their gender. For example, this document provides methods and materials for using sGC agonists or a combination of sGC agonists and PDE5A inhibitors in male patients to reduce calcification of heart valves and/or vessels or to slow progression of aortic sclerosis to calcific aortic valve stenosis. As described herein, sGC agonists such as ataciguat can be used to slow progression of aortic sclerosis to calcific aortic valve stenosis, but such treatment is more effective in males than in females. Having the ability to effectively slow progression of aortic sclerosis to calcific aortic valve stenosis can allow male patients to live longer and happier lives. In some cases, selectively slowing progression of aortic sclerosis to calcific aortic valve stenosis in male patients can allow female patients to avoid unnecessary treatment with sGC agonists. This document also provides methods and materials for using anti-fibrotic agents to treat females identified as having aortic sclerosis. In some cases, such as when calcification is observed after treatment with an anti-fibrotic agent, females can be treated with one or more sGC agonists. The methods disclosed herein also can be used to reduce blood pressure in mammals who have, or who are at risk of having, hypertension, particularly in a supine position. In addition, the methods disclosed herein can include treatment of diastolic dysfunction, mitigation of elevated pulse pressure, and reduction of blood pressure, particularly in a supine position; in some cases, these methods can be carried out on a gender-dependent basis in which males are treated and females are excluded from treatment.

In one example, this document features a method for treating a mammal on the basis of the mammal's gender, where the method includes (a) identifying a mammal as having, or as being at risk of developing, heart valve calcification or vessel calcification, (b) identifying the mammal as a male mammal or a female mammal, and (c) when the mammal is a male mammal, administering a sGC agonist to the male mammal, thereby slowing progression of calcification of a heart valve or vessel within the male mammal, and when the mammal is a female mammal, not administering a sGC agonist to the female mammal and, optionally, administering a treatment that is not a sGC agonist to the female mammal to slow progression of calcification of a heart valve or vessel within the female mammal. In one aspect, the present disclosure provides use of a sGC agonist in the manufacture of a medicament slowing progression of calcification of a heart valve or vessel in a mammal~~for treating a mammal on the basis of the mammal's gender~~, said use comprising: (a) identifying a mammal as having, or as being at risk of developing, heart valve calcification or vessel calcification, (b) identifying said mammal as a male mammal or a female mammal, and (c) when said mammal is a male mammal, the sGC agonist is to be administered to said male mammal, ~~thereby slowing progression of calcification of a heart valve or vessel within said male mammal,~~ and when said mammal is a female mammal, the sGC agonist is not to be administered to said female mammal~~and, optionally, a treatment that is not a sGC agonist is to be administered to said female mammal to slow progression of calcification of a heart valve or vessel within said female mammal~~. The mammal can be a human. The sGC agonist can be ataciguat (5-chloro-2-[[(5-chloro-2-thienyl)sulfonyl]amino]-N-[4-(4-morpholinylsulfonyl)phenyl]-benzamide; HMR1766), YC-I (5-[1-(phenylmethyl)-1H-indazol-3-yl]-2-furanmethanol), BAY 58-

include administering an anti-fibrotic agent to the mammals identified as being female mammals.

In still another example, this document features a method for avoiding the unnecessary use of a sGC agonist to treat a mammal having, or at risk of developing, heart valve calcification or vessel calcification, where the method includes identifying the mammal as being a female mammal and as having, or at risk of developing, the heart valve calcification or vessel calcification, and excluding the female mammal from treatment with the sGC agonist based, at least in part, on the female gender of the female mammal. The mammal can be a human. The sGC agonist can be ataciguat, YC-I, BAY 58-2667, BAY 41-2272, BAY-41-8543, BAY 63-2521, CFM-1571, A-350619, vericiguat, praliciguat, olinciguat, bis-heteroaryl pyrazole IWP-051, IW-6463, GSK2181236A, IWP-550, IWP-854, IWP-953, nelociguat, MGV354, BI 703704, S3448, or BAY 60-2770.

