Title: VASOACTIVE HORMONE-BASED STRATIFICATION OF PATIENTS SUFFERING FROM DISEASES RELATED TO ENDOTHELIAL FUNCTION/DYSFUNCTION

Abstract: The present invention relates to a method for the stratification of a subject having an acute or a chronic disease, wherein said disease affects endothelial function/dysfunction, comprising the steps of (i) taking a sample of bodily fluid from said subject; (ii) determining in said sample of bodily fluid the concentration of a vasoactive hormone or fragments thereof or precursors or fragments thereof having a length of at least 12 amino acid residues; (iii) stratifying said subjects into either of the categories: (a) responder to a medication for treatment of said disease, (b) non-responder to a medication for treatment of said disease not showing an unfavourable effect after having received said medication; (c) subjects showing an unfavourable effect after having received said medication. The invention also relates to the use of an antibody or a functional fragment thereof in the method according to the invention.
Vasoactive hormone-based stratification of patients suffering from diseases related to endothelial function/dysfunction

Field of the invention

The present invention is in the field of clinical diagnostics. Particularly the present invention relates to the determination of the concentration of vasoactive hormones and their precursors and fragments thereof in a sample derived from a bodily fluid of a patient and the stratification of patients suffering from a disease related to endothelial function/dysfunction.

Background of the Invention


It has been investigated whether vasoactive biomarkers and their precursors and fragments thereof stratify patients exhibiting a positive effect due to a specific medication. For example, the use of NT-proBNP for stratification of HF patients for medication was presented in the PRIMA-Study at the ACC Congress Orlando (29th March 2009). Moreover, the utility of NT-proBNP measurements to identify patients with enhanced benefit from clopidogrel therapy was investigated by Tang et al., but no NT-proBNP subgroup could be identified with an overproportional benefit from clopidogrel therapy (Tang et al. Risk stratification for patients undergoing nonurgent percutaneous coronary intervention using N-terminal pro-B-type natriuretic peptide: a Clopidogrel for the Reduction of Events During Obsen'ation (CREDO)
substudy. American Heart Journal 2007; 153:36-41). Kropp et al. hypothesized that NT-proBNP could be used as a marker for the tolerability and safety of antipsychotic drugs. (Kropp, et al. N-terminal fragment of B-type natriuretic peptide (NT-proBNP), a marker of cardiac safety during antipsychotic treatment. Annals of General Psychiatry 2005;4: W). In addition, it has been contemplated that other neuroendocrine markers, e.g. AVP, ET-I, Big-ET-L, [NT-pro]ANP and [NT-pro]BNP. may be of value in the choice and titration of medical treatment for an individual patient in the future (Kjaer 2000; Videnskab og Praksis 162:5910-3). For example, it has been shown that elevated ANP levels before treatment with the beta-blocker carvedilol are predictive for reductions of mortality, and ANP and BNP are predictive for reductions of hospital admission in patients with chronic stable heart failure (Richards et al. Neurohumoral prediction of benefit from carvedilol in ischemic left ventricular dysfunction. Australia-New Zealand Heart Failure Group. Circulation 1999;99:786-92). In contrast to the cardiac peptides, higher plasma levels of Arg-Vasopressin (AVP) did not predict benefit from carvedilol in this study. In addition the same study group revealed, that carvedilol reduced mortality and heart failure in patients with chronic ischemic left ventricular dysfunction exhibiting a higher pre-treatment plasma NT-proBNP and adrenomedullin (ADM) (Richards et al. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin prognostic utility and prediction of benefit from carvedilol in chronic ischemic left ventricular dysfunction. Journal of the American College of Cardiology 2001:37:1 781-7).

However, patients were stratified according to peptide concentrations below and above median and a beneficial effect of carvediilol was not apparent until 300 days after treatment initiation, indicating that elevated plasma levels of the measured peptides may only predict a long-term benefit of the Beta-blocker carvedilol. Swedberg et al. demonstrated, that markedly elevated levels of ANP before ACE inhibitor treatment (namely elanapril) were related to reductions in mortality levels in patients with severe congestive heart failure in NYHA class IV (Swedberg et al. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial study group. Circulation 1990;82:1730-6). Again, patients were stratified according to peptide concentrations below and above median in this study. A beneficial effect of elanapril was demonstrated for mortality after 6 months.

In the patent application WO 2009/123730 methods for diagnosis and prognosis of pulmonary hypertension are described. A variety of markers lias been suggested.
Description of the invention

The present invention is based on the surprising finding of the inventors that the levels of vasoactive hormones and their precursors and fragments thereof in samples of bodily fluids do not only correlate with a prognosis or diagnosis for a variety of diseases but can also be used to stratify patients into risk groups with respect to certain medications. In other words, the inventors have found that certain populations of patients exist for which the administration of particular medications has no effect on their outcome or even has an adverse (i.e. unfavourable) effect, e.g. a higher mortality as compared to patients that did not receive said medication. Such groups of patients can be identified with the methods of the present invention. This enables to avoid unnecessary or even harmful medications. Thus, one important object of the present methods of stratification is to avoid medication which is harmful to the patient.

In the context of the present invention vasoactive hormones are molecules, e.g. peptides, causing constriction or dilation of blood vessels.

Vasoactive hormones, in particular vasoactive peptides, are unstable in bodily fluids like blood, urine or cerebrospinal fluid. Therefore, direct measurement of vasoactive peptides in bodily fluids is challenging. However, the precursors or precursor fragments of vasoactive peptides are more stable than the mature hormones, and their measurement can be used as a substitute or surrogate measurement for the mature vasoactive peptides. This has already been shown for a number of vasoactive peptides e.g. insulin and its stable precursor fragment C-peptide (Melani et al. Identification of proinsulin and C-peptide in human serum by a specific immunoassay. PNAS 197Q:67:148-55), Arginine-Vasopressin and its stable precursor fragment copeptin (Struck et al. Copeptin, a stable peptide derived from the vasopressin precursor, is elevated in serum of sepsis patients. Peptides 2005;25:2500-4; Morgenthaler et al. Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. Clinical Chemistry 2006;52:112-9). adrenomedullin and its stable precursor fragment MR-proADM (Struck et al. Identification of an adrenomedullin precursor fragment in plasma of sepsis patients. Peptides 2004;25:1369-72; Morgenthaler et al. Measurement of midregional proadrenomedullin in plasma with an immunoassay. Clinical Chemistry? 2005;51:1823-9), atrial natriuretic peptide and its stable precursor fragment MR-proANP (Morgenthaler et al. Immunoluminometric assay for the indregion of pro-atrial natriuretic peptide in human plasma. Clinical Chemistry 2004;50:234-6), endothelin-1 and its stable precursor fragment CT-proET-1 (Struck et al. Proteolytic processing pattern of the

Endothelial dysfunction is a physiological dysfunction of normal biochemical processes carried out by the endothelium, the cells lining the inner surface of blood vessels. Endothelial dysfunction is characterized by an impaired vasodilation (imbalance between relaxing and contracting factors) as well as changes in the proinflammatory state and prothrombic properties (Endemann and Schiffrin, Endothelial Dysfunction. Journal American Society of Nephrology 2004;15:1983-92). It is associated with cardiovascular diseases, such as hypertension, coronary artery disease, heart failure, peripheral artery disease, diabetes, and chronic renal failure. Moreover, endothelial dysfunction is thought to be a key event in the development of atherosclerosis and predates clinically obvious vascular pathology by many years. Endothelial dysfunction has also been shown to be of prognostic significance in predicting vascular events including stroke and myocardial infarctions. In addition, endothelial dysfunction was shown to be implicated in inflammation and infection (Ste\(\text{\text_en}winket. Endothelial dysfunction and inflammation is there a link? Nephrology Dialysis and Transplantation 2001;16:1968-71), sepsis (Vallet. Bench-to-bedside review: Endothelial cell dysfunction in severe sepsis: a role in organ dysfunction? Critical Care 2003:7:130-8; Peters et al. Molecular basis of endothelial dysfunction in sepsis. Cardiovascular Research 2003;6:40:49-57) as well as COPD (Moro. Endothelial dysfunction in chronic obstructive pulmonary disease. Angiology 2008;59:357-64).

Thus, the present invention pertains to a method for the stratification of a subject having an acute or a chronic disease, wherein said disease effects endothelial function/dysfunction, comprising the steps of:

- taking a sample of bodily fluid from said subject;
determining in said sample of bodily fluid the concentration of a vasoactive hormone or fragments thereof or precursors or fragments thereof having a length of at least 12 amino acids:

- stratifying said subjects into one of the following categories:
  1. responder to a medication for treatment of said disease.
  2. non-responder to a medication for treatment of said disease not showing an unfavourable effect after having received said medication;
  3. subjects showing an unfavourable effect after having received said medication.

In one embodiment the methods of the present invention comprise the provision of a system comprising the three categories (i), (ii) and (iii). In an even more preferred embodiment the methods of the present invention comprise the provision of at least two thresholds that are used in order to establish said system comprising and/or consisting of the three categories (i), (ii) and (iii).

In the context of the present invention the term "responder" refers to a subject showing a favourable effect after having received a medication for treatment of a disease.

The term "non-responder" in the context of the present invention refers to a subject showing no effect (neither a favourable nor an unfavourable effect) after having received a medication for treatment of a disease.

In some embodiments according to the invention, categories (i) and (ii) are pooled and distinguished from category (iii). i.e. the subjects are stratified into subjects showing an unfavourable effect and subjects not showing an unfavourable effect.

In this embodiment the methods of the present invention comprise the provision of a system comprising and/or consisting of two categories. In an even more preferred embodiment this includes the provision of at least one threshold that is used to establish said two-categories-system. The ultimate object the two-categories-system is the prevention of harm by medications.
The invention also relates to a method for the stratification of a subject having an acute or a chronic disease, wherein said disease effects endothelial function/dysfunction, comprising the steps of:

- taking a sample of bodily fluid from said subject;
- determining in said sample of bodily fluid the concentration of a vasoactive hormone or fragments thereof or precursors or fragments thereof having a length of at least 12 amino acid residues;
- stratifying said subjects into one of the following categories:
  (i) responder or non-responder to a medication for treatment of said disease not showing an unfavourable effect after having received said medication;
  (ii) subjects showing an unfavourable effect after having received said medication.

In a particular aspect the present invention also relates to a method for the stratification of a subject having an acute or a chronic disease, wherein said disease effects endothelial function/dysfunction, comprising the steps of:

- taking a sample of bodily fluid from said subject;
- determining in said sample of bodily fluid the concentration of a vasoactive hormone or fragments thereof or precursors or fragments thereof having a length of at least 12 amino acid residues;
- attributing the concentration of the vasoactive hormone or fragments thereof or precursors or fragments thereof in the sample to a risk of the subject of experiencing an unfavourable effect after receiving a particular medication.

"Subjects showing an unfavourable effect after having received said medication" in the context of the present invention are subjects which are expected to experience an unfavourable effect upon administration of said medication.

Preferably herein, the vasoactive hormone is:

(i) a peptide hormone selected from the group consisting of AdrenomedulHπ (ADM), Atrial Natriuretic Peptide (ANP), Brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), Endothelin-1, Endothelin-2, Endothelin-3, Arginin-Vasopressin (AVP), Dendrōaspis natriuretic peptide (DNP), Urodilarin, Angiotensin II, Urocortin, Urocortin-2 (Stresscopin-related peptide), Urocortin-3
(Stresscopin), Urotensin-II, Urotensin II-related protein (URP), Neuropeptide Y (NPY), Vasoactive intestinal peptide (VIP), Calcitonin gene-related peptide I (CGRP I) and Calcitonin gene-related peptide II (CGRP II), Insulin, Proenkephalin (PENK), Endokinin A, Dynorphin, Ghrelin, Relaxin or fragments thereof or precursors or fragments thereof having a length of at least 12 amino acid residues or

(ii) a small peptide hormone selected from the group consisting of Bradykinin, Apelin, Neurotensin, Substance P, Neurokinin A (Substance K), Endokinin A/B, Endokinin C, Methionin-Enkephalin, Leucin-Enkephalin, or fragments thereof or precursors or fragments thereof having a length of at least 12 amino acid residues or

(iii) a hormone selected from the group consisting of Serotonin, Prostaglandins and Thromboxane.

More preferably herein, the vasoactive hormone is:

(i) a peptide hormone selected from the group consisting of Adrenomedullin (ADM), Atria! Natriuretic Peptide (ANP), Brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), Endothelin-1, Endothelin-2, Endothelin-3, Arginin-Vasopressin (AVP), Dendroaspis natriuretic peptide (DNP), L'rodilarin, Angiotensin II, Urocortin, Urocortin-2 (Stresscopin-related peptide), Urocortin-3 (Stresscopin), Urotensin-II, Urotensin II-related protein (URP), Neuropeptide Y (NPY), Vasoactive intestinal peptide (VIP), Calcitonin gene-related peptide I (CGRP I) and Calcitonin gene-related peptide II (CGRP II), Endokinin A, Relaxin or fragments thereof or precursors or fragments thereof having a length of at least 12 amino acid residues or

(ii) a small peptide hormone selected from the group consisting of Bradykinin, Apelin, Neurotensin, Substance P, Neurokinin A (Substance K), Endokinin A/B, Endokinin C, Methionin-Enkephalin, Leucin-Enkephalin, or fragments thereof or precursors or fragments thereof having a length of at least 12 amino acid residues or

(iii) a hormone selected from the group consisting of Serotonin, Prostaglandins and Thromboxane.
“Small” peptide hormones in the context of the present invention are peptide hormones comprising 13 or less amino acid residues, in particular Bradykinin, Apelin, Neurotensin, Substance P, Neurokinin A (Substance K), Methionin-Enkephalin and Leucin-Enkephalin.

Proenkephalin (PENK) is the precursor polypeptide of Methionin-Enkephalin and Leucin-Enkephalin.

In one particularly preferred embodiment the precursor fragment of the vasoactive hormone ADM is Midregional pro-Adrenomedullin (MR-proADM) or a fragment thereof having a length of at least 12 amino acid residues.

In another particularly preferred embodiment the precursor fragment of the vasoactive hormone ANP is Midregional pro-Atrial Natriuretic Peptide (MR-proANP) or a fragment thereof having a length of at least 12 amino acid residues.

In yet another particularly preferred embodiment the precursor fragment of the vasoactive hormone ET-1 is C-terminal pro-Endothelin-1 (CT-proET-1) or a fragment thereof having a length of at least 12 amino acid residues.

In yet another particularly preferred embodiment the precursor fragment of the vasoactive hormone AVP is C-terminal pro-AVP (Copeptin) or a fragment thereof having a length of at least 12 amino acid residues.

The disease may, e.g., be selected from the group consisting of: chronic heart failure, shortness of breath (SOB), acute coronary syndrome, acute heart failure (AHF), arrhythmia, asthma exacerbation, bronchitis, chest pain, influenza, chronic obstructive pulmonary disease (COPD), pneumonia and pulmonary embolism, pulmonary arterial hypertension (PAH), post stroke condition, post myocardial infarct condition, diabetes type IL cancer, atherosclerosis, infections, inflammatory diseases, and post surgery condition.

The disease may, e.g., be selected from the group consisting of: chronic heart failure, shortness of breath (SOB), acute coronary syndrome, acute heart failure (AHF), arrhythmia, asthma exacerbation, bronchitis, chest pain, influenza, chronic obstructive pulmonary disease (COPD), pneumonia and pulmonary embolism, post stroke condition, post myocardial infarct
condition, diabetes type II, cancer, atherosclerosis, infections, inflammatory diseases, and post surgery condition.

In one particularly preferred embodiment, the disease is selected from the group consisting of shortness of breath (SOB), acute coronary syndrome, acute heart failure (AHF), arrhythmia, asthma exacerbation, bronchitis, chest pain, influenza, chronic obstructive pulmonary disease (COPD), pneumonia and pulmonary embolism and pulmonary arterial hypertension (PAH).

In one particularly preferred embodiment, the disease is selected from the group consisting of shortness of breath (SOB), acute coronary syndrome, acute heart failure (AHF), arrhythmia, asthma exacerbation, bronchitis, chest pain, influenza, chronic obstructive pulmonary disease (COPD), pneumonia and pulmonary embolism.

In another particularly preferred embodiment, the disease is a post stroke condition, i.e. is related to subjects having suffered from ischemic or haemorrhagic stroke or transient ischemic attack (TIA).

Heart failure (HF), also termed congestive heart failure (CHF) is a cardiac condition that occurs when a problem with the structure or function of the heart impairs its ability to supply sufficient blood flow to meet the body’s needs. Chronic heart failure is a long term situation, usually with stable treated symptomatology. Acute heart failure is a term used to describe exacerbated or decompensated heart failure, referring to episodes in which a patient can be characterized as having a change in heart failure signs and symptoms resulting in a need for urgent therapy or hospitalization.

Shortness of breath (SoB; also known as dyspnea or difficