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 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, the present disclosure refers to use of an anti-hypertensive agent in the manufacture of a medicament for reducing the risk of developing hypertension in a subject whose second biological sample obtained from the subject at a second time point has an elevated second level of soluble ST2 as compared to a first level of soluble ST2 in a first biological sample obtained from the subject at a first time point.

In one aspect, the present disclosure refers to a method for evaluating the risk of developing hypertension in a healthy subject who does not have hypertension, the method comprising:

determining a first level of soluble ST2 in a first biological sample obtained from the subject at a first time point;

determining a second level of soluble ST2 in a second biological sample obtained from the subject at a second time point;

comparing the second level of soluble ST2 to the first level of soluble ST2; and

identifying a subject having an elevated second level of soluble ST2 as compared to the first level of soluble ST2 as having an increased risk of developing hypertension, or identifying a subject having a decreased second level of soluble ST2 as compared to the first level of soluble ST2 as having a decreased risk of developing hypertension.

In any of the methods described herein, the subject is a healthy subject who does not have hypertension. In other examples 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.

In any of the methods described herein, the reference value of soluble ST2 or the one or more additional markers is the level of soluble ST2 or the one or more additional markers in a control subject (e.g., a healthy subject) who does not have hypertension and is not at risk or has a low risk of developing hypertension.

Also provided is the use of a pharmaceutical agent for reducing hypertension (e.g., any of exemplary pharmaceutical agents for reducing hypertension described herein) for treating a subject identified as having an increased risk of developing hypertension using any of the methods described herein.

By the term hypertension is meant a medical condition that is characterized by an abnormal, elevated blood pressure (i.e., a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg).

By the term "soluble ST2" is meant a soluble protein containing a sequence at least 90% identical (e.g., at least 95%, 96%, 97%, 98%, 99%, or 100% identical) to NCBI Accession No. NP_003847.2 (SEQ ID NO: 1) or containing a sequence at least 90% identical (e.g., at least 95%, 96%, 97%, 98%, 99%, or 100% identical) to amino acids 19-328 of SEQ ID NO: 1, or a nucleic acid containing a sequence at least 90% identical (e.g., at least 95%, 96%, 97%, 98%, 99%, or 100% identical) to NCBI Accession No. NM_003856.2 or containing a sequence at least 90% identical (e.g., at least 95%, 96%, 97%, 98%, 99%, or 100% identical) to nucleotides 285 to 1214 of NCBI Accession No. NM_003856.2.

By the term "elevated" or "elevation" is meant a difference, e.g., a statistically significant or detectable increase in a determined or measured level (e.g., a human soluble ST2 protein level) compared to a reference level (e.g., a level of human soluble ST2 in a subject (or population of subjects) not having an increased risk of developing hypertension, or a threshold level of human soluble ST2). In some examples, the reference is a threshold level, and any level above that is considered "elevated." Additional reference levels of human soluble ST2 are described herein and are known in the art.

As used herein, a "biological sample" includes one or more of blood, serum, plasma, urine, and body tissue. Generally, a biological sample is a sample containing serum, blood, or plasma.

By the term "health care facility" is meant a location where a subject may receive medical care or treatment from a health care professional (e.g., a nurse, a physician, or a physician's assistant). Non-limiting examples of health care facilities include hospitals, clinics, surgical centers, and assisted care facilities (e.g., a nursing home).

By the term "reference level" is meant a threshold level or a level in a control subject or control patient population. A reference level will depend on the assay performed and can be determined by one of ordinary skill in the art. A reference level may be a baseline level or a level in the same patient measured at an earlier point in time. In some examples, a reference level is a level of soluble ST2 in a control subject or population of control subjects that does not have an increased risk of developing hypertension. In some examples, a reference level is a level of soluble ST2 in a healthy subject. Additional examples of reference levels of soluble ST2 and methods of determining the same are known in the art and are described herein.

In some examples, the ratio of two soluble ST2 levels in a subject is compared to a reference ratio (e.g., a ratio of soluble ST2 levels measured in a control subject, e.g., any of the control subjects described herein or the same subject at earlier time points). Additional examples of reference ratios of soluble ST2 are known in the art and are described herein.

As used herein, a "subject" is a mammal, e.g., a human. In all examples, human nucleic acids, human polypeptides, and human subjects can be used.

By the term "healthy subject" is meant a subject that does not have a disease (e.g., a cardiac disease). For example, a healthy subject has not been diagnosed as having a disease and is not presenting with two or more (e.g., two, three, four, or five) symptoms of a disease state.

In some examples, the healthy subject does not have hypertension.

By the term "disease state" is meant the manifestation of one or more (e.g., at least two, three, four, or five) symptoms in a subject that indicate either an abnormal decrease in the viability and/or an abnormal decrease/malfunction of a biological activity of one or more (e.g., at least two, three, four, or five) tissues in the body of the subject. Non-limiting examples of disease states in a subject include a cardiac disease (e.g., arrhythmia, heart failure, heart attack, coronary artery disease, cardiovascular disease, acute coronary syndrome, and angina), inflammation, stroke, renal failure, obesity, high cholesterol, and dyslipidemia.

By the phrase "physical symptoms associated with a disease state" is meant the one or more (e.g., at least two, three, or four) symptoms that are manifested by a subject having a particular disease state. Physical symptoms associated with several disease states are known in the art by medical health professionals (e.g., physicians). Non-limiting examples of physical symptoms associated with a cardiac disease (e.g., arrhythmia, heart failure, coronary

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 disclosure belongs. Methods and materials are described herein for use in the present disclosure; 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 examples of the disclosure are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the disclosure 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. Use of an anti-hypertensive agent in the manufacture of a medicament for reducing the risk of developing hypertension in a subject whose second biological sample obtained from the subject at a second time point has an elevated second level of soluble ST2 as compared to a first level of soluble ST2 in a first biological sample obtained from the subject at a first time point.

2. The use of claim 1, wherein the first biological sample and the second biological sample each comprise blood, serum, or plasma.

3. The use of claim 1, wherein the second biological has been further determined to have an elevated second level of 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) compared to a first level of the one or more additional biomarkers in the first biological sample.

4. The use of claim 3, wherein the one or more additional biomarkers are selected from the group consisting of BNP, proBNP, and NT-proBNP.

5. The use of claim 1, wherein the anti-hypertensive agent is selected from the group consisting of nitrates, diuretics, thrombolytic agents, 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.

6. A method for evaluating the risk of developing hypertension in a healthy subject who does not have hypertension, the method comprising:

determining a first level of soluble ST2 in a first biological sample obtained from the subject at a first time point;

determining a second level of soluble ST2 in a second biological sample obtained from the subject at a second time point;

comparing the second level of soluble ST2 to the first level of soluble ST2; and

identifying a subject having an elevated second level of soluble ST2 as compared to the first level of soluble ST2 as having an increased risk of developing hypertension, or identifying a subject having a decreased second level of soluble ST2 as compared to the first level of soluble ST2 as having a decreased risk of developing hypertension.

7. The method of claim 5, wherein the risk of developing hypertension is the risk of developing hypertension within three years.

8. The method of claim 5, wherein the first biological sample and the second biological sample each comprise blood, serum, or plasma.

9. The method of claim 5, further comprising:

determining a first level of 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 first biological sample;

determining a second level of the one or more additional biomarkers in the second biological sample;

comparing the second level of the one or more additional biomarkers to the first level of the one or more additional biomarkers;

further identifying a subject having an elevated second level of the one or more biomarkers as compared to the first level of the one or more biomarkers as having an increased risk of developing hypertension.

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

11. The method of claim 5, further comprising selecting an anti-hypertensive agent for a subject identified as having an increased risk of developing hypertension.

12. The method of claim 11, wherein the anti-hypertension agent is selected from the group consisting of: nitrates, diuretics, thrombolytic agents, 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.

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