2281-2299; 2283-2301; 2284-2302; 2285-2303; 2286-2304; 2288-2306; 2290-2308; 2291-2309; 2292-2310; 2294-2312; 2296-2314; 2299-2317; 2304-2322; 2306-2324; 2307-2325; 2309-2327; 2314-2332; 2316-2334; 2317-2335; 2320-2338; 2321-2339; 2323-2341; 2325-2343; 2326-2344; 2328-2346; 2329-2347; 2331-2349; 2333-2351; 2334-2352; 2335-2353; 2339-2357; 2340-2358; or 2341-2359 of the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleoides from the nucleotides at the corresponding position of the nucleotide sequence of SEQ ID NO:2 such that the antisense strand is substantially complementary to the at least 15 contiguous nucleotides in the sense strand. In certain examples, substantially all of the nucleotides of the sense strand are modified nucleotides. In other examples, substantially all of the nucleotides of the antisense strand are modified nucleotides. In yet other examples, substantially all of the nucleotides of both strands are modified nucleotides. In one example, the sense strand is conjugated to a ligand attached at the 3'-terminus.

In one example, the sense strand and the antisense strand comprise a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 3, 4, 7, 8, 11, 13, and 15. For example, in certain examples, the sense strand and the antisense strand comprise a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences of the duplexes AD-52433.1, AD-52438.1, AD-52439.1, AD-52445.1, AD-52449.1, AD-52451.1, AD-52456.1, AD-52457.1, AD-52462.1, AD-52463.1, AD-52469.1, AD-52474.1, AD-55976.1, AD-55978.1, AD-55979.1, AD-55980.1, AD-55981.1, AD-55982.1, AD-

55983.1, AD-55984.1, AD-55987.1, AD-55988.1, AD-55989.1, AD-55990.1, AD-55991.1, AD-55994.1, AD-55995.1, AD-55996.1, AD-55999.1, AD-56000.1, AD-56001.1, AD-56002.1, AD-56003.1, AD-56006.1, AD-56007.1, AD-56008.1, AD-56009.1, AD-56011.1, AD-56012.1, AD-56013.1, AD-56016.1, AD-56017.1, AD-56019.1, AD-56020.1, AD-56021.1, AD-56022.1, AD-56024.1, AD-56026.1, AD-56027.1, AD-56029.1, AD-56030.1, AD-56031.1, AD-56032.1, AD-56035.1, AD-56039.1, AD-56041.1, AD-56043.1, AD-56044.1, AD-56047.1, AD-56048.1, AD-56051.1, AD-56053.1, AD-56054.1, AD-56059.1, AD-56062.1, AD-56065.1, AD-56066.1, AD-60770.1, AD-60771.1, AD-60776.1, AD-60777.1, AD-60778.1, AD-60779.1, AD-60780.1, AD-60781.1, AD-60783.1, AD-60784.1, AD-60785.1, AD-60788.1, AD-60789.1, AD-60791.1, AD-60793.1, AD-60795.1, AD-60798.1, AD-60801.1, AD-67903.1, AD-67906.1, AD-67923.1, AD-67924.1, AD-67925.1, AD-67926.1, AD-67935.1, AD-67965.1, AD-67994.1, AD-67995.1, AD-67996.1, AD-68017.1, AD-68022.1, AD-68035.1, AD-68036.1, AD-68037.1, AD-68084.2, AD-68085.2, AD-68086.2, AD-68087.2, AD-68090.2, AD-68091.2, AD-68092.2, AD-68093.2, AD-68116.1, AD-68117.1, AD-68118.1, AD-68124.1, AD-68125.1, or AD-68126.1. In certain examples, the sense strand and the antisense strand comprise a region of complementarity which comprises at least 15 contiguous nucleotides of the region of complementarity of any one of duplexes AD-52433.1, AD-52438.1, AD-52439.1, AD-52445.1, AD-52449.1, AD-52451.1, AD-52456.1, AD-52457.1, AD-52462.1, AD-52463.1, AD-52469.1, AD-52474.1, AD-55976.1, AD-55978.1, AD-55979.1, AD-55980.1, AD-55981.1, AD-55982.1, AD-55983.1, AD-55984.1, AD-55987.1, AD-55988.1, AD-55989.1, AD-55990.1, AD-55991.1, AD-55994.1, AD-55995.1, AD-55996.1, AD-55999.1, AD-56000.1, AD-56001.1, AD-56002.1, AD-56003.1, AD-56006.1, AD-56007.1, AD-56008.1, AD-56009.1, AD-56011.1, AD-56012.1, AD-56013.1, AD-56016.1, AD-56017.1, AD-56019.1, AD-56020.1, AD-56021.1, AD-56022.1, AD-56024.1, AD-56026.1, AD-56027.1, AD-56029.1, AD-56030.1, AD-56031.1, AD-56032.1, AD-56035.1, AD-56039.1, AD-56041.1, AD-56043.1, AD-56044.1, AD-56047.1, AD-56048.1, AD-56051.1, AD-56053.1, AD-56054.1, AD-56059.1, AD-56062.1, AD-56065.1, AD-56066.1, AD-60770.1, AD-60771.1, AD-60776.1, AD-60777.1, AD-60778.1, AD-60779.1, AD-60780.1, AD-60781.1, AD-60783.1, AD-60784.1, AD-60785.1, AD-60788.1, AD-60789.1, AD-60791.1, AD-60793.1, AD-60795.1, AD-60798.1, AD-60801.1, AD-67903.1, AD-67906.1, AD-67923.1, AD-67924.1, AD-67925.1, AD-67926.1, AD-67935.1, AD-67965.1, AD-67994.1, AD-67995.1, AD-67996.1, AD-68017.1, AD-68022.1, AD-68035.1, AD-68036.1, AD-68037.1, AD-68084.2, AD-68085.2, AD-68086.2, AD-68087.2, AD-68090.2, AD-68091.2, AD-68092.2, AD-68093.2, AD-68116.1, AD-68117.1, AD-68118.1, AD-68124.1, AD-68125.1, or AD-68126.1.