This document also features a method for treating a mammal on the basis of the mammal's gender, where the method includes (a) identifying a mammal as having, or as being at risk of developing, aortic sclerosis, (b) identifying the mammal as a male mammal or a female mammal, and (c) when the mammal is a male mammal, administering a sGC agonist to the male mammal, thereby slowing progression of aortic sclerosis to calcific aortic valve stenosis within the male mammal, and when the mammal is a female mammal, not administering a sGC agonist to the female mammal and, optionally, administering a treatment that is not a sGC agonist to the female mammal to slow progression of aortic sclerosis to calcific aortic valve stenosis within the female mammal. In another aspect, the present disclosure provides use of a sGC agonist in the manufacture of a medicament for slowing progression of aortic sclerosis to calcific aortic valve stenosis in a mammal ~~treating a mammal on the basis of the mammal's gender~~, said use comprising: (a) identifying a mammal as having, or as being at risk of developing, aortic sclerosis, (b) identifying said mammal as a male mammal or a female mammal, and (c) when said mammal is a male mammal, the sGC agonist is to be administered to said male mammal, ~~thereby slowing progression of aortic sclerosis to calcific aortic valve stenosis within said male mammal,~~ and when said mammal is a female mammal, the sGC agonist is not to be administered to said female mammal ~~and, optionally, a treatment that is not a sGC agonist is to be administered to said female mammal to slow progression of aortic sclerosis to calcific aortic valve stenosis within said female mammal~~. The mammal can be a human. The sGC agonist can be ataciguat, YC-I, BAY 58-2667, BAY 41-2272, BAY-41-8543, BAY 63-2521, CFM-1571, A-350619, vericiguat, praliciguat, olinciguat, bis-heteroaryl pyrazole IWP-051, IW-6463, GSK2181236A, IWP-550, IWP-854, IWP-953, nelociguat, MGV354, BI 703704, S3448, or BAY 60-2770. The method can further include administering a PDE5A inhibitor to the male mammal. The method can further include identifying the male mammal as having an elevated plasma level of LPA. The method can include administering an anti-fibrotic agent to the female mammal.

In another example, this document features a method for treating a population of mammals identified as having, or as being at risk for developing, aortic sclerosis,

heteroaryl pyrazole IWP-051, IW-6463, GSK2181236A, IWP-550, IWP-854, IWP-953, nelociguat, MGV354, BI 703704, S3448, or BAY 60-2770.

In another example, this document features a method for treating a mammal, where the method includes (a) identifying the mammal as having, or as being at risk for, hypertension when in a supine position, and (b) administering to a sGC agonist to the mammal, thereby reducing blood pressure in the supine position. ~~In one aspect, the present disclosure provides use of a sGC agonist in the manufacture of a medicament for treating a mammal, comprising identifying said mammal as having, or as being at risk for, hypertension when in a supine position, wherein the sGC agonist is to be administered to said mammal, thereby reducing blood pressure in the supine position.~~ The mammal can be a human. The sGC agonist can be ataciguat, YC-I, BAY 58-2667, BAY 41-2272, BAY-41-8543, BAY 63-2521, CFM-1571, A-350619, vericiguat, praliciguat, olinciguat, bis-heteroaryl pyrazole IWP-051, IW-6463, GSK2181236A, IWP-550, IWP-854, IWP-953, nelociguat, MGV354, BI 703704, S3448, or BAY 60-2770. The method can further include administering a PDE5A inhibitor to the mammal. The method can further include identifying the mammal as being a male mammal prior to the administering. The administering may not reduce blood pressure when the mammal is in an upright position.

In still another example, this document features a method for treating a population of mammals identified as having, or as being at risk for developing hypertension in a supine position, wherein the population includes at least one male mammal and at least one female mammal, and where the method includes administering a sGC agonist to the at least one male mammal, thereby reducing blood pressure and preventing deleterious side effects of hypertension while in the supine position in the at least one male mammal, and not administering the sGC agonist to the at least one female mammal. The mammals can be human. The sGC agonist can be ataciguat, YC-I, BAY 58-2667, BAY 41-2272, BAY-41-8543, BAY 63-2521, CFM-1571, A-350619, vericiguat, praliciguat, olinciguat, bis-heteroaryl pyrazole IWP-051, IW-6463, GSK2181236A, IWP-550, IWP-854, IWP-953, nelociguat, MGV354, BI 703704, S3448, or BAY 60-2770. The method can further include administering a PDE5A inhibitor to the at least one male mammal. The method can include administering an anti-fibrotic agent to the at least one female mammal. The administering may not reduce blood pressure when the mammal is in an upright position.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure pertains. Although methods and materials similar or equivalent

WHAT IS CLAIMED IS:

