METHODS FOR PREDICTING RISK OF DEVELOPING HYPERTENSION

Cross-Reference to Related Applications

This application claims priority to United States provisional patent application serial number 61/683,956, filed August 16, 2012, the contents of which are incorporated herein by reference in their entirety.

Technical Field

This invention relates to the field of molecular biology and cardiovascular medicine, including methods using biomarkers, e.g., serum levels of ST2, to predict risk of developing hypertension, as well as methods for treating subjects to reduce the risk of developing hypertension and methods for selecting and/or stratifying subjects for clinical trials of treatments to reduce the risk of hypertension.

Background of the Invention

Hypertension, often referred to colloquially as "high blood pressure" is a condition characterized by the presence of a systolic blood pressure ≥140 mmHg and a diastolic blood pressure ≥90 mmHg (referred to as 140/90). Blood pressures between 120/80 and 140/90 are typically considered prehypertension, while pressure below 120/80 is normal. Other than pregnancy, the treatment of hypertension is the most common reason for physician office visits and use of prescription drugs among US adults (Egan et al., JAMA 303(20):2043, 2010). Hypertension is a major risk factor for cardiovascular disease: an estimated 69% of patients with incident myocardial infarction, and 74% with incident heart failure have preceding hypertension (Roger et al., Circulation 125:e2-e220, 2012). Treatment and control of hypertension reduces the risk of these cardiovascular diseases (Meredith, Journal of Renin-Angiotensin-Aldosterone System, 7(2):64-73, 2006). Therefore, identifying subjects who are at risk of developing hypertension, and treating them to reduce that risk, would reduce their risk of cardiovascular disease.

Summary

The ~~invention~~ disclosure is based, at least in part, on the discovery that subjects who do not have hypertension but have an elevated level of soluble ST2 are at increased risk of developing hypertension. Thus, provided herein are methods for selecting a treatment for a subject that

include determining a level of soluble ST2 in a biological sample from a subject, comparing the level of soluble ST2 in the biological sample to a reference level of soluble ST2, and selecting an anti-hypertensive treatment (also referred to herein as anti-hypertensive therapy) for a subject having an elevated level of soluble ST2 in the biological sample compared to the reference level of soluble ST2. Also provided are methods of treating a subject that include determining a level of soluble ST2 in a biological sample from a subject, comparing the level of soluble ST2 in the biological sample to a reference level of soluble ST2, and administering to a subject having an elevated level of soluble ST2 in the biological sample compared to the reference level of soluble ST2 an anti-hypertensive agent. Also provided are methods for selecting a subject for participation in a clinical study of a treatment for reducing the risk of developing hypertension, and methods of evaluating the risk of developing hypertension in a subject that include determining a level of soluble ST2 in a biological sample from a subject. Also provided are kits that contain an antibody that specifically binds to soluble ST2 for use in any of the methods described herein.

Also provided are methods for determining the efficacy of a treatment for reducing the risk of developing hypertension in a subject that include determining a first level of soluble ST2 in a biological sample obtained from a subject at a first time point, (2) determining a second level level of soluble ST2 in a biological sample obtained from the subject at a second time point, wherein between the first time point and the second time point, the subject is administered two or more (e.g., more than five, more than ten, or more than twenty) doses of a treatment (e.g., anti-hypertensive treatment, e.g., one or more anti-hypertensive agents), (3) comparing the second level and first level of soluble ST2, and (4) identifying the treatment administered to a subject having a decrease in the second level of soluble ST2 as compared to the first level of soluble ST2 as being effective for reducing the risk of developing hypertension in the subject, or alternatively, identifying the treatment administered to a subject having no substantial change or an elevation in the second level of soluble ST2 as compared to the first level of soluble ST2 as not being effective for reducing the risk of developing hypertension in a subject.

In one aspect, there is provided a method for selecting a treatment for a healthy subject who does not have hyptertension, the method comprising:

determining a level of soluble ST2 in a biological sample from a subject;

comparing the level of soluble ST2 in the biological sample to a reference level of soluble ST2; and

selecting an anti-hypertensive therapy for a subject having an elevated level of soluble ST2 in the biological sample compared to the reference level of soluble ST2.

In one aspect, there is provided use of an anti-hypertensive agent in the manufacture of a medicament for treating a healthy subject who does not have hypertension, wherein the subject is

one whose biological sample has been determined to have an elevated level of soluble ST2 compared to a reference level of soluble ST2.