In one example, the antisense strand comprises a region of complementarity which comprises at least 15 contiguous unmodified nucleotides differing by no more than 3

nucleotides from the antisense nucleotide sequence of AD-67327 (5'-AUUAGAAGAAAAGGUGGGAGACU-3'; SEQ ID NO:537). In another example, the region of complementarity consists of the antisense unmodified nucleotide sequence of AD-67327 (5'- AUUAGAAGAAAAGGUGGGAGACU-3'; SEQ ID NO:537). In one example, the dsRNA comprises a sense strand consisting of the nucleotide sequence of 5'-UCUCCCACCUUUUCUUCUAAU-3' (SEQ ID NO:499), and an antisense strand consisting of the nucleotide sequence of 5'-UUAGAAGAAAAGGUGGGAGACU-3' (SEQ ID NO:537). In one example, the double-stranded RNAi agent comprises the modified nucleotide sequence of AD-67327 (5'-uscsucccAfcCfUfUfuucuucuaau-3'; SEQ ID NO:1037 and 5'-asUfsuagAfagaaaagGfuGfggagascsu-3'; SEQ ID NO:1038.

In some examples, the modified nucleotide(s) is independently selected from the group consisting of a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a nucleotide comprising a 5'-phosphorothioate group, and a terminal nucleotide linked to a cholesteryl derivative or a dodecanoic acid bisdecylamide group. In further examples, the modified nucleotide is selected from the group consisting of a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide a conformationally restricted nucleotide, a contrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a 2'-O-allyl modified nucleotide, a 2'-C-allyl modified nucleotide, a 2'-hydroxyl modified nucleotide, a morpholino nucleotide, a phosphoramidate, and a non-natural base comprising nucleotide.

In another example of the double-stranded RNAi agent, at least one strand comprises a 3' overhang of at least 1 nucleotide. In another example, at least one strand comprises a 3' overhang of at least 2 nucleotides.

Also disclosed are RNAi agents, *e.g.*, double-stranded ribonucleic acid (RNAi) agents capable of inhibiting the expression of angiotensinogen (AGT) in a cell, wherein the double-stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding AGT, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double-stranded RNAi agent is represented by formula (III):

sense: $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (III)

wherein:

i, j, k, and l are each independently 0 or 1;

p, p', q, and q' are each independently 0-6;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each

sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

each n_p, n_p', n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y'; and

wherein the sense strand is conjugated to at least one ligand.

In one example, i is 0; j is 0; i is 1; j is 1; both i and j are 0; or both i and j are 1. In another example, k is 0; l is 0; k is 1; l is 1; both k and l are 0; or both k and l are 1.

In one example, XXX is complementary to X'X'X', YYY is complementary to Y'Y'Y', and ZZZ is complementary to Z'Z'Z'.

In one example, the YYY motif occurs at or near the cleavage site of the sense strand.

In another example, the Y'Y'Y' motif occurs at the 11, 12 and 13 positions of the antisense strand from the 5'-end.

In one example, Y' is 2'-O-methyl.

In one example, formula (III) is represented by formula (IIIa):

sense: 5' n_p -N_a -Y Y Y -N_a - n_q 3'

antisense: 3' $n_{p'}$-$N_{a'}$- Y'Y'Y'- $N_{a'}$- $n_{q'}$ 5' (IIIa).

In another example, formula (III) is represented by formula (IIIb):

sense: 5' n_p -N_a -Y Y Y -N_b -Z Z Z -N_a - n_q 3'

antisense: 3' $n_{p'}$-$N_{a'}$- Y'Y'Y'-$N_{b'}$-Z'Z'Z'- $N_{a'}$- $n_{q'}$ 5' (IIIb)

wherein each N_b and N_b' independently represents an oligonucleotide sequence comprising 1-5 modified nucleotides.

In yet another example, formula (III) is represented by formula (IIIc):

sense: 5' n_p -N_a –X X X -N_b -Y Y Y -N_a - n_q 3'

antisense: 3' $n_{p'}$-$N_{a'}$- X'X'X'-$N_{b'}$- Y'Y'Y'- $N_{a'}$- $n_{q'}$ 5' (IIIc)

wherein each N_b and N_b' independently represents an oligonucleotide sequence comprising 1-5 modified nucleotides.

In a further example, formula (III) is represented by formula (IIId):

sense: 5' n_p -N_a –X X X- N_b -Y Y Y -N_b -Z Z Z -N_a - n_q 3'

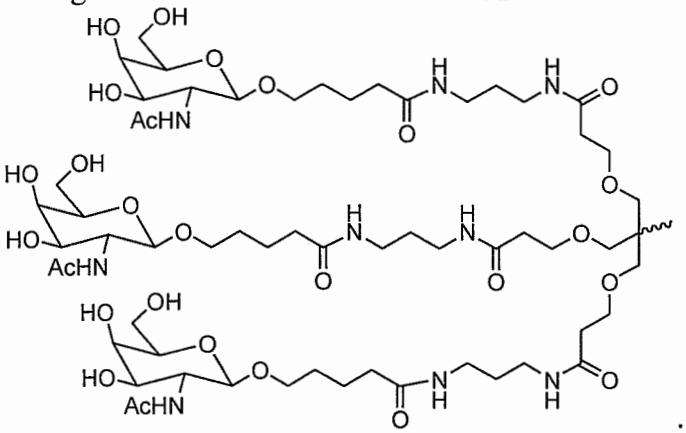
antisense: 3' $n_{p'}$-$N_{a'}$- X'X'X'- $N_{b'}$-Y'Y'Y'-$N_{b'}$-Z'Z'Z'- $N_{a'}$- $n_{q'}$ 5' (IIId)

wherein each N_b and N_b' independently represents an oligonucleotide sequence comprising 1-5 modified nucleotides and each N_a and N_a' independently represents an oligonucleotide sequence comprising 2-10 modified nucleotides.

In one example, the double-stranded region is 15-30 nucleotide pairs in length. In another example, the double-stranded region is 17-23 nucleotide pairs in length. In yet another example, the double-stranded region is 17-25 nucleotide pairs in length. In a further example, the double-stranded region is 23-27 nucleotide pairs in length. In another example, the double-stranded region is 19-21 nucleotide pairs in length. In another example, the double-stranded region is 19-23 nucleotide pairs in length. In another example, the double-stranded region is 21-23 nucleotide pairs in length. In yet another example, each strand has 15-30 nucleotides. In yet another example, each strand has 19-30 nucleotides.

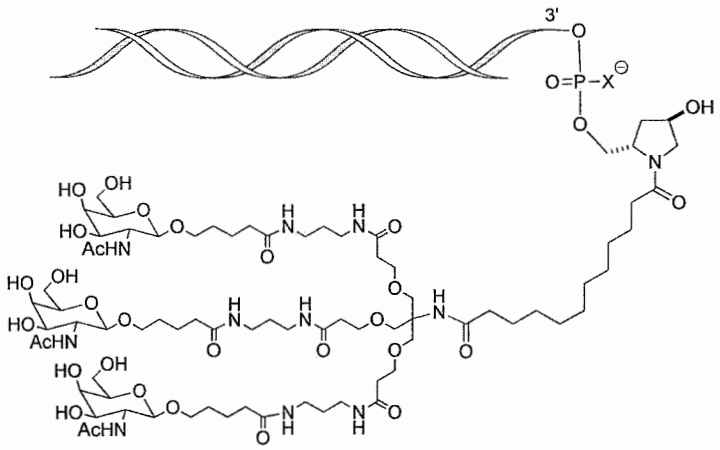
In one example, the modifications on the nucleotides are selected from the group consisting of LNA, UNA, CRN, cEt, HNA, CeNA, 2′-methoxyethyl, 2′-O-alkyl, 2′-O-allyl, 2′-C- allyl, 2′-fluoro, 2′-deoxy, 2'-hydroxyl, and combinations thereof. In another example, the modifications on the nucleotides are 2′-O-methyl or 2′-fluoro modifications.

In one example, the ligand the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker. In another example, the ligand is



In one example, the ligand is attached to the 3′ end of the sense strand.

In another example, the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S. In a specific example, X is O.

In one example, the agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

In a further example, the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand. In another example, the strand is the antisense strand. In another example, the strand is the sense strand.

In one example, the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand. In another example, the strand is the antisense strand. In a further example, the strand is the sense strand.

In one example, the phosphorothioate or methylphosphonate internucleotide linkage is at the both the 5'- and 3'-terminus of one strand. In another example, the strand is the antisense strand.

In another example, the double-stranded RNAi agent comprises 6-8 phosphorothioate internucleotide linkages. In a further example, the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and the sense strand comprises at least two phosphorothioate internucleotide linkages at either the 5'-terminus or the 3'-terminus of the sense strand.

In one example, the base pair at the 1 position of the 5'-end of the antisense strand of the duplex is an AU base pair. In another example, the Y nucleotides contain a 2'-fluoro modification. In a further example, the Y' nucleotides contain a 2'-O-methyl modification.

In one example, p'>0. In another example, p'=2. In a further example, q'=0, p=0, q=0, and p' overhang nucleotides are complementary to the target mRNA. In yet a further example, q'=0, p=0, q=0, and p' overhang nucleotides are non-complementary to the target mRNA.

In one example, the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.

In another example, at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage. In a further example, all n_p' are linked to neighboring nucleotides via phosphorothioate linkages.

In another example, the RNAi agent is selected from the group of RNAi agents listed in any one of Tables 3, 4, 7, 8, 11, 13, and 15.

Also disclosed are double-stranded ribonucleic acid (RNAi) agents for inhibiting expression of angiotensinogen (AGT). The double-stranded RNAi agents include a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2, wherein substantially all of the nucleotides of the sense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification wherein the sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus, wherein substantially all of the nucleotides of the antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,wherein the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and wherein the sense strand is conjugated to one or more GalNAc derivatives attached through a branched bivalent or trivalent linker at the 3'-terminus.

In one example, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

Also disclosed are RNAi agents, *e.g.*, double-stranded ribonucleic acid (RNAi) agents capable of inhibiting the expression of AGT (angiotensinogen) in a cell, wherein the double-stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding AGT, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double-stranded RNAi agent is represented by formula (III):

sense: $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (III)

wherein:

i, j, k, and l are each independently 0 or 1;

p, p', q, and q' are each independently 0-6;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each

sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

each n_p, n_p', n_q, and n_q', each of which may or may not be present independently represents an overhang nucleotide;

XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2'-O-methyl or 2'-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y'; and

wherein the sense strand is conjugated to at least one ligand.

Also disclosed are RNAi agents, *e.g.*, double-stranded ribonucleic acid (RNAi) agents capable of inhibiting the expression of angiotensinogen (AGT) in a cell, wherein the double-stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding AGT, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double-stranded RNAi agent is represented by formula (III):

sense: $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (III)

wherein:

i, j, k, and l are each independently 0 or 1;

each n_p, n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q' are each independently 0-6;

$n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2'-O-methyl or 2'-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ

from the modification on Y′; and

wherein the sense strand is conjugated to at least one ligand.

Also disclosed are RNAi agents, *e.g.*, double-stranded ribonucleic acid (RNAi agent) capable of inhibiting the expression of angiotensinogen (AGT) in a cell, wherein the double-stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding AGT, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double-stranded RNAi agent is represented by formula (III):

sense: $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (III)

wherein:

i, j, k, and l are each independently 0 or 1;

each n_p, n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q′ are each independently 0-6;

$n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y′; and

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

Also disclosed are RNAi agents, *e.g.*, double-stranded ribonucleic acid (RNAi) agents capable of inhibiting the expression of angiotensinogen (AGT) in a cell, wherein the double-stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding AGT, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double-stranded RNAi agent is represented by formula (III):

sense: $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}\ n_q'\ 5'$ (III)

wherein:

i, j, k, and l are each independently 0 or 1;

each n_p, n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q′ are each independently 0-6;

$n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y′;

wherein the sense strand comprises at least one phosphorothioate linkage; and

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

Also disclosed are RNAi agents, *e.g.*,double-stranded ribonucleic acid (RNAi) agent capable of inhibiting the expression of angiotensinogen (AGT) in a cell, wherein the double-stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding AGT, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double-stranded RNAi agent is represented by formula (III):

sense: $5'\ n_p\text{-}N_a\text{-}Y\ Y\ Y\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}Y'Y'Y'\text{-}N_a'\text{-}n_q'\ 5'$ (IIIa)

wherein:

each n_p, n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q′ are each independently 0-6;

$n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-

25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

YYY and Y'Y'Y' each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2'-O-methyl or 2'-fluoro modifications;

wherein the sense strand comprises at least one phosphorothioate linkage; and

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

Also disclosed is a double-stranded RNAi agent comprising the RNAi agents listed in any one of Tables 3, 4, 7, 8, 11, 13, and 15.

Also disclosed is a composition comprising a modified antisense polynucleotide agent, wherein the agent is capable of inhibiting the expression of angiotensinogen (AGT) in a cell, and comprises a sequence complementary to a sense sequence selected from the group of the sequences listed in Tables 3, 4, 7, 8, 11, 13, and 15, wherein the polynucleotide is about 14 to about 30 nucleotides in length.

The present disclosure also provides cells, vectors, host cells and pharmaceutical compositions comprising the double-stranded RNAi agents of the disclosure.

In one example, a cell contains the double-stranded RNAi agent.

In some examples, the double-stranded RNAi agent or the composition comprising a modified antisense polynucleotide agent is administered using a pharmaceutical composition.

In one example, the pharmaceutical compositions of the disclosure comprise a lipid formulation, such as XTC or MC3.

In preferred examples, the double-stranded RNAi agent is administered in a solution. In some examples, the double-stranded RNAi agent is administered in an unbuffered solution. In another example, the unbuffered solution is saline or water. In another example, the double-stranded RNAi agent is administered with a buffer solution. In yet another example, the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof. In some example, the buffer solution is phosphate buffered saline (PBS).

Also disclosed are methods of inhibiting angiotensinogen (AGT) expression in a cell. The methods include contacting the cell with the double-stranded RNAi agent, a pharmaceutical composition, a composition comprising a modified antisense polynucleotide agent, or a vector comprising the RNAi agent and maintaining the cell produced for a time sufficient to obtain degradation of the mRNA transcript of a AGT gene, thereby inhibiting expression of the AGT gene in the cell.

In one example, the cell is within a subject. In a further example, the subject is a human. In a further example, the subject suffers from an angiotensinogen-associated disease.

In one example, the AGT expression is inhibited by at least about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98% or about 100%.

In one example, the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from nucleotides 2801-2101; 803-843; 834-859; 803-859; 803-875; 834-875; 847-875; 1247-1271; 1566-1624; 1570-1624; 1584-1624; 1584-1624; 1584-1621; 2035-2144; 2070-2144; 2070-2103; 2201-2223; 2227-2360; 2227-2304; 2290-2318; 2304-2350; 2304-2326; 2320-2342; 2333-2360; 2333-2358; 485-503; 517-535; 560-578; 635-653; 803-821; 814-832; 822-840; 825-843; 834-852; 837-855; 841-859; 855-873; 967-985; 1247-1265; 1248-1266; 1249-1267; 1251-1269; 1253-1271; 1566-1584; 1570-1588; 1572-1590; 1574-1592; 1584-1602; 1587-1605; 1591-1609; 1592-1610; 1595-1613; 1601-1619; 1602-1620; 1605-1623; 1729-1747; 1738-1756; 1739-1757; 1741-1769; 1767-1785; 1810-1828; 1827-1845; 1880-1989; 1892-1914; 1894-1914;1894-2012; 2035-2053; 2046-2064; 2057-2075; 2070-2088; 2072-2090; 2078-2096; 2078-2107; 2078-2011; 2080-2098; 2081-2099; 2081-2104; 2081-2011; 2082-2100; 2084-2102; 2084-2011; 2090-2108; 2100-2118; 2111-2129; 2124-2142; 2125-2143; 2167-2185; 2179-2197; 2201-2219; 2202-2220; 2203-2221; 2204-2222; 2227-2245; 2230-2248; 2234-2252; 2244-2264; 2255-2273; 2266-2284; 2268-2286; 2270-2288; 2279-2297; 2281-2299; 2283-2301; 2284-2302; 2285-2303; 2286-2304; 2288-2306; 2290-2308; 2291-2309; 2291-2311; 2291-2318; 2291-2315; 2292-2310; 2294-2312; 2296-2314; 2299-2317; 2304-2322; 2304-2329; 2306-2324; 2307-2325; 2309-2327; 2309-2329; 2309-2342; 2309-2350; 2309-2358; 2314-2332; 2316-2334; 2317-2335; 2320-2338; 2321-2339; 2323-2341; 2325-2343; 2326-2344; 2328-2346; 2329-2347; 2331-2349; 2333-2351; 2334-2352; 2335-2353; 2339-2357; 2340-2358; or 2341-2359 of the nucleotide sequence of SEQ ID NO:1.

Also disclosed are methods of treating a subject having a angiotensinogen (AGT)-associated disorder, comprising administering to the subject a therapeutically effective amount of the double-stranded RNAi agent, a composition comprising a modified antisense polynucleotide agent, or a pharmaceutical composition comprising the double-stranded RNAi agent, thereby treating the subject.

Also disclosed are methods of treating a subject having a angiotensinogen (AGT)-associated disorder which include subcutaneously administering to the subject a therapeutically effective amount of a double-stranded ribonucleic acid (RNAi agent), wherein the double-stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises at least 15

contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2, wherein substantially all of the nucleotides of the antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoromodification, wherein the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, wherein substantially all of the nucleotides of the sense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification, wherein the sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and, wherein the sense strand is conjugated to one or more GalNAc derivatives attached through a branched bivalent or trivalent linker at the 3'-terminus.

