were developed providing goals for even lower blood pressure to further decrease risk of development of diseases and disorders associated with hypertension (see, *e.g.*, Reboussin *et al.* Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2017 Nov 7. pii: S0735-1097(17)41517-8. doi: 10.1016/j.jacc.2017.11.004; and Whelton *et al.* (2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2017 Nov 7. pii: S0735-1097(17)41519-1. doi: 10.1016/j.jacc.2017.11.006).

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 adherence is reduced and side-effects are increased with increasing numbers of medications. Furthermore, several studies have suggested a potential relationship between chronic use of antihypertensive medications and deterioration in kidney function finding that antihypertensive agents to control blood pressure also impact kidney function independently of their effect on blood pressure (Tomlinson,*et al* (2013) *PLoS ONE* 8(11) Article ID e78465; The SPRINT Research Group (2015) *NEJM* 373(22):2103–2116, ClinicalTrials.gov number, NCT01206062; Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) *Kidney International Supplements* 3:1–150; Kamaroff, *et al.* (2018(*Hindawi International J Chron Dis* Article ID 1382705 | https://doi.org/10.1155/2018/1382705).

Accordingly, there is a need in the art for additional methods and therapies to treat subjects having hypertension.

Summary

The disclosure provides methods and compositions for inhibiting the expression of an angiotensinogen (AGT) gene, for treating a subject having a disorder that would benefit from reduction in AGT expression, for treating a subject having an AGT-associated disorder, and for decreasing blood pressure in a subject. The methods include administering to the subject a fixed dose of an RNAi agent, *e.g.,* a double stranded RNAi agent, targeting an AGT gene.

In one aspect, the present disclosure refers to the use of a fixed dose of 50 mg to 800 mg of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof in the manufacture of a medicament for inhibiting the expression of an angiotensinogen (AGT) gene in a subject, wherein the double-stranded RNAi agent or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID

NO: 9) and the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10); wherein the double-stranded RNAi agent, or salt thereof, comprises at least one modified nucleotide; and wherein at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification, thereby inhibiting the expression of the AGT gene in the subject.

In another aspect, the present disclosure refers to the use of a fixed dose of 50 mg to 800 mg of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof in the manufacture of a medicament for treating a subject that would benefit from reduction in angiotensinogen (AGT) expression, wherein the double-stranded RNAi agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10); wherein the double-stranded RNAi agent, or salt thereof, comprises at least one modified nucleotide; and wherein at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification, thereby treating the subject that would benefit from reduction in AGT expression.

In another aspect, the present disclosure refers to the use of a fixed dose of 50 mg to 800 mg of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof in the manufacture of a medicament for treating a subject having an angiotensinogen- (AGT-) associated disorder, wherein the double-stranded RNAi agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO:10); wherein the double-stranded RNAi agent, or salt thereof, comprises at least one modified nucleotide; wherein at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification, thereby treating the subject having the AGT-associated disorder.

In another aspect, the present disclosure refers to the use of a fixed dose of 50 mg to 800 mg of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof in the manufacture of a medicament for decreasing blood pressure level in a subject, wherein the double-stranded RNAi agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10); wherein the double-stranded RNAi agent, or salt thereof, comprises at least one modified nucleotide; wherein at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification, thereby decreasing the blood pressure level in the subject.

In yet another aspect, the present disclosure refers to the use of a fixed dose of 50 mg to 800 mg of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof in the manufacture of a medicament for inhibiting the expression of an angiotensinogen (AGT) gene in a subject, wherein the double-stranded RNAi agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12); wherein a is 2'-O-methyladenosine-3'-phosphate, c is 2'-O-methylcytidine-3'-phosphate, g is 2'-O-methylguanosine-3'-phosphate, u is 2'-O-methyluridine-3'-phosphate, Af is 2'-fluoroadenosine-3'-phosphate, Cf is 2'-fluorocytidine-3'-phosphate, Gf is 2'-fluoroguanosine-3'-phosphate, Uf is 2'-fluorouridine-3'-phosphate, (Tgn) is thymidine-glycol nucleic acid (GNA) S-Isomer, and s is a phosphorothioate linkage, thereby inhibiting the expression of the AGT gene in the subject.

In yet another aspect, the present disclosure refers to the use of a fixed dose of 50 mg to 800 mg of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof in the manufacture of a medicament for treating a subject that would benefit from reduction in AGT expression, wherein the double-stranded RNAi agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12); wherein a is 2'-O-methyladenosine-3'-phosphate, c is 2'-O-methylcytidine-3'-phosphate, g is 2'-O-methylguanosine-3'-phosphate, u is 2'-O-methyluridine-3'-phosphate, Af is 2'-fluoroadenosine-3'-phosphate, Cf is 2'-fluorocytidine-3'-phosphate, Gf is 2'-fluoroguanosine-3'-phosphate, Uf is 2'-fluorouridine-3'-phosphate, (Tgn) is thymidine-glycol nucleic acid (GNA) S-Isomer, and s is a phosphorothioate linkage, thereby treating the subject that would benefit from reduction in AGT expression.

In yet another aspect, the present disclosure refers to the use of a fixed dose of 50 mg to 800 mg of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof in the manufacture of a medicament for treating a subject having an AGT-associated disorder, wherein the double-stranded RNAi agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12); wherein a is 2'-O-methyladenosine-3'-phosphate, c is 2'-O-methylcytidine-3'-phosphate, g is 2'-O-methylguanosine-3'-phosphate, u is 2'-O-methyluridine-3'-phosphate, Af is 2'-fluoroadenosine-3'-phosphate, Cf is 2'-fluorocytidine-3'-phosphate, Gf is 2'-fluoroguanosine-3'-phosphate, Uf is 2'-fluorouridine-3'-phosphate, (Tgn) is

thymidine-glycol nucleic acid (GNA) S-Isomer, and s is a phosphorothioate linkage, thereby treating the subject having the AGT-associated disorder.

In yet another aspect, the present disclosure refers to the use of a fixed dose of 50 mg to 800 mg of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof in the manufacture of a medicament for decreasing blood pressure level in a subject, wherein the double-stranded RNAi agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12); wherein a is 2'-O-methyladenosine-3'-phosphate, c is 2'-O-methylcytidine-3'-phosphate, g is 2'-O-methylguanosine-3'-phosphate, u is 2'-O-methyluridine-3'-phosphate, Af is 2'-fluoroadenosine-3'-phosphate, Cf is 2'-fluorocytidine-3'-phosphate, Gf is 2'-fluoroguanosine-3'-phosphate, Uf is 2'-fluorouridine-3'-phosphate, (Tgn) is thymidine-glycol nucleic acid (GNA) S-Isomer, and s is a phosphorothioate linkage, thereby decreasing the blood pressure level in the subject.

In yet another aspect, the present disclosure refers to a kit for performing the use as disclosed herein, comprising a) the RNAi agent, or salt thereof, and b) instructions for use, and c) optionally, means for administering the RNAi agent, or salt thereof, to the subject.

In one example, the present disclosure provides a method for inhibiting the expression of an angiotensinogen (AGT) gene in a subject. The method includes administering to the subject a fixed dose of about 50 mg to about 800 mg (*e.g.,* about 50 to about 200 mg, about 50 mg to about 500 mg, about 100 mg to about 800 mg, about 100 mg to about 500 mg, about 100 mg to about 300 mg, about 200 mg to about 300 mg, about 200 mg to about 400 mg, about 200 mg to about 500 mg, about 200 mg to about 800 mg, about 300 mg to about 800 mg, about 300 mg to about 500 mg, about 300 mg to

about 4000 mg, about 400 mg to about 800 mg, about 400 mg to about 500 mg, *e.g.,* about 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, or about 800 mg) of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof, wherein the double-stranded RNAi agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10); wherein the double-stranded RNAi agent, or salt thereof, comprises at least one modified nucleotide; and wherein at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification, thereby inhibiting the expression of the AGT gene in the subject.