1. Use of a sGC agonist in the manufacture of a medicament for ~~treating a mammal on the basis of the mammal's gender~~ slowing progression of calcification of a heart valve or vessel in a mammal, said use comprising:

(a) identifying a mammal as having, or as being at risk of developing, heart valve calcification or vessel calcification,

(b) identifying said mammal as a male mammal or a female mammal, and

(c) when said mammal is a male mammal, the sGC agonist is to be administered to said male mammal, ~~thereby slowing progression of calcification of a heart valve or vessel within said male mammal,~~ and when said mammal is a female mammal, the sGC agonist is not to be administered to said female mammal ~~and, optionally, a treatment that is not a sGC agonist is to be administered to said female mammal to slow progression of calcification of a heart valve or vessel within said female mammal~~.

2. The use of claim 1, wherein a treatment that is not a sGC agonist is to be administered to said female mammal to slow progression of calcification of a heart valve or vessel within said female mammal.

~~2~~3. The use of claim 1 or 2, wherein said mammal is a human.

~~3~~4. The use of any one of claims ~~1 or claim 2~~1-3, wherein said sGC agonist is:

ataciguat (5-chloro-2-[[(5-chloro-2-thienyl)sulfonyl]amino]-N-[4-(4-morpholinylsulfonyl)phenyl]-benzamide; HMR1766),

YC-I (5-[1-(phenylmethyl)-1H-indazol-3-yl]-2-furanmethanol),

BAY 58-2667 (4-[((4-carboxybutyl)(2-[(4-phenethylbenzyl)oxy] phenethyl)amino)methyl[benzoic]acid hydrochloride),

BAY 41-2272 (3-(4-amino-5-cyclopropylpyrimidin-2-yl)-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine),

BAY-41-8543 (2-[1-[(2-fluorophenyl)methyl]-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-(4-morpholinyl)-4,6-pyrimidinediamine),

BAY 63-2521 (methyl (4,6-diamino-2-(1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-5-yl)(methyl)carbamate),

CFM-1571 (3-[3-(dimethylamino)propoxy]-N-(4-methoxyphenyl)-1-(phenylmethyl)-1H-pyrazole-5-carboxamide hydrochloride),

A-350619 (3-[2-(4-chlorophenylthio)phenyl]-N-(4-dimethylaminobutyl)acrylamide),

vericiguat (methyl (4,6-diamino-2-(5-fluoro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-5-yl)carbamate),

praliciguat (1,1,1,3,3,3-hexafluoro-2-[({5-fluoro-2-[1-(2-fluorobenzyl)-5-(1,2-oxazol-3-yl)-1H-pyrazol-3-yl]pyrimidin-4-yl}amino)methyl]propan-2-ol),

olinciguat ((2R)-3,3,3-trifluoro-2-{[(5-fluoro-2-{1-[(2-fluorophenyl)methyl]-5-(1,2-oxazol-3-yl)-1H-pyrazol- 3-yl}pyrimidin-4-yl)amino]methyl}-2-hydroxypropanamide),

bis-heteroaryl pyrazole IWP-051 (5-fluoro-2-(1-(2-fluorobenzyl)-5-(isoxazol-3-yl)-1H-pyrazol-3-yl)pyrimidin-4(3H)-one),

IW-6463,

GSK2181236A (1-(6-{2-[({3-methyl-4′-[(trifluoromethyl)oxy]-4-biphenylyl}methyl)oxy]phenyl}-2-pyridinyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid),

IWP-550,

IWP-854 (4-(5-fluoro-2-(1-(2-fluorobenzyl)-5-(isoxazol-3-yl)-1H-pyrazol-3-yl)pyrimidin-4-yl)-1-(3-methyl-3H-diazirin-3-yl)-N-(37-oxo-41-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-3,6,9,12,15,18,21,24,27,30,33-undecaoxa-36-azahentetracontyl)-7,10,13,16-tetraoxa-4-azanonadecan-19-amide),

IWP-953,

nelociguat (methyl (4,6-diamino-2-(1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-5-yl)carbamate),

MGV354 ((S)-1-(6-(3-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenyl)amino)-2,3-dihydro-1H-inden-4-yl)pyridin-2-yl)-5-methyl-1H-pyrazole-4-carboxylic acid),

BI 703704 ((1R,5S,8s)-3-(4-(5-methyl-2-((2-methyl-4-(piperidine-1-carbonyl)benzyl)oxy)phenyl)thiazol-2-yl)-3-azabicyclo[3.2.1]octane-8-carboxylic acid),

S3448 (2-[[(4-chlorophenyl)sulfonyl]amino]-4,5-dimethoxy-N-[4-(4-thiomorpholinylsulfonyl)phenyl]benzamide), or

BAY 60-2770 (4-[[(4-carboxybutyl)[2-[5-fluoro-2-[[4′-(trifluoromethyl)[1,1′-biphenyl]-4-yl]methoxy]phenyl]ethyl]amino]methyl]benzoic acid).

~~4~~5. The use of any one of claims 1-~~3~~4, wherein said medicament is to be administered to said male mammal with a PDE5A inhibitor.

~~5~~6. The use of any one of claims 1-~~4~~5, wherein said use further comprises identifying said male mammal as having an elevated plasma level of lysophosphatidic acid (LPA).

~~6~~7. The use of any one of claims ~~1 or claim 2~~1-3, wherein said mammal is a female and an anti-fibrotic agent is to be administered to said female mammal to slow progression of calcification of a heart valve or vessel within said female mammal.

~~7~~8. Use of a sGC agonist in the manufacture of a medicament for slowing progression of aortic sclerosis to calcific aortic valve stenosis in a mammal~~treating a mammal on the basis of the mammal's gender~~, said use comprising:

(a) identifying a mammal as having, or as being at risk of developing, aortic sclerosis,

(b) identifying said mammal as a male mammal or a female mammal, and

(c) when said mammal is a male mammal, the sGC agonist is to be administered to said male mammal, ~~thereby slowing progression of aortic sclerosis to calcific aortic valve stenosis within said male mammal,~~ and when said mammal is a female mammal, the sGC agonist is not to be administered to said female mammal ~~and, optionally, a treatment that is not a sGC agonist is to be administered to said female mammal to slow progression of aortic sclerosis to calcific aortic valve stenosis within said female mammal~~.

9. The use of claim 8, wherein a treatment that is not a sGC agonist is to be administered to said female mammal to slow progression of aortic sclerosis to calcific aortic valve stenosis within said female mammal.

~~8~~10. The use of claim ~~7~~8 or 9, wherein said mammal is a human.

~~9~~11. The use of any one of claims ~~7 or claim 8~~8-10, wherein said sGC agonist is ataciguat, YC-I, BAY 58-2667, BAY 41-2272, BAY-41-8543, BAY 63-2521, CFM-

1571, A-350619, vericiguat, praliciguat, olinciguat, bis-heteroaryl pyrazole IWP-051, IW-6463, GSK2181236A, IWP-550, IWP-854, IWP-953, nelociguat, MGV354, BI 703704, S3448, or BAY 60-2770.

~~10~~12. The use of any one of claims ~~7-9~~8-11, wherein said medicament is to be administered to said male mammal with a PDE5A inhibitor.

~~11~~13. The use of any one of claims ~~7-10~~8-12, wherein said use further comprises identifying said male mammal as having an elevated plasma level of LPA.

~~12~~14. The use of any one of claims ~~7 or claim 8~~8-10, wherein an anti-fibrotic agent is to be administered to said female mammal.

~~13. Use of a sGC agonist in the manufacture of a medicament for treating a mammal, comprising~~

~~identifying said mammal as having, or as being at risk for, hypertension when in a supine position, wherein the sGC agonist is to be administered to said mammal, thereby reducing blood pressure in the supine position.~~

~~14. The use of claim 13, wherein said mammal is a human.~~

~~15. The use of claim 13 or claim 14, wherein said sGC agonist is ataciguat, YC-I, BAY 58-2667, BAY 41-2272, BAY 41-8543, BAY 63-2521, CFM-1571, A-350619, vericiguat, praliciguat, olinciguat, bis-heteroaryl pyrazole IWP-051, IW-6463, GSK2181236A, IWP-550, IWP-854, IWP-953, nelociguat, MGV354, BI 703704, S3448, or BAY 60-2770.~~

~~16. The use of any one of claims 13-15, wherein said medicament is to be administered to said mammal with a PDE5A inhibitor.~~

~~17. The use of any one of claims 13-16, wherein said use further comprises identifying said mammal as being a male mammal prior to said administration.~~

~~18. The use of any one of claims 13-17, wherein said use does not reduce blood pressure when the mammal is in an upright position.~~