In one example, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

Also disclosed are methods of treating a subject having a angiotensinogen (AGT)-associated disorder which include administering to the subject a therapeutically effective amount of a double-stranded ribonucleic acid (RNAi agent), wherein the double-stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from nucleotides 2801-2101; 803-843; 834-859; 803-859; 803-875; 834-875; 847-875; 1247-1271; 1566-1624; 1570-1624; 1584-1624; 1584-1624; 1584-1621; 2035-2144; 2070-2144; 2070-2103; 2201-2223; 2227-2360; 2227-2304; 2290-2318; 2304-2350; 2304-2326; 2320-2342; 2333-2360; 2333-2358; 485-503; 517-535; 560-578; 635-653; 803-821; 814-832; 822-840; 825-843; 834-852; 837-855; 841-859; 855-873; 967-985; 1247-1265; 1248-1266; 1249-1267; 1251-1269; 1253-1271; 1566-1584; 1570-1588; 1572-1590; 1574-1592; 1584-1602; 1587-1605; 1591-1609; 1592-1610; 1595-1613; 1601-1619; 1602-1620; 1605-1623; 1729-1747; 1738-1756; 1739-1757; 1741-1769; 1767-1785; 1810-1828; 1827-1845; 1880-1989; 1892-1914; 1894-1914;1894-2012; 2035-2053; 2046-2064; 2057-2075; 2070-2088; 2072-2090; 2078-2096; 2078-2107; 2078-2011; 2080-2098; 2081-2099; 2081-2104; 2081-2011; 2082-2100; 2084-2102; 2084-2011; 2090-2108; 2100-2118; 2111-2129; 2124-2142; 2125-2143; 2167-2185; 2179-2197; 2201-2219; 2202-2220; 2203-2221; 2204-2222; 2227-2245; 2230-2248; 2234-2252; 2244-2264; 2255-2273; 2266-2284; 2268-2286; 2270-2288; 2279-2297; 2281-2299; 2283-2301; 2284-2302; 2285-2303; 2286-2304; 2288-2306; 2290-2308; 2291-2309; 2291-2311; 2291-2318; 2291-2315; 2292-2310; 2294-2312; 2296-2314; 2299-2317; 2304-2322; 2304-2329; 2306-2324; 2307-2325; 2309-2327; 2309-2329; 2309-2342; 2309-2350; 2309-2358; 2314-2332; 2316-2334;

2317-2335; 2320-2338; 2321-2339; 2323-2341; 2325-2343; 2326-2344; 2328-2346; 2329-2347; 2331-2349; 2333-2351; 2334-2352; 2335-2353; 2339-2357; 2340-2358; or 2341-2359 of the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotides at the corresponding position of the nucleotide sequence of SEQ ID NO:2 such that the antisense strand is substantially complementary to the at least 15 contiguous nucleotides in the sense strand. In certain examples, substantially all of the nucleotides of the sense strand are modified nucleotides. In other examples, substantially all of the nucleotides of the antisense strand are modified nucleotides. In yet other examples, substantially all of the nucleotides of both strands are modified nucleotides. In one example, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides. In one example, the sense strand is conjugated to a ligand attached at the 3'-terminus.

Also disclosed are methods of treating a subject having a angiotensinogen (AGT)-associated disorder which include administering to the subject a therapeutically effective amount of a double-stranded ribonucleic acid (RNAi agent), wherein the double-stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides from nucleotides 803-843; 834-859; 803-859; 1247-1271; 1566-1624; 1570-1624; 1584-1624; 1584-1624; 1584-1621; 2035-2144; 2070-2144; 2070-2103; 2201-2223; 2227-2360; 2227-2304; 2290-2318; 2304-2350; 2304-2326; 2320-2342; 2333-2360; 2333-2358; 485-503; 517-535; 560-578; 635-653; 803-821; 814-832; 822-840; 825-843; 834-852; 837-855; 841-859; 855-873; 967-985; 1247-1265; 1248-1266; 1249-1267; 1251-1269; 1253-1271; 1566-1584; 1570-1588; 1572-1590; 1574-1592; 1584-1602; 1587-1605; 1591-1609; 1592-1610; 1595-1613; 1601-1619; 1602-1620; 1605-1623; 1729-1747; 1738-1756; 1739-1757; 1741-1769; 1767-1785; 1810-1828; 1827-1845; 1880-1989; 1894-2012; 2035-2053; 2046-2064; 2057-2075; 2070-2088; 2072-2090; 2078-2096; 2080-2098; 2081-2099; 2082-2100; 2084-2102; 2090-2108; 2100-2118; 2111-2129; 2124-2142; 2125-2143; 2167-2185; 2179-2197; 2201-2219; 2202-2220; 2203-2221; 2204-2222; 2227-2245; 2230-2248; 2234-2252; 2244-2264; 2255-2273; 2266-2284; 2268-2286; 2270-2288; 2279-2297; 2281-2299; 2283-2301; 2284-2302; 2285-2303; 2286-2304; 2288-2306; 2290-2308; 2291-2309; 2292-2310; 2294-2312; 2296-2314; 2299-2317; 2304-2322; 2306-2324; 2307-2325; 2309-2327; 2314-2332; 2316-2334; 2317-2335; 2320-2338; 2321-2339; 2323-2341; 2325-2343; 2326-2344; 2328-2346; 2329-2347; 2331-2349; 2333-2351; 2334-2352; 2335-2353; 2339-2357; 2340-2358; or 2341-2359 of the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides from the nucleotides at the corresponding position of the nucleotide sequence of SEQ ID NO:2 such that the antisense strand is

substantially complementary to the at least 15 contiguous nucleotides in the sense strand. In certain examples, substantially all of the nucleotides of the sense strand are modified nucleotides. In other examples, substantially all of the nucleotides of the antisense strand are modified nucleotides. In yet other examples, substantially all of the nucleotides of both strands are modified nucleotides. In one example, the sense strand is conjugated to a ligand attached at the 3'-terminus.

In one example, the subject is a human.

In one example, the angiotensinogen-associated disease is selected from the group consisting of hypertension, borderline hypertension, primary hypertension, secondary hypertension, hypertensive emergency, hypertensive urgency, isolated systolic or diastolic hypertension, pregnancy-associated hypertension, diabetic hypertension, resistant hypertension, refractory hypertension, paroxysmal hypertension, renovascular hypertension, Goldblatt hypertension, ocular hypertension, glaucoma, pulmonary hypertension, portal hypertension, systemic venous hypertension, systolic hypertension, labile hypertension; hypertensive heart disease, hypertensive nephropathy, atherosclerosis, arteriosclerosis, vasculopathy, diabetic nephropathy, diabetic retinopathy, chronic heart failure, cardiomyopathy, diabetic cardiac myopathy,glomerulosclerosis, coarctation of the aorta, aortic aneurism, ventricular fibrosis, Cushing's syndrome, and other glucocorticoid excess states including chronic steroid therapy, pheochromocytoma, reninoma, secondary aldosteronism and other mineralocorticoid excess states, sleep apnea, thyroid/parathyroid disease, heart failure, myocardial infarction, angina, stroke, diabetes mellitus, renal disease, renal failure, systemic sclerosis, intrauterine growth restriction (IUGR) , and fetal growth restriction.