In another example, the present disclosure provides a method for treating a subject that would benefit from reduction in angiotensinogen (AGT) expression, *e.g.,* a subject at risk of developing an AGT-associated disorder, *e.g.,* hypertension. The method includes administering to the subject a fixed dose of about 50 mg to about 800 mg (*e.g.,* about 50 to about 200 mg, about 50 mg to about 500 mg, about 100 mg to about 800 mg, about 100 mg to about 500 mg, about 100 mg to about 300 mg, about 200 mg to about 300 mg, about 200 mg to about 400 mg, about 200 mg to about 500 mg, about 200 mg to about 800 mg, about 300 mg to about 800 mg, about 300 mg to about 500 mg, about 300 mg to about 4000 mg, about 400 mg to about 800 mg, about 400 mg to about 500 mg, *e.g.,* about 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, or about 800 mg) of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof, wherein the double-stranded RNAi agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10); wherein the double-stranded RNAi agent, or salt thereof, comprises at least one modified nucleotide; and wherein at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification, thereby treating the subject that would benefit from reduction in AGT expression.

In one example, the present disclosure provides a method for treating a subject having an angiotensinogen- (AGT-) associated disorder, *e.g.,* hypertension. The method includes administering to the subject a fixed dose of about 50 mg to about 800 mg (*e.g.,* about 50 to about 200 mg, about 50 mg to about 500 mg, about 100 mg to about 800 mg, about 100 mg to about 500 mg, about 100 mg to about 300 mg, about 200 mg to about 300 mg, about 200 mg to about 400 mg, about 200 mg to about 500 mg, about 200 mg to about 800 mg, about 300 mg to about 800 mg, about 300 mg to about 500 mg, about 300 mg to about 4000 mg, about 400 mg to about 800 mg, about 400 mg to about 500 mg, *e.g.,* about 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, or about 800 mg) of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof, wherein the double-stranded RNAi agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a nucleotide sequence comprising at least 19

contiguous nucleotides of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10); wherein the double-stranded RNAi agent, or salt thereof, comprises at least one modified nucleotide; wherein at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification, thereby treating the subject having the AGT-associated disorder.

In another example, the present disclosure provides a method for decreasing blood pressure level in a subject, sich as a subject having an AGT-associated disorder,*e.g.,* hypdertension. The method includes administering to the subject a fixed dose of about 50 mg to about 800 mg (*e.g.,* about 50 to about 200 mg, about 50 mg to about 500 mg, about 100 mg to about 800 mg, about 100 mg to about 500 mg, about 100 mg to about 300 mg, about 200 mg to about 300 mg, about 200 mg to about 400 mg, about 200 mg to about 500 mg, about 200 mg to about 800 mg, about 300 mg to about 800 mg, about 300 mg to about 500 mg, about 300 mg to about 4000 mg, about 400 mg to about 800 mg, about 400 mg to about 500 mg, *e.g.,* about 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, or about 800 mg) of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof, wherein the double-stranded RNAi agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10); wherein the double-stranded RNAi agent, or salt thereof, comprises at least one modified nucleotide; wherein at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification, thereby decreasing the blood pressure level in the subject.

In some examples, the fixed dose is administered to the subject at an interval of once a month. In other examples, the fixed dose is administered to the subject at an interval of once a quarter. In some examples, the fixed dose is administered to the subject at an interval of bianually.

In some examples, the subject is administered a fixed dose of about 50 mg to about 200 mg. In other examples, the subject is administered a fixed dose of about 200 mg to about 400 mg. In some examples, the subject is administered a fixed dose of about 400 mg to about 800 mg.

In some examples, the subject is administered a fixed dose of about 100 mg. In some examples, the subject is administered a fixed dose of about 200 mg. In some examples, the subject is administered a fixed dose of about 300 mg. In some examples, the subject is administered a fixed dose of about 400 mg. In some examples, the subject is administered a fixed dose of about 500 mg. In other examples, the subject is administered a fixed dose of about 600 mg. In some examples, the subject is administered a fixed dose of about 800 mg.

In some examples, the double stranded RNAi agent, or salt thereof, is administered to the subject subcutaneously or intravenously. In some examples, the subcutaneous administration is subcutaneous injection, *e.g.,* subcutaneous self-administration. In other examples, the intravenous administration is intravenous injection.

In some examples, the antisense strand comprises a nucleotide sequence comprising at least 20 contiguous nucleotides of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand comprises a nucleotide sequence comprising at least 20 contiguous nucleotides of the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10).

In other examples, the antisense strand comprises a nucleotide sequence comprising at least 21 contiguous nucleotides of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand comprises a nucleotide sequence comprising at least 20 contiguous nucleotides of the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10).

In some examples, the antisense strand comprises a nucleotide sequence comprising at least 22 contiguous nucleotides of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand comprises a nucleotide sequence comprising at least 20 contiguous nucleotides of the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10).

In some examples, the antisense strand comprises the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand comprises the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10).

In some examples, the antisense strand consists of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand consists of the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10).

In some 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 some examples, all of the nucleotides of the sense strand are modified nucleotides. In some examples, all of the nucleotides of the antisense strand are modified nucleotides.

In some examples, at least one of the nucleotide modifications is selected from the group consisting of a deoxy-nucleotide, 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’-O-allyl-modified nucleotide, 2’-C-alkyl-modified nucleotide, 2’-hydroxly-modified nucleotide, a 2’-methoxyethyl modified nucleotide, a 2’-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5’-phosphate, a nucleotide comprising a 5’-phosphate mimic, a thermally destabilizing nucleotide, a glycol modified nucleotide (GNA), and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

In some examples, at least one of the nucleotide modifications is selected from the group consisting of a deoxy-nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide,

a 2'-deoxy-modified nucleotide, a glycol modified nucleotide (GNA), and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

In some examples, the double stranded region is 19-23 nucleotide pairs in length, 19- 21 nucleotide pairs in length, 21-23 nucleotide pairs in length, or 21 nucleotide pairs in length.

In some examples, each strand is independently 19-23 nucleotides in length, 19-25 nucleotides in length, or 21-23 nucleotides in length. In some examples, the sense strand is 21 nucleotides in length, and the antisense strand is 23 nucleotides in length.

In some examples, at least one strand comprises a 3' overhang of at least 1 nucleotide or a 3' overhang of at least 2 nucleotides.

In some examples, the double-stranded RNAi agent, or salt thereof, further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage. In some examples, the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand. In some examples, the strand is the antisense strand. In other examples, the strand is the sense strand.

In some examples, the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand. In some examples, the strand is the antisense strand. In other examples, the strand is the sense strand.

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

In one example, the present disclosure provides a method for inhibiting the expression of an angiotensinogen (AGT) gene in a subject. The method includes administering to the subject a fixed dose of about 50 mg to about 800 mg (*e.g.,* about 50 to about 200 mg, about 50 mg to about 500 mg, about 100 mg to about 800 mg, about 100 mg to about 500 mg, about 100 mg to about 300 mg, about 200 mg to about 300 mg, about 200 mg to about 400 mg, about 200 mg to about 500 mg, about 200 mg to about 800 mg, about 300 mg to about 800 mg, about 300 mg to about 500 mg, about 300 mg to about 4000 mg, about 400 mg to about 800 mg, about 400 mg to about 500 mg, *e.g.,* about 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, or about 800 mg) of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof, wherein the double-stranded RNAi agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12); wherein the chemical modifiecations are defined as follows: a is 2'-O-methyladenosine-3'-phosphate, c is 2'-O-methylcytidine-3'-phosphate, g is 2'-O-methylguanosine-3'-phosphate, u is 2'-O-methyluridine-3'-phosphate, Af is 2'-fluoroadenosine-3'-phosphate, Cf is 2'-fluorocytidine-3'-phosphate, Gf is 2'-fluoroguanosine-3'-phosphate, Uf is 2'-fluorouridine-3'-phosphate, (Tgn) is thymidine-glycol nucleic acid (GNA) S-Isomer, and s is phosphorothioate linkage, thereby inhibiting the expression of the AGT gene in the subject.