In one aspect, there is provided a method for selecting a subject for participation in a clinical study of a treatment for reducing the risk of developing hypertension, the method comprising:

determining a level of soluble ST2 in a biological sample from a healthy subject who does not have hypertension;

comparing the level of soluble ST2 in the biological sample to a reference level of soluble ST2; and

selecting a subject having an elevated level of soluble ST2 in the biological sample compared to the reference level of soluble ST2 for participation in a clinical trial of a treatment for reducing the risk of developing hypertension.

In one aspect, there is provided a method for evaluating the risk of developing hypertension in a healthy subject who does not have hypertension, the method comprising:

determining a level of soluble ST2 in a biological sample from a subject;

comparing the level of soluble ST2 in the biological sample to a reference level of soluble ST2; and

identifying a subject having an elevated level of soluble ST2 in the biological sample compared to the reference level of soluble ST2 as having an increased risk of developing hypertension, or identifying a subject having decreased low level of soluble ST2 in the biological sample compared to the reference level of soluble ST2 as having a decreased risk of developing hypertension.

In one aspect, there is provided a kit comprising an antibody that specifically binds to soluble ST2 for use in a method as described herein, or use as described herein, and optionally instructions for performing any of the methods or use as described herein.

In any of the methods described herein, the subject is a healthy subject who does not have hypertension. In other embodiments of any of the methods described herein, the subject is a healthy subject who does not have hypertension and is not diagnosed with or presenting with two or more symptoms of any one of a cardiac disease, a cardiovascular disease, or a kidney disease.

artery disease, cardiovascular disease, acute coronary syndrome, and angina) include shortness of breath, heart palpitations, increased heart rate, weakness, dizziness, nausea, sweating, chest discomfort or pressure, chest pain, arm pain, fullness, indigestion, sweating, wheezing, sleep apnea, and anxiety.

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 ~~invention~~ disclosure belongs. Methods and materials are described herein for use in the present disclosure~~invention~~; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

The details of one or more embodiments of the disclosure~~invention~~ are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the disclosure~~invention~~ will be apparent from the description and drawings, and from the claims.

DETAILED DESCRIPTION

The invention is based, in part, on the discovery that subjects having an elevated level of soluble ST2 or an increase in soluble ST2 over time have an increased risk of developing hypertension. Thus, provided herein are methods for identifying subjects who are at increased risk of developing hypertension. Also described herein are methods for selecting a treatment for a subject that include determining a level of soluble ST2 in a biological sample from a subject, comparing the level of soluble ST2 in the biological sample to a reference level of soluble ST2, and selecting an anti-hypertensive therapy (also referred to herein as anti-hypertensive treatment) for a subject having an elevated level of soluble ST2 in the biological sample compared to the reference level of soluble ST2. Also provided are methods of treating a subject that include determining a level of soluble ST2 in a biological sample from a subject, comparing the level of soluble ST2 in the biological sample to a reference level of soluble ST2, and administering to a subject having an elevated level of soluble ST2 in the biological sample compared to the reference level of soluble ST2 an anti-hypertensive therapy. Also provided are methods for selecting a subject for participation in a clinical study of a treatment for reducing the risk developing hypertension, and methods of evaluating the risk of developing hypertension in a subject that include determining a level of soluble ST2 in a biological sample from a subject. Also provided are kits that contain an antibody that

WHAT IS CLAIMED IS:

1. A method for selecting a treatment for a healthy subject who does not have hyptertension, the method comprising:

determining a level of soluble ST2 in a biological sample from a subject;

comparing the level of soluble ST2 in the biological sample to a reference level of soluble ST2; and

selecting an anti-hypertensive therapy for a subject having an elevated level of soluble ST2 in the biological sample compared to the reference level of soluble ST2.

2. The method of claim 1, wherein the reference level of soluble ST2 is a level of soluble ST2 in a healthy subject who has a low risk of developing hypertension.

3. The method of claim 1, wherein the biological sample comprises blood, serum, or plasma.

4. The method of claim 1, further comprising:

determining the level of one of more additional biomarkers selected from the group consisting of: atrial natriuretic peptide (ANP), proANP, N-terminal (NT)-proANP, brain natriuretic peptide (BNP), proBNP, NT-proBNP, cardiac troponin I, C-reactive protein, creatinine, and Blood Urea Nitrogen (BUN) in the biological sample;

comparing the level of the one or more additional biomarkers in the biological sample to a reference level of the one of more additional biomarkers; and

selecting an anti-hypertensive therapy for a subject having an elevated level of the one or more additional biomarkers in the biological sample compared to the reference level of the one or more additional biomarkers.

5. The method of claim 4, wherein the one or more additional biomarkers are selected from the group consisting of BNP, proBNP, and NT-proBNP.

6. Use of an anti-hypertensive agent in the manufacture of a medicament for~~A method of~~ treating a healthy subject who does not have hypertension, ~~the method comprising:~~wherein the subject is one whose biological sample has been determined to have an elevated level of soluble ST2 compared to a reference level of soluble ST2.

~~determining a level of soluble ST2 in a biological sample from a subject;~~

~~comparing the level of soluble ST2 in the biological sample to a reference level of soluble ST2; and~~

~~administering to a subject having an elevated level of soluble ST2 in the biological sample compared to the reference level of soluble ST2 an anti-hypertensive therapy, or monitoring a subject decreased low level of soluble ST2 in the biological sample compared to the reference level of soluble ST2.~~

7. The ~~method~~ use of claim 6, wherein the reference level of soluble ST2 is a level of soluble ST2 in a healthy subject who has a low risk of developing hypertension.

8. The ~~method~~ use of claim 6, wherein the biological sample comprises blood, serum, or plasma.

9. The ~~method~~ use of claim 6, ~~further comprising~~wherein the biological sample has been further determined to have~~:~~

~~determining the level of one of more additional biomarkers selected from the group consisting of: atrial natriuretic peptide (ANP), proANP, N-terminal (NT)-proANP, brain natriuretic peptide (BNP), proBNP, NT-proBNP, cardiac troponin I, C-reactive protein, creatinine, and Blood Urea Nitrogen (BUN) in the biological sample;~~

~~comparing the level of the one or more additional biomarkers in the biological sample to a reference level of the one of more additional biomarkers; and~~

~~administering to a subject having~~ an elevated level of ~~the~~ one or more additional biomarkers selected from the group consisting of: atrial natriuretic peptide (ANP), proANP, N-terminal (NT)-proANP, brain natriuretic peptide (BNP), proBNP, NT-proBNP, cardiac troponin I, C-reactive protein, creatinine, and Blood Urea Nitrogen (BUN) ~~in the biological sample~~ compared to ~~the~~ a reference level of the one or more additional biomarkers ~~an anti-hypertensive therapy, or monitoring a subject having decreased low level of the one or more additional biomarkers in the biological sample compared to the reference level of the one or more additional biomarkers~~.

10. The ~~method~~ use of claim ~~6~~9, wherein the one or more additional biomarkers are selected from the group consisting of BNP, proBNP, and NT-proBNP.

11. A method for selecting a subject for participation in a clinical study of a treatment for reducing the risk of developing hypertension, the method comprising:

determining a level of soluble ST2 in a biological sample from a healthy subject who does not have hypertension;

identifying a subject having an elevated level of soluble ST2 in the biological sample compared to the reference level of soluble ST2 as having an increased risk of developing hypertension, or identifying a subject having decreased low level of soluble ST2 in the biological sample compared to the reference level of soluble ST2 as having a decreased risk of developing hypertension.

17. The method of claim 16, wherein the reference level of soluble ST2 is a level of soluble ST2 in a healthy subject who has a low risk of developing hypertension.

18. The method of claim 16, wherein the risk of developing hypertension is the risk of developing hypertension within three years.

19. The method of claim 16, wherein the biological sample comprises blood, serum, or plasma.

20. The method of claim 16, further comprising:

determining the level of one of more additional biomarkers selected from the group consisting of: atrial natriuretic peptide (ANP), proANP, N-terminal (NT)-proANP, brain natriuretic peptide (BNP), proBNP, NT-proBNP, cardiac troponin I, C-reactive protein, creatinine, and Blood Urea Nitrogen (BUN) in the biological sample;

comparing the level of the one or more additional biomarkers in the biological sample to a reference level of the one of more additional biomarkers; and

identifying a subject having an elevated level of the one or more additional biomarkers in the biological sample compared to the reference level of the one or more additional biomarkers as having an increased risk of developing hypertension.

21. The method of claim 20, wherein the one or more additional biomarkers are selected from the group consisting of BNP, proBNP, and NT-proBNP.

22. The method of any one of claims 1-~~21~~5 and 11-20, or the use of any one of claims 6-10, wherein the subject is human.

23. A kit comprising an antibody that specifically binds to soluble ST2 for use in a method of claims 1-~~22~~5 and 11-20, or use of claims 6-10, and optionally instructions for performing any of the methods of claims 1-~~22~~5 and 11-20 or use of claims 6-10.

24. The use of claim 6, wherein the anti-hypertensive agent is selected from the group consisting of Diuretics, Beta-blockers, Angiotensin-converting enzyme inhibitors (ACE inhibitors), Angiotensin II receptor blockers (ARBs), Calcium channel blockers, Alpha-blockers, Centrally acting drugs, Vasodilators, and Renin inhibitors.