In another example, the angiotensinogen-associated disease is selected from the group consisting of hypertension, hypertensive heart disease, hypertensive nephropathy, pregnancy-associated hypertension, atherosclerosis, arteriosclerosis, chronic kidney disease, glomerulosclerosis, coarctation of the aorta, aortic aneurism, ventricular fibrosis, Cushing's syndrome, and other glucocorticoid excess states including chronic steroid therapy, pheochromocytoma, primary aldosteronism and other mineralocorticoid excess states, sleep apnea, thyroid/parathyroid disease, heart failure, myocardial infarction, stroke, diabetes mellitus, renal failure, and systemic sclerosis.

In one example, the angiotensinogen-associated disease is pregnancy-associated hypertension (*e.g.,* pregnancy-induced hypertension, preeclampsia, and eclampsia) and administration of an iRNA of the disclosure to a subject results in a decrease in maternal blood pressure; a decrease in maternal albuminuria; an increase in uteroplacental unit weight; an increase in fetal weight; normalization of the fetal brain:liver ratio; a decrease in AGT mRNA expression in the maternal liver and no significant decrease in hAGT mRNA

expression in the placenta; an increase in overall placenta size; an increase in the size of the villous placenta; no significant change in the size of the trophospongium of the placenta; a reduction in the ratio of sFLT1:PLGF mRNA expression in the maternal kidney; a reduction in the ratio of serum sFLT1:PLGF levels; and/or a decrease in the level of agonistic autoantibodies to AT1.

In one example, the double-stranded RNAi agent is administered at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 50 mg/kg. In a preferred example, the double-stranded RNAi agent is administered at a dose of about 10 mg/kg, about 30 mg/kg, or about 3.0 mg/kg. In one example, the double-stranded RNAi agent is administered at a dose of about 10 mg/kg. In one example, the double-stranded RNAi agent is administered at a dose of about 0.5 mg/kg twice per week. In another example, the double-stranded RNAi agent is administered at a dose of about 10 mg/kg every other week. In another example, the double-stranded RNAi agent is administered at a dose of about 0.5-1.0 mg/kg once per week. In another example, the RNAi agent is administered about once per week, once per month, once every other two months, or once a quarter (*i.e.*, once every three months) at a dose of about 0.1 mg/kg to about 5.0 mg/kg.

In one example, the double-stranded RNAi agent is administered subcutaneously or intravenously.

In one example, the RNAi agent is administered in two or more doses.

In one example, the RNAi agent is administered at intervals selected from the group consisting of once every about 12 hours, once every about 24 hours, once every about 48 hours, once every about 72 hours, and once every about 96 hours.

In one example, the RNAi agent is administered twice per week.

In one example, the RNAi agent is administered every other week.

In certain examples, the RNAi agent is administered once per month.

In certain examples, the RNAi agent is administered once every other month.

In certain examples, the RNAi agent is administered once per quarter (*i.e.*, every three months).

In yet another example, the methods further comprise administering to the subject, an additional therapeutic agent. In some examples, the additional therapeutic agent is selected from the group consisting of a diuretic, an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, a beta-blocker, a vasodialator, a calcium channel blocker, an aldosterone antagonist, an alpha$_2$-agonist, a renin inhibitor, an alpha-blocker, a peripheral acting adrenergic agent, a selective D1 receptor partial agonist, a nonselective alpha-adrenergic antagonist, a synthetic, steroidal antimineralocorticoid agent, or a combination of any of the foregoing, and a hypertension therapeutic agent formulated as a combination of agents.

We claim:

1. A double-stranded ribonucleic acid (RNAi) agent for inhibiting expression of angiotensinogen (AGT) in a cell, wherein said double-stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from nucleotides 2081-2104 of the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotides at the corresponding position of the nucleotide sequence of SEQ ID NO:2, and

wherein the antisense strand is substantially complementary to the sense strand,

wherein "substantially complementary" refers to not more than 5, 4, 3 or 2 mismatched base pairs upon hybridization.

2. The double-stranded RNAi agent of claim 1, wherein substantially all of the nucleotides of said sense strand are modified nucleotides, substantially all of the nucleotides of said antisense strand are modified nucleotides, or substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, wherein preferably all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand are modified nucleotides, wherein "substantially all" refers to not more than 5, 4, 3, 2 or 1 unmodified nucleotides.

3. The double-stranded RNAi agent of claims 1 or 2, wherein said sense strand is conjugated to a ligand attached at the 3'-terminus.

4. The double-stranded RNAi agent of any one of claims 1 to 3, wherein said sense strand and said antisense strand

(a) comprise a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the sequences of SEQ ID NO: 537 and SEQ ID NO: 499;

(b) comprise SEQ ID NO: 499 and SEQ ID NO: 537; or

(c) consist of SEQ ID NO: 499 and SEQ ID NO: 537.

5. The double-stranded RNAi agent of any one of claims 2 to 4, wherein at least one of said modified nucleotides is selected from the group consisting of a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide,

a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a nucleotide comprising a 5'-phosphorothioate group, and a terminal nucleotide linked to a cholesteryl derivative or a dodecanoic acid bisdecylamide group.

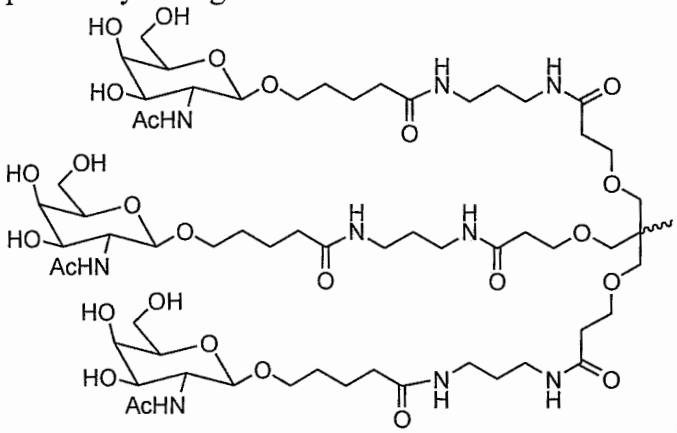
6. The double-stranded RNAi agent of any one of claims 1 to 5, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide or of at least 2 nucleotides.

7. The double-stranded RNAi agent of any one of claims 1 to 6, wherein the double-stranded region is

(a) 15-30 nucleotide pairs in length;
(b) 17-23 nucleotide pairs in length;
(c) 17-25 nucleotide pairs in length;
(d) 23-27 nucleotide pairs in length;
(e) 19-21 nucleotide pairs in length; or
(f) 21-23 nucleotide pairs in length.

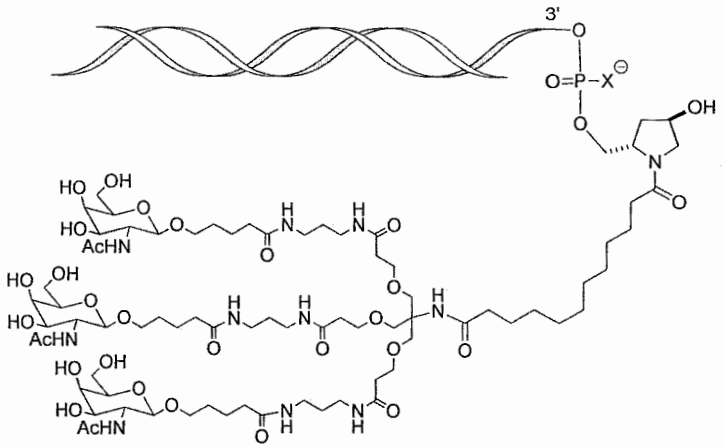
8. The double-stranded RNAi agent of any one of claims 1 to 7, wherein each strand has 15-30 nucleotides or 19-30 nucleotides.

9. The double-stranded RNAi agent of claim 3, wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, wherein preferably the ligand is



, and

wherein preferably the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

10. The double-stranded RNAi agent of any one of claims 1 to 9, wherein said RNAi agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

11. The double-stranded RNAi agent of claim 10, wherein the phosphorothioate or methylphosphonate internucleotide linkage is

(a) at the 3'-terminus of one strand, wherein said strand is the antisense strand or the sense strand;

(b) at the 5'-terminus of one strand, wherein said strand is the antisense strand or the sense strand; or

(c) at the both the 5'- and 3'-terminus of one strand, wherein preferably said strand is the antisense strand.

12. The double-stranded RNAi agent of claim 10, wherein said RNAi agent comprises 6-8 phosphorothioate internucleotide linkages, wherein preferably the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and the sense strand comprises at least two phosphorothioate internucleotide linkages at either the 5'-terminus or the 3'-terminus.

13. The double-stranded RNAi agent of any one of claims 1 to 12, wherein the base pair at the 1 position of the 5′-end of the antisense strand is an AU base pair.

14. The double stranded ribonucleic acid (RNAi) agent of any one of claims 1 to 3, wherein said RNAi agent consists of the modified nucleotide sequences of

uscsucccAfcCfUfUfuucuucuaauL96 (SEQ ID NO: 1037) and asUfsuagAfagaaaagGfuGfggagascsu (SEQ ID NO: 1038), wherein a, c, g, and u are 2'-O-methyladenosine-3'-phosphate, 2'-O-methylcytidine-3'-phosphate, 2'-O-methylguanosine-3'-phosphate, and 2'-O-methyluridine-3'-phosphate, respectively; as, cs, and us are 2'-O-methyladenosine-3'-phosphorothioate, 2'-O-methylcytidine-3'-phosphorothioate, and 2'-O-methyluridine-3'-phosphorothioate, respectively; Af, Cf, Gg, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively; Ufs is 2'-fluorouridine-3'-phosphorothioate; and L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol (Hyp-(GalNAc-alkyl)$_3$).

15. The double-stranded ribonucleic acid (RNAi) agent of claim 1

wherein substantially all of the nucleotides of said sense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus,

wherein substantially all of the nucleotides of said antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and

wherein said sense strand is conjugated to one or more GalNAc derivatives attached through a branched bivalent or trivalent linker at the 3'-terminus,

wherein "substantially all" refers to not more than 5, 4, 3, 2 or 1 unmodified nucleotides.

16. A composition comprising a modified antisense polynucleotide agent, wherein said agent is capable of inhibiting the expression of AGT in a cell, and comprises a sequence complementary to the sequence of SEQ ID NO: 499, wherein the polynucleotide is 14 to 30 nucleotides in length.

17. A pharmaceutical composition comprising the double-stranded RNAi agent of any one of claims 1 to 15, or the composition comprising a modified antisense polynucleotide agent of claim 16.

18. A double-stranded RNAi agent of any one of claims 1 to 15, or the composition comprising a modified antisense polynucleotide agent of claim 16, or the pharmaceutical composition of claim 17 for use in a method of treating a subject having a angiotensinogen (AGT)-associated disorder.

19. A double-stranded ribonucleic acid (RNAi) agent for use in a method of treating a subject having a angiotensinogen (AGT)-associated disorder,

wherein said double-stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from nucleotides 2081-2104 of the nucleotide sequence of SEQ ID NO:1, and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotides at the corresponding position of the nucleotide sequence of SEQ ID NO:2,

wherein substantially all of the nucleotides of said antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus,

wherein substantially all of the nucleotides of said sense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus,

wherein said sense strand is conjugated to one or more GalNAc derivatives attached through a branched bivalent or trivalent linker at the 3'-terminus, thereby treating the subject, and

wherein said agent is to be administered subcutaneously,

wherein "substantially all" refers to not more than 5, 4, 3, 2 or 1 unmodified nucleotides.

20. The agent for use of claim 19, wherein

(a) all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand comprise a modification;

(b) the subject is a human; and/or

(c) the angiotensinogen-associated disease is selected from the group consisting of hypertension, borderline hypertension, primary hypertension, secondary hypertension, hypertensive emergency, hypertensive urgency, isolated systolic or diastolic hypertension, pregnancy-associated hypertension, diabetic hypertension, resistant hypertension, refractory hypertension, paroxysmal hypertension, renovascular hypertension, Goldblatt hypertension, ocular hypertension, glaucoma, pulmonary hypertension, portal hypertension, systemic venous hypertension, systolic hypertension, labile hypertension; hypertensive heart disease, hypertensive nephropathy, atherosclerosis, arteriosclerosis, vasculopathy, diabetic nephropathy, diabetic retinopathy, chronic heart failure, cardiomyopathy, diabetic cardiac myopathy, glomerulosclerosis, coarctation of the aorta, aortic aneurism, ventricular fibrosis, Cushing's syndrome, and other glucocorticoid excess states including chronic steroid therapy, pheochromocytoma, reninoma, secondary aldosteronism and other mineralocorticoid excess states, sleep apnea, thyroid/parathyroid disease, heart failure, myocardial infarction, angina, stroke, diabetes mellitus, renal disease, renal failure, systemic sclerosis, intrauterine growth restriction (IUGR), and fetal growth restriction, preferably pregnancy-associated hypertension.

21. The agent for use of claim 20, wherein the double-stranded RNAi agent is to be administered at a dose of 0.01 mg/kg to 10 mg/kg or 0.5 mg/kg to 50 mg/kg, wherein preferably the double-stranded RNAi agent is to be administered

(a) at a dose of 10 mg/kg to 30 mg/kg;

(b) at a dose of 3 mg/kg;

(c) at a dose of 10 mg/kg;

(d) at a dose of 0.5 mg/kg twice per week;

(e) at a dose of 10 mg/kg every other week;

(f) at a dose of 0.5-1 mg/kg once per week;

(g) subcutaneously;

(h) intravenously; or

(i) in two or more doses, wherein said RNAi agent is to be administered

(i1) at intervals selected from the group consisting of once every 12 hours, once every 24 hours, once every 48 hours, once every 72 hours, and once every 96 hours;

(i2) twice per week; or

(i3) every other week.

22. The agent for use of claim 20, further comprising administering to the subject an additional therapeutic agent, wherein preferably the additional therapeutic agent is selected

from the group consisting of a diuretic, an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, a beta-blocker, a vasodilator, a calcium channel blocker, an aldosterone antagonist, an alpha$_2$-agonist, a renin inhibitor, an alpha-blocker, a peripheral acting adrenergic agent, a selective D1 receptor partial agonist, a nonselective alpha-adrenergic antagonist, a synthetic, steroidal antimineralocorticoid agent, or a combination of any of the foregoing, and a hypertension therapeutic agent formulated as a combination of agents.

23. Use of a double-stranded RNAi agent of any one of claims 1 to 15, or the composition comprising a modified antisense polynucleotide agent of claim 16, or the pharmaceutical composition of claim 17 in the manufacture of a medicament for treating a subject having a angiotensinogen (AGT)-associated disorder.

24. Use of a double-stranded ribonucleic acid (RNAi) agent in the manufacture of a medicament for treating a subject having a angiotensinogen (AGT)-associated disorder, wherein said double-stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region,

wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from nucleotides 2081-2104 of the nucleotide sequence of SEQ ID NO:1, and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotides at the corresponding position of the nucleotide sequence of SEQ ID NO:2,

wherein substantially all of the nucleotides of said antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus,

wherein substantially all of the nucleotides of said sense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus,

wherein said sense strand is conjugated to one or more GalNAc derivatives attached through a branched bivalent or trivalent linker at the 3'-terminus, thereby treating the subject, and

wherein said agent is to be administered subcutaneously,

wherein "substantially all" refers to not more than 5, 4, 3, 2 or 1 unmodified nucleotides.

25. The use of claim 24, wherein

(a) all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand comprise a modification;

(b) the subject is a human; and/or

(c) the angiotensinogen-associated disease is selected from the group consisting of hypertension, borderline hypertension, primary hypertension, secondary hypertension, hypertensive emergency, hypertensive urgency, isolated systolic or diastolic hypertension, pregnancy-associated hypertension, diabetic hypertension, resistant hypertension, refractory hypertension, paroxysmal hypertension, renovascular hypertension, Goldblatt hypertension, ocular hypertension, glaucoma, pulmonary hypertension, portal hypertension, systemic venous hypertension, systolic hypertension, labile hypertension; hypertensive heart disease, hypertensive nephropathy, atherosclerosis, arteriosclerosis, vasculopathy, diabetic nephropathy, diabetic retinopathy, chronic heart failure, cardiomyopathy, diabetic cardiac myopathy,glomerulosclerosis, coarctation of the aorta, aortic aneurism, ventricular fibrosis, Cushing's syndrome, and other glucocorticoid excess states including chronic steroid therapy, pheochromocytoma, reninoma, secondary aldosteronism and other mineralocorticoid excess states, sleep apnea, thyroid/parathyroid disease, heart failure, myocardial infarction, angina, stroke, diabetes mellitus, renal disease, renal failure, systemic sclerosis, intrauterine growth restriction (IUGR), and fetal growth restriction, preferably pregnancy-associated hypertension.

26. The use of claim 25, wherein the double-stranded RNAi agent is to be administered at a dose of 0.01 mg/kg to 10 mg/kg or 0.5 mg/kg to 50 mg/kg, wherein preferably the double-stranded RNAi agent is to be administered

(a) at a dose of 10 mg/kg to 30 mg/kg;

(b) at a dose of 3 mg/kg;

(c) at a dose of 10 mg/kg;

(d) at a dose of 0.5 mg/kg twice per week;

(e) at a dose of 10 mg/kg every other week;

(f) at a dose of 0.5-1 mg/kg once per week;

(g) subcutaneously;

(h) intravenously; or

(i) in two or more doses, wherein said RNAi agent is to be administered

(i1) at intervals selected from the group consisting of once every 12 hours, once every 24 hours, once every 48 hours, once every 72 hours, and once every 96 hours;

(i2) twice per week; or

(i3) every other week.

27. The use of claim 25, further comprising an additional therapeutic agent to be administered to the subject, wherein preferably the additional therapeutic agent is selected from the group consisting of a diuretic, an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, a beta-blocker, a vasodilator, a calcium channel blocker, an aldosterone antagonist, an alpha$_2$-agonist, a renin inhibitor, an alpha-blocker, a peripheral acting adrenergic agent, a selective D1 receptor partial agonist, a nonselective alpha-adrenergic antagonist, a synthetic, steroidal antimineralocorticoid agent, or a combination of any of the foregoing, and a hypertension therapeutic agent formulated as a combination of agents.