In another example, the present disclosure provides a method for treating a subject that would benefit from reduction in AGT expression, *e.g.,* a subject at risk of developing an AGT-associated disorder, *e.g.,* hypertension. The method includes administering to the subject a fixed dose of about 50 mg to about 800 mg (*e.g.,* about 50 to about 200 mg, about 50 mg to about 500 mg, about 100 mg to about 800 mg, about 100 mg to about 500 mg, about 100 mg to about 300 mg, about 200 mg to about 300 mg, about 200 mg to about 400 mg, about 200 mg to about 500 mg, about 200 mg to about 800 mg, about 300 mg to about 800 mg, about 300 mg to about 500 mg, about 300 mg to about 4000 mg, about 400 mg to about 800 mg, about 400 mg to about 500 mg, *e.g.,* about 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, or about 800 mg) of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof, wherein the double-stranded RNAi, or salt thereof, agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12); wherein chemical modifiecations are defined as follows: a is 2'-O-methyladenosine-3'-phosphate, c is 2'-O-methylcytidine-3'-phosphate, g is 2'-O-methylguanosine-3'-phosphate, u is 2'-O-methyluridine-3'-phosphate, Af is 2'-fluoroadenosine-3'-phosphate, Cf is 2'-fluorocytidine-3'-phosphate, Gf is 2'-fluoroguanosine-3'-phosphate, Uf is 2'-fluorouridine-3'-phosphate, (Tgn) is thymidine-glycol nucleic acid (GNA) S-Isomer, and s is phosphorothioate linkage, thereby treating the subject that would benefit from reduction in AGT expression.

In one example, the present disclosure provides a method for treating a subject having an AGT-associated disorder, *e.g.,* hypertension. The method includes administering to the subject a fixed dose of about 50 mg to about 800 mg (*e.g.,* about 50 to about 200 mg, about 50 mg to about 500 mg, about 100 mg to about 800 mg, about 100 mg to about 500 mg, about 100 mg to about 300 mg, about 200 mg to about 300 mg, about 200 mg to about 400 mg, about 200 mg to about 500 mg, about 200 mg to about 800 mg, about 300 mg to about 800 mg, about 300 mg to about 500 mg, about 300 mg to about 4000 mg, about 400 mg to about 800 mg, about 400 mg to about 500 mg, *e.g.,* about 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, or about 800 mg) of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof, wherein the double-stranded RNAi agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12); wherein chemical modifiecations are defined as follows: a is 2'-O-methyladenosine-3'-phosphate, c is 2'-O-methylcytidine-3'-phosphate, g is 2'-O-methylguanosine-3'-phosphate, u is 2'-O-methyluridine-3'-phosphate, Af is 2'-fluoroadenosine-3'-phosphate, Cf is 2'-fluorocytidine-3'-phosphate, Gf is 2'-fluoroguanosine-3'-phosphate, Uf is 2'-fluorouridine-3'-phosphate, (Tgn) is thymidine-glycol nucleic

acid (GNA) S-Isomer, and s is phosphorothioate linkage, thereby treating the subject having the AGT-associated disorder.

In another example, the present disclosure provides a method for decreasing blood pressure level in a subject. The method includes administering to the subject a fixed dose of about 50 mg to about 800 mg (*e.g.,* about 50 to about 200 mg, about 50 mg to about 500 mg, about 100 mg to about 800 mg, about 100 mg to about 500 mg, about 100 mg to about 300 mg, about 200 mg to about 300 mg, about 200 mg to about 400 mg, about 200 mg to about 500 mg, about 200 mg to about 800 mg, about 300 mg to about 800 mg, about 300 mg to about 500 mg, about 300 mg to about 4000 mg, about 400 mg to about 800 mg, about 400 mg to about 500 mg, *e.g.,* about 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, or about 800 mg) of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof, wherein the double-stranded RNAi agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12); wherein chemical modifiecations are defined as follows: a is 2'-O-methyladenosine-3'-phosphate, c is 2'-O-methylcytidine-3'-phosphate, g is 2'-O-methylguanosine-3'-phosphate, u is 2'-O-methyluridine-3'-phosphate, Af is 2'-fluoroadenosine-3'-phosphate, Cf is 2'-fluorocytidine-3'-phosphate, Gf is 2'-fluoroguanosine-3'-phosphate, Uf is 2'-fluorouridine-3'-phosphate, (Tgn) is thymidine-glycol nucleic acid (GNA) S-Isomer, and s is phosphorothioate linkage, thereby decreasing the blood pressure level in the subject.

In some examples, the fixed dose is administered to the subject at an interval of once a month. In other examples, the fixed dose is administered to the subject at an interval of once a quarter. In some examples, the fixed dose is administered to the subject at an interval of bianually.

In some examples, the subject is administered a fixed dose of about 50 mg to about 200 mg. In other examples, the subject is administered a fixed dose of about 200 mg to about 400 mg. In some examples, the subject is administered a fixed dose of about 400 mg to about 800 mg.

In some examples, the subject is administered a fixed dose of about 100 mg. In some examples, the subject is administered a fixed dose of about 200 mg. In some examples, the subject is administered a fixed dose of about 300 mg. In some examples, the subject is administered a fixed dose of about 400 mg. In some examples, the subject is administered a fixed dose of about 500 mg. In other examples, the subject is administered a fixed dose of about 600 mg. In some examples, the subject is administered a fixed dose of about 800 mg.

In some examples, the double stranded RNAi agent, or salt thereof, is administered to the subject subcutaneously or intravenously. In some examples, the subcutaneous administration is subcutaneous injection, *e.g.,* subcutaneous self-administration. In other examples, the intravenous administration is intravenous injection.

In some examples, the antisense strand comprises a modified nucleotide sequence comprising at least 20 contiguous nucleotides of the modified nucleotide sequence

usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand comprises a modified nucleotide sequence comprising at least 20 contiguous nucleotides of the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12).

In some examples, the antisense strand comprises a modified nucleotide sequence comprising at least 21 contiguous nucleotides of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand comprises a modified nucleotide sequence comprising at least 20 contiguous nucleotides of the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12).

In some examples, the antisense strand comprises a modified nucleotide sequence comprising at least 22 contiguous nucleotides of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand comprises a modified nucleotide sequence comprising at least 20 contiguous nucleotides of the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12).

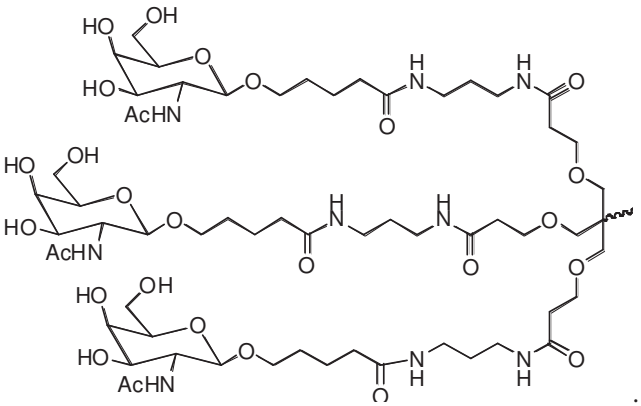
In some examples, the antisense strand comprises a modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand comprises a modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12).

In other examples, the antisense strand consists of a modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand consists of a modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12).

In some examples, the double stranded RNAi agent**,** or salt thereof, further comprises a ligand. In other examples, the ligand is conjugated to the 3' end of the sense strand.

In some examples, the ligand is an N-acetylgalactosamine (GalNAc) derivative. In other examples, the GalNAc derivative comprises one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

In some examples, the ligand is



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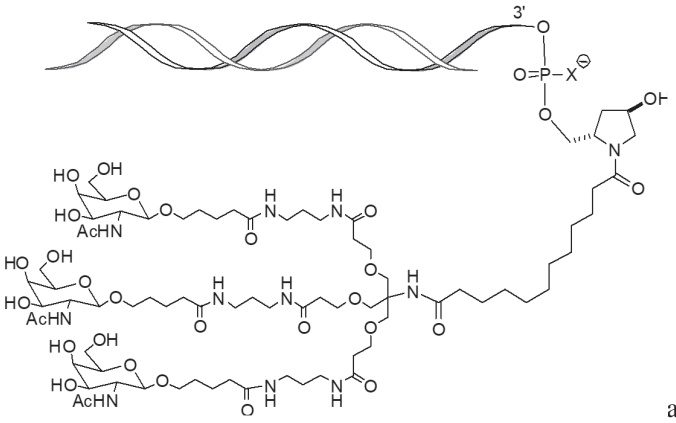
In other examples, the 3' end of the sense strand is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

In some examples, the subject is a human. In some examples, the subject has a systolic blood pressure of at least 130 mm Hg or a diastolic blood pressure of at least 80 mm Hg. In other examples, the subject has a systolic blood pressure of at least 140 mm Hg or a diastolic blood pressure of at least 80 mm Hg.

In some examples, the subject is part of a group susceptible to salt sensitivity, is overweight, is obese, is pregnant, is planning to become pregnant, has type 2 diabetes, has type 1 diabetes, or has reduced kidney function.

In some examples, the disorder that would benefit from reduction in AGT expression is an AGT-associated disorder. In one example, the AGT-associated disorder is hypertension. In other examples, the AGT –associated disorder is selected from the group consisting of high blood pressure, hypertension, borderline hypertension, primary hypertension, secondary hypertension 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, nocturnal hypotension, glomerulosclerosis, coarctation of the aorta, aortic aneurism, ventricular fibrosis, heart failure, myocardial infarction, angina, stroke, renal disease, renal failure, systemic sclerosis, intrauterine growth restriction (IUGR) , fetal growth restriction, obesity, liver steatosis/ fatty liver, non-alcoholic Steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD); glucose intolerance, type 2 diabetes, and metabolic syndrome. In one example, the AGT-associated disorder is hypertension. In one example, the hypertension is selected from the group consisting of high blood pressure, hypertension, borderline hypertension, primary hypertension, secondary hypertension 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, and hypertensive nephropathy.

In some examples, the blood pressure comprises systolic blood pressure and/or diastolic blood pressure.

In some examples, administering results in a decrease in AGT expression by at least 30%, 40% 50%, 60%, 70%, 80%, 90%, or 95%. In some examples, the AGT protein level in blood or serum sample of the subject is decreased by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95%.

In some examples, administering results in a decrease in systolic blood pressure and/or diastolic blood pressure. In some examples, the systolic blood pressure and/or diastolic blood pressure is decreased by at least 4 mmHg, 5 mmHg, 6 mmHg, 7 mmHg, 8 mmHg, 9 mmHg or 10 mmHg.

In some examples, the methods further comprise administering to the subject an additional therapeutic agent for treatment of hypertension. 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 alpha2-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, a steroidal antimineralocorticoid agent; a combination of any of the foregoing; and a hypertension therapeutic agent formulated as a combination of agents. In some examples, the additional therapeutic agent comprises an angiotensin II receptor antagonist. In other examples, the angiotensin II receptor antagonist is selected from the group consisting of losartan, valsartan, olmesartan, eprosartan, and azilsartan.

In some examples, the RNAi agent is administered as a pharmarceutical composition.

In some examples, the RNAi agent is administered in an unbuffered solution. In some examples, the unbuffered solution is saline or water.

In some examples, the RNAi agent is administered with a buffer solution. In some examples, the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof. In some examples, the buffer solution is phosphate buffered saline (PBS).

The present disclosure also provides a kit for performing the methods of the disclosure, as described hererin. The kit comprises a) the RNAi agent, and b) instructions for use, and c) optionally, means for administering the RNAi agent to the subject.

In another example, the present disclosure also provides a pharmaceutical composition for treating an AGT-associated disorder comprising a double stranded ribonucleic acid (RNAi) agent, or salt thereof, for inhibiting expression of angiotensinogen (AGT). The pharmaceutical composition comprises a dsRNA agent comprising a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence of UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence of GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10); wherein no more than five of the nucleotides do not comprise a modification; wherein at least one of

the nucleotide modifications is a thermally destabilizing nucleotide modification; wherein the double stranded RNAi agent is administered at a dose of at least 50 mg/dose no more than once per month, *e.g.*. a dose of about 50 mg to about 800 mg about once per month (*e.g.,* about 50 to about 200 mg, about 50 mg to about 500 mg, about 100 mg to about 800 mg, about 100 mg to about 500 mg, about 100 mg to about 300 mg, about 200 mg to about 300 mg, about 200 mg to about 400 mg, about 200 mg to about 500 mg, about 200 mg to about 800 mg, about 300 mg to about 800 mg, about 300 mg to about 500 mg, about 300 mg to about 4000 mg, about 400 mg to about 800 mg, about 400 mg to about 500 mg, *e.g.,* about 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, or about 800 mg).

In certain examples, the antisense strand comprises a nucleotide sequence comprising at least 20 contiguous nucleotides of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9), In certain examples, the sense strand further comprises a nucleotide sequence comprising at least 20 contiguous nucleotides of the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10).

In certain examples, the antisense strand comprises a nucleotide sequence comprising at least 21 contiguous nucleotides of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9). In certain examples, the sense strand further comprises the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10).

In certain examples, the antisense strand a nucleotide sequence comprising comprises at least 22 contiguous nucleotides of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9), In certain examples, the sense strand further comprises the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10)

In certain examples, antisense strand comprises the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9). In certain examples, the sense strand further comprises the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO:10).

In certain examples, the nucleotide sequence of the antisense strand consists of UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9). In certain examples, the nucleotide sequence of the sense strand further consists of GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10).

In certain examples, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a nucleotide modification.

In certain examples, at least one of the nucleotide modifications is selected from the group consisting of a deoxy-nucleotide, 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’-O-allyl-modified nucleotide, 2’-C-alkyl-modified nucleotide, 2’-hydroxly-modified nucleotide, a 2’-methoxyethyl modified nucleotide, a 2’-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate

group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, a nucleotide comprising a 5'-phosphate mimic, a thermally destabilizing nucleotide, a glycol modified nucleotide (GNA), and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof. In certain examples, at least one of the nucleotide modifications is selected from the group consisting of a deoxy-nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a glycol modified nucleotide (GNA), and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

In certain examples, the nucleotide modifications are selected from the group consisting of 2'-methoxyethyl, 2'-fluoro, a 2'-deoxy-modified nucleotide, and GNA; and combinations thereof.

In certain examples, the double stranded region is of a length selected from: 19-23 nucleotide pairs in length, 19- 21 nucleotide pairs in length, 21-23 nucleotide pairs in length, 21 nucleotide pairs in length, 19-30 nucleotide pairs in length, 19-25 nucleotide pairs in length, 23-27 nucleotide pairs in length. In certain examples, the double stranded region has a length of 19-21 nucleotiede pairs in length.

In certain examples, each strand of the double stranded RNAi or salt thereof, is independently of a length selected from 19-30 nucleotides in length 19-23 nucleotides in length, and 21-23 nucleotides in length. In certain examples, each strand is independently 21-23 nucleotides in length. In certain examples, the sense strand is 21 nucleotides in length, and the antisense strand is 23 nucleotides in length.

In certain examples, at least one strand comprises a 3' overhang of at least 1 nucleotide. In certain examples, at least one strand comprises a 3' overhang of at least 2 nucleotides.

In certain examples, the agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage. In certain examples, the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand. In certain examples, the strand is the antisense strand. In certain examples, the strand is the sense strand.

In certain examples, the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand. In certain examples, the strand is the antisense strand. In certain examples, the strand is the sense strand.

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

The disclosure provides a pharmaceutical composition for treating an AGT-associated disorder comprising a double stranded ribonucleic acid (RNAi) agent, or salt thereof, for inhibiting expression of angiotensinogen (AGT). The pharmaceutical composition comprises a double stranded RNAi agent, or salt thereof, agent comprising a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12); wherein chemical modifiecations are

defined as follows: a is 2'-O-methyladenosine-3'-phosphate, c is 2'-O-methylcytidine-3'-phosphate, g is 2'-O-methylguanosine-3'-phosphate, u is 2'-O-methyluridine-3'-phosphate, Af is 2'-fluoroadenosine-3'-phosphate, Cf is 2'-fluorocytidine-3'-phosphate, Gf is 2'-fluoroguanosine-3'-phosphate, Uf is 2'-fluorouridine-3'-phosphate, (Tgn) is thymidine-glycol nucleic acid (GNA) S-Isomer, and s is phosphorothioate linkage; and wherein the pharmaceutical composition is administered at a dose of at least 50 mg/dose no more than once per month.

In certain examples, the antisense strand comprises a modified nucleotide sequence comprising at least 20 contiguous nucleotides of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11). In certain examples, the sense strand further comprises a modified nucleotide sequence comprising at least 20 contiguous nucleotides of the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12).

In certain examples, the antisense strand comprises a modified nucleotide sequence comprising at least 21 contiguous nucleotides of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11). In certain examples, the sense strand further comprises the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO:12).

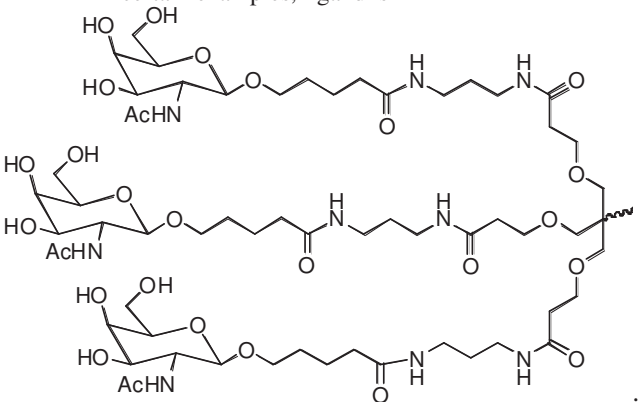
In certain examples, the antisense strand comprises a modified nucleotide sequence comprising at least 22 contiguous nucleotides of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11). In certain examples, the sense strand further comprises the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12).

In certain examples, the antisense strand comprises the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11). In certain examples, the sense strand further comprises the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12).

In certain examples, the modified nucleotide sequence of the antisense strand consists of usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11). In certain examples, the modified nucleotide sequence of the sense strand consists of gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12).

In certain examples, the double stranded RNAi agent, or salt thereof, further comprises a ligand. In certain examples, the ligand is conjugated to the 3' end of the sense strand. In certain examples, the ligand is an N-acetylgalactosamine (GalNAc) derivative. In certain examples, the GalNAc derivative comprises one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

In certain examples, ligand is



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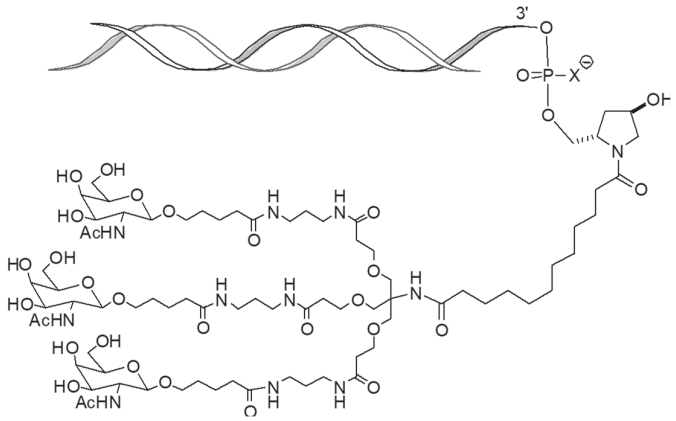
In certain examples, the 3’ end of the sense strand is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S. In certain examples, the X is O.

In certain examples, the sense strand comprises the nucleotide sequence gsuscaucCfaCfAfAfugagaguaca wherein the 3’ end of the sense strand is conjugated to L96 (N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol Hyp-(GalNAc-alkyl)3) and the antisense strand comprises the nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa; wherein chemical modifiecations are defined as follows: a is 2'-O-methyladenosine-3’-phosphate, c is 2'-O-methylcytidine-3’-phosphate, g is 2'-O-methylguanosine-3’-phosphate, u is 2'-O-methyluridine-3’-phosphate, Af is 2’-fluoroadenosine-3’-phosphate, Cf is 2’-fluorocytidine-3’-phosphate, Gf is 2’-fluoroguanosine-3’-phosphate, Uf is 2’-fluorouridine-3’-phosphate, (Tgn) is thymidine-glycol nucleic acid (GNA) S-Isomer, and s is phosphorothioate linkage.

In certain examples, the double stranded RNAi agent, or salt thereof, is administered at a dose of 50 mg to 500 mg per dose. In certain examples, the double stranded RNAi agent, or salt thereof, is administered at a dose of 50 to 400 mg per dose. In certain embodi double stranded RNAi ments, the double stranded RNAi agent, or salt thereof, is administered at a dose of 50 to 300 mg per dose.

In some examples, the double stranded RNAi agent, or salt thereof, is administered at fixed dose of about 50 mg to about 200 mg. In other examples, the double stranded RNAi agent, or salt thereof, is administered at a fixed dose of about 200 mg to about 400 mg. In some examples, the double stranded RNAi agent, or salt thereof, is administered at a fixed dose of about 400 mg to about 800 mg.

In some examples, the double stranded RNAi agent, or salt thereof, is administered at a fixed dose of about 100 mg. In some examples, the double stranded RNAi agent, or salt thereof, is administered at a fixed dose of about 200 mg. In some examples, the double stranded RNAi agent, or salt thereof, is administered at a fixed dose of about 300 mg. In some examples, the double stranded RNAi agent, or salt thereof, is administered at a fixed dose of about 400 mg. In some examples, the double stranded RNAi agent, or salt thereof, is administered at a fixed dose of about 500 mg. In other examples, the double stranded RNAi agent, or salt thereof, is administered at

fixed dose of about 600 mg. In some examples, the double stranded RNAi agent, or salt thereof, is administered ata fixed dose of about 800 mg.

In certain examples, the pharmaceutical composition is administered at a frequency of once per month to once per six months. In certain examples, the pharamaceutical composition is administered at a frequency of once per month to once per three months. In certain examples, the pharmaceutical composition is administered at a frequency of once per three months to once per six months.

In some examples, the pharmaceutical composition is administered to the subject at an interval of once a month. In other examples, the pharmaceutical composition is administered to the subject at an interval of once a quarter. In some examples, the pharmaceutical composition is administered to the subject at an interval of bianually.

In certain examples, the double stranded RNAi agent is administered at a dose of 50 to 400 mg per dose at a frequency of once per month to once per six months.

In certain examples, the AGT –associated disorder is selected from the group consisting of high blood pressure, hypertension, borderline hypertension, primary hypertension, secondary hypertension 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, nocturnal hypotension, glomerulosclerosis, coarctation of the aorta, aortic aneurism, ventricular fibrosis, heart failure, myocardial infarction, angina, stroke, renal disease, renal failure, systemic sclerosis, intrauterine growth restriction (IUGR) , fetal growth restriction, obesity, liver steatosis/ fatty liver, non-alcoholic Steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD); glucose intolerance, type 2 diabetes, and metabolic syndrome.

In certain examples, the subject has a systolic blood pressure of at least 130 mm Hg or a diastolic blood pressure of at least 80 mm Hg. In certain examples, the subject has a systolic blood pressure of at least 140 mm Hg and a diastolic blood pressure of at least 80 mm Hg.

In certain examples, the subject is part of a group susceptible to salt sensitivity, is overweight, is obese, is pregnant, is planning to become pregnant, has type 2 diabetes, or has type 1 diabetes.

In certain examples, the subject has an AGT-associated disorder and is further part of a group susceptible to salt sensitivity, is overweight, is obese, is pregnant, is planning to become pregnant, has type 2 diabetes, or has type 1 diabetes.

In certain examples, subject has reduced kidney function. In certain examples, the subject has an AGT-associated disorder and is further has reduced kidney function.

In certain examples, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

In certain examples, the pharmaceutical composition is for administration by subcutaneous or intravenous injection.

The disclosure further provides for the use of a pharmaceutical composition of any in a method of treating an AGT-associated disorder or for use in the method of preparation of a medicament for use in a method of treating an AGT-associated disorder.

Brief Description of the Drawings

Figure 1 is a graph showing percent change in serum AGT relative to AGT baseline at day 0 after a single placebo, 10 mg, 25 mg, 50 mg, 100 mg, or 200 mg subcutaneous dose of AD-85481.

Figure 2 is a graph showing changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at Week 8 relative to baseline after a single placebo, 10 mg, 25 mg, 50 mg, 100 mg, or 200 mg subcutaneous dose of AD-85481. The number of subjects in each group are shown along the x axis.

Detailed Description of the Invention

The present invention provides methods for inhibiting the expression of an angiotensinogen (AGT) gene. The present invention also provides methods for treating a subject having a disorder that would benefit from reduction in AGT expression, or treating an AGT-associated disorder in a subject. In addition, the present invention provides methods for decreasing blood pressure level in a subject. The methods include administering to the subject a fixed dose, *e.g.,* about 50 mg to about 800 mg, of a double stranded RNAi agent, or salt thereof, targeting AGT, as described herein.

The following detailed description discloses methods for inhibiting the expression of an AGT gene, methods for treating subjects that would benefit from reduction of the expression of an AGT gene, *e.g.*, subjects susceptible to or diagnosed with an AGT-associated disorder, *e.g.*, hypertension, using an double stranded RNAi agent, or salt thereof, targeting AGT, and pharmaceutical compositions comprising fixed doses of such RNAi agents, or salt thereof, for inhibiting the expression of an AGT gene.

I. Definitions

In order that the present invention may be more readily understood, certain terms are first defined. In addition, it should be noted that whenever a value or range of values of a parameter are recited, it is intended that values and ranges intermediate to the recited values are also intended to be part of this invention.

The articles “a” and “an” are used herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element, *e.g.*, a plurality of elements.

The term "including" is used herein to mean, and is used interchangeably with, the phrase "including but not limited to".

We claim:

1. Use of a fixed dose of 50 mg to 800 mg of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof in the manufacture of a medicament for inhibiting the expression of an angiotensinogen (AGT) gene in a subject,

wherein the double-stranded RNAi agent or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10);

wherein the double-stranded RNAi agent, or salt thereof, comprises at least one modified nucleotide; and

wherein at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification, thereby inhibiting the expression of the AGT gene in the subject.

2. Use of a fixed dose of 50 mg to 800 mg of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof in the manufacture of a medicament for treating a subject that would benefit from reduction in angiotensinogen (AGT) expression,

wherein the double-stranded RNAi agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10);

wherein the double-stranded RNAi agent, or salt thereof, comprises at least one modified nucleotide; and

wherein at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification, thereby treating the subject that would benefit from reduction in AGT expression.

3. Use of a fixed dose of 50 mg to 800 mg of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof in the manufacture of a medicament for treating a subject having an angiotensinogen-(AGT-) associated disorder,

wherein the double-stranded RNAi agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO:10);

wherein the double-stranded RNAi agent, or salt thereof, comprises at least one modified nucleotide;

wherein at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification, thereby treating the subject having the AGT-associated disorder.

4. Use of a fixed dose of 50 mg to 800 mg of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof in the manufacture of a medicament for decreasing blood pressure level in a subject,

wherein the double-stranded RNAi agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides of the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10);

wherein the double-stranded RNAi agent, or salt thereof, comprises at least one modified nucleotide;

wherein at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification, thereby decreasing the blood pressure level in the subject.

5. The use of any one of claims 1-4, wherein the fixed dose is to be administered to the subject at an interval of once a month.

6. The use of any one of claims 1-4, wherein the fixed dose is to be administered to the subject at an interval of once every six months.

7. The use of any one of claims 1-4, wherein the fixed dose is to be administered to the subject at an interval of once every six months.

8. The use of any one of claims 1-7, wherein the subject is to be administered a fixed dose of 50 mg to 200 mg.

9. The use of any one of claims 1-7, wherein the subject is to be administered a fixed dose of 200 mg to 400 mg.

10. The use of any one of claims 1-7, wherein the subject is to be administered a fixed dose of 400 mg to 800 mg.

11. The use of any one of claims 1-7, wherein the subject is to be administered a fixed dose of about 100 mg.

12. The use of any one of claims 1-7, wherein the subject is to be administered a fixed dose of about 200 mg.

13. The use of any one of claims 1-7, wherein the subject is to be administered a fixed dose of about 300 mg.

14. The use of any one of claims 1-7, wherein the subject is to be administered a fixed dose of about 400 mg.

15. The use of any one of claims 1-7, wherein the subject is to be administered a fixed dose of about 500 mg.

16. The use of any one of claims 1-7, wherein the subject is to be administered a fixed dose of about 600 mg.

17. The use of any one of claims 1-7, wherein the subject is to be administered a fixed dose of about 700 or 800 mg.

18. The use of any one of claims 1-17, wherein the double stranded RNAi agent, or salt thereof, is to be administered to the subject subcutaneously or intravenously.

19. The use of claim 18, wherein the subcutaneous administration is subcutaneous injection.

20. The use of claim 18, wherein the intravenous administration is intravenous injection.

21. The use of any one of claims 1-20, wherein the antisense strand comprises a nucleotide sequence comprising at least 20 contiguous nucleotides of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand comprises a nucleotide sequence comprising at least 20 contiguous nucleotides of the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10).

22. The use of any one of claims 1-21, wherein the antisense strand comprises a nucleotide sequence comprising at least 21 contiguous nucleotides of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand comprises a nucleotide sequence comprising at least 20 contiguous nucleotides of the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10).

23. The use of any one of claims 1-22, wherein the antisense strand comprises a nucleotide sequence comprising at least 22 contiguous nucleotides of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand comprises a nucleotide

sequence comprising at least 20 contiguous nucleotides of the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10).

24. The use of any one of claims 1-23, wherein the antisense strand comprises the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand comprises the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10).

25. The use of any one of claims 1-24, wherein the antisense strand consists of the nucleotide sequence UGUACUCUCAUUGUGGAUGACGA (SEQ ID NO: 9) and the sense strand consists of the nucleotide sequence GUCAUCCACAAUGAGAGUACA (SEQ ID NO: 10).

26. The use of any one of claims 1-25, wherein substantially all of the nucleotides of the sense strand are modified nucleotides.

27. The use of any one of claims 1-25, wherein substantially all of the nucleotides of the antisense strand are modified nucleotides.

28. The use of any one of claims 1-25, wherein all of the nucleotides of the sense strand are modified nucleotides.

29. The use of any one of claims 1-25, wherein all of the nucleotides of the antisense strand are modified nucleotides.

30. The use of any one of claims 1-29, wherein at least one of the nucleotide modifications is selected from the group consisting of a deoxy-nucleotide, 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’-O-allyl-modified nucleotide, 2’-C-alkyl-modified nucleotide, 2’-hydroxly-modified nucleotide, a 2’-methoxyethyl modified nucleotide, a 2’-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5’-phosphate, a nucleotide comprising a 5’-phosphate mimic, a thermally destabilizing nucleotide, a glycol modified nucleotide (GNA), and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

31. The use of claim 30, wherein at least one of the nucleotide modifications is selected from the group consisting of a deoxy-nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a glycol modified nucleotide (GNA), and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

32. The use of any one of claims 1-31, wherein the double stranded region is 19-23 nucleotide pairs in length, 19- 21 nucleotide pairs in length, 21-23 nucleotide pairs in length, or 21 nucleotide pairs in length.

33. The use of any one of claims 1-32, wherein each strand is independently 19-23 nucleotides in length, 19-25 nucleotides in length, or 21-23 nucleotides in length.

34. The use of claim 33, wherein the sense strand is 21 nucleotides in length, and the antisense strand is 23 nucleotides in length.

35. The use of any one of claims 1-34, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide or a 3' overhang of at least 2 nucleotides.

36. The use of any one of claims 1-35, wherein the double-stranded RNAi agent, or salt thereof, further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

37. The use of claim 36, where the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand.

38. The use of claim 37, wherein the strand is the antisense strand.

39. The use of claim 37, wherein the strand is the sense strand.

40. The use of claim 36, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand.

41. The use of claim 40, wherein the strand is the antisense strand.

42. The use of claim 40, wherein the strand is the sense strand.

43. The use of claim 36, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at both the 5'- and 3'-terminus of one strand.

44. The use of claim 43, wherein the strand is the antisense strand.

45. Use of a fixed dose of 50 mg to 800 mg of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof in the manufacture of a medicament for inhibiting the expression of an angiotensinogen (AGT) gene in a subject,

wherein the double-stranded RNAi agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa

(SEQ ID NO: 11) and the sense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12);

wherein a is 2'-O-methyladenosine-3'-phosphate, c is 2'-O-methylcytidine-3'-phosphate, g is 2'-O-methylguanosine-3'-phosphate, u is 2'-O-methyluridine-3'-phosphate, Af is 2'-fluoroadenosine-3'-phosphate, Cf is 2'-fluorocytidine-3'-phosphate, Gf is 2'-fluoroguanosine-3'-phosphate, Uf is 2'-fluorouridine-3'-phosphate, (Tgn) is thymidine-glycol nucleic acid (GNA) S-Isomer, and s is a phosphorothioate linkage, thereby inhibiting the expression of the AGT gene in the subject.

46. Use of a fixed dose of 50 mg to 800 mg of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof in the manufacture of a medicament for treating a subject that would benefit from reduction in AGT expression,

wherein the double-stranded RNAi agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12);

wherein a is 2'-O-methyladenosine-3'-phosphate, c is 2'-O-methylcytidine-3'-phosphate, g is 2'-O-methylguanosine-3'-phosphate, u is 2'-O-methyluridine-3'-phosphate, Af is 2'-fluoroadenosine-3'-phosphate, Cf is 2'-fluorocytidine-3'-phosphate, Gf is 2'-fluoroguanosine-3'-phosphate, Uf is 2'-fluorouridine-3'-phosphate, (Tgn) is thymidine-glycol nucleic acid (GNA) S-Isomer, and s is a phosphorothioate linkage, thereby treating the subject that would benefit from reduction in AGT expression.

47. Use of a fixed dose of 50 mg to 800 mg of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof in the manufacture of a medicament for treating a subject having an AGT-associated disorder,

wherein the double-stranded RNAi agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12);

wherein a is 2'-O-methyladenosine-3'-phosphate, c is 2'-O-methylcytidine-3'-phosphate, g is 2'-O-methylguanosine-3'-phosphate, u is 2'-O-methyluridine-3'-phosphate, Af is 2'-fluoroadenosine-3'-phosphate, Cf is 2'-fluorocytidine-3'-phosphate, Gf is 2'-fluoroguanosine-3'-phosphate, Uf is 2'-

fluorouridine-3’-phosphate, (Tgn) is thymidine-glycol nucleic acid (GNA) S-Isomer, and s is a phosphorothioate linkage, thereby treating the subject having the AGT-associated disorder.

48. Use of a fixed dose of 50 mg to 800 mg of a double-stranded ribonucleic acid (RNAi) agent, or salt thereof in the manufacture of a medicament for decreasing blood pressure level in a subject,

wherein the double-stranded RNAi agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand comprises a modified nucleotide sequence comprising at least 19 contiguous nucleotides of the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12);

wherein a is 2'-O-methyladenosine-3’-phosphate, c is 2'-O-methylcytidine-3’-phosphate, g is 2'-O-methylguanosine-3’-phosphate, u is 2'-O-methyluridine-3’-phosphate, Af is 2’-fluoroadenosine-3’-phosphate, Cf is 2’-fluorocytidine-3’-phosphate, Gf is 2’-fluoroguanosine-3’-phosphate, Uf is 2’-fluorouridine-3’-phosphate, (Tgn) is thymidine-glycol nucleic acid (GNA) S-Isomer, and s is a phosphorothioate linkage, thereby decreasing the blood pressure level in the subject.

49. The use of any one of claims 45-48, wherein the fixed dose is to be administered to the subject at an interval of once a month.

50. The use of any one of claims 45-48, wherein the fixed dose is to be administered to the subject at an interval of once every 3 months.

51. The use of any one of claims 45-48, wherein the fixed dose is to be administered to the subject at an interval of every six months.

52. The use of any one of claims 45-51, wherein the subject is to be administered a fixed dose of 50 mg to 200 mg.

53. The use of any one of claims 45-51, wherein the subject is to be administered a fixed dose of 200 mg to 400 mg.

54. The use of any one of claims 45-51, wherein the subject is to be administered a fixed dose of 400 mg to 800 mg.

55. The use of any one of claims 45-51, wherein the subject is to be administered a fixed dose of about 100 mg.

56. The use of any one of claims 45-51, wherein the subject is to be administered a fixed dose of about 200 mg.

57. The use of any one of claims 45-51, wherein the subject is to be administered a fixed dose of about 300 mg.

58. The use of any one of claims 45-51, wherein the subject is to be administered a fixed dose of about 400 mg.

59. The use of any one of claims 45-51, wherein the subject is to be administered a fixed dose of about 500 mg.

60. The use of any one of claims 45-51, wherein the subject is to be administered a fixed dose of about 600 mg.

61. The use of any one of claims 45-51, wherein the subject is to be administered a fixed dose of about 700 or 800 mg.

62. The use of any one of claims 45-61, wherein the double stranded RNAi agent, or salt thereof, is to be administered to the subject subcutaneously or intravenously.

63. The use of claim 62, wherein the subcutaneous administration is subcutaneous injection.

64. The use of claim 62, wherein the intravenous administration is intravenous injection.

65. The use of any one of claims 45-64, wherein the antisense strand comprises a modified nucleotide sequence comprising at least 20 contiguous nucleotides of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand comprises a modified nucleotide sequence comprising at least 20 contiguous nucleotides of the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12).

66. The use of any one of claims 45-65, wherein the antisense strand comprises a modified nucleotide sequence comprising at least 21 contiguous nucleotides of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand comprises a modified nucleotide sequence comprising at least 20 contiguous nucleotides of the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12).

67. The use of any one of claims 45-66, wherein the antisense strand comprises a modified nucleotide sequence comprising at least 22 contiguous nucleotides of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand comprises a modified nucleotide sequence comprising at least 20 contiguous nucleotides of the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12).

68. The use of any one of claims 45-67, wherein the antisense strand comprises the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand comprises the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12).

69. The use of any one of claims 45-68, wherein the antisense strand consists of the modified nucleotide sequence usGfsuac(Tgn)cucauugUfgGfaugacsgsa (SEQ ID NO: 11) and the sense strand consists of the modified nucleotide sequence gsuscaucCfaCfAfAfugagaguaca (SEQ ID NO: 12).

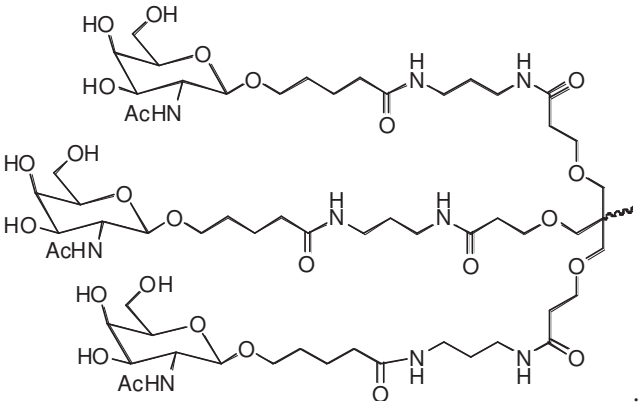
70. The use of any one of claims 45-69, wherein the double stranded RNAi agent, or salt thereof, further comprises a ligand.

71. The use of claim 70, wherein the ligand is conjugated to the 3’ end of the sense strand.

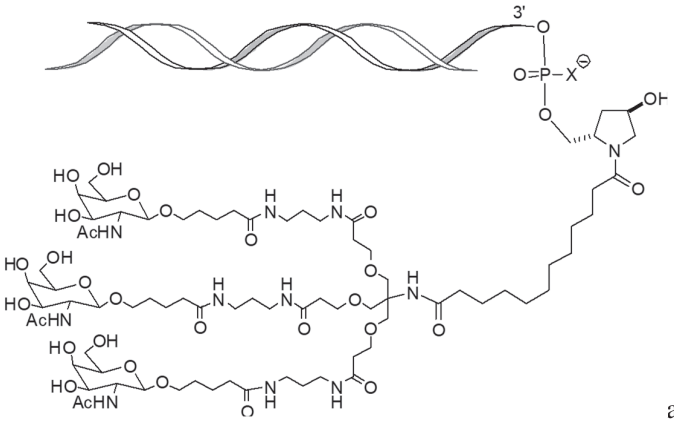
72. The use of claim 70 or 71, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

73. The use of claim 72, wherein the GalNAc derivative comprises one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

74. The use of claim 72, wherein the ligand is



75. The use of claim 74, wherein the 3’ end of the sense strand is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S or wherein X is O.

76. The use of any one of claims 1-4 and 45-48, where the subject is a human.

77. The use of claim 76, wherein the subject has a systolic blood pressure of at least 130 mm Hg or a diastolic blood pressure of at least 80 mm Hg.

78. The use of claim 76, wherein the subject has a systolic blood pressure of at least 140 mm Hg or a diastolic blood pressure of at least 80 mm Hg.

79. The use of any one of claims 1-4 and 45-48, wherein the subject is part of a group susceptible to salt sensitivity, is overweight, is obese, is pregnant, is planning to become pregnant, has type 2 diabetes, has type 1 diabetes, or has reduced kidney function.

80. The use of claim 2 or 46, wherein the disorder that would benefit from reduction in AGT expression is an AGT-associated disorder.

81. The use of claim 3, 47 or 80, wherein the AGT associated disorder is selected from the group consisting of high blood pressure, hypertension, borderline hypertension, primary hypertension, secondary hypertension 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, nocturnal hypotension, glomerulosclerosis, coarctation of the aorta, aortic aneurism, ventricular fibrosis, heart failure, myocardial infarction, angina, stroke, renal disease, renal failure, systemic sclerosis, intrauterine growth restriction (IUGR) , fetal growth restriction, obesity, liver steatosis/ fatty liver, non-alcoholic Steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD); glucose intolerance, type 2 diabetes, and metabolic syndrome.

82. The use of claim 4 or 48, wherein the blood pressure comprises systolic blood pressure and/or diastolic blood pressure.

83. The use of any one of claims 1-4 and 45-48, wherein the use results in a decrease in AGT expression by at least 30%, 40% 50%, 60%, 70%, 80%, 90%, or 95%.

84. The use of claim 83, wherein the AGT protein level in a blood or a serum sample of the subject is decreased by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95%.

85. The use of any one of claims 1-4 and 45-48, where the use results in a decrease in systolic blood pressure and/or diastolic blood pressure.

86. The use of claim 85, wherein the systolic blood pressure and/or diastolic blood pressure is decreased by at least 4 mmHg, 5 mmHg, 6 mmHg, 7 mmHg, 8 mmHg, 9 mmHg or 10 mmHg.

87. The use of any one of claims 1-86, further comprising that an additional therapeutic agent for treatment of hypertension is to be administered to the subject.

88. The use of claim 87, wherein 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 alpha2-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, a steroidal

antimineralocorticoid agent; a combination of any of the foregoing; and a hypertension therapeutic agent formulated as a combination of agents.

89. The use of claim 87, where wherein the additional therapeutic agent comprises an angiotensin II receptor antagonist.

90. The use of claim 89, wherein the angiotensin II receptor antagonist is selected from the group consisting of losartan, valsartan, olmesartan, eprosartan, and azilsartan.

91. The use of any one of claims 1-4 and 45-48, wherein the RNAi agent, or salt thereof, is to be administered in a pharmarceutical composition.

92. The use of claim 91, wherein the RNAi agent, or salt thereof, is to be administered in an unbuffered solution.

93. The use of claim 92, wherein the unbuffered solution is saline or water.

94. The use of claim 91, wherein the RNAi agent, or salt thereof, is to be administered in a buffer solution.

95. The use of claim 94, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

96. The use of claim 95, wherein the buffer solution is phosphate buffered saline (PBS).

97. A kit for performing the use of any one of claims 1-4, and 45-48, comprising

a) the RNAi agent, or salt thereof,and

b) instructions for use, and

c) optionally, means for administering the RNAi agent, or salt thereof, to the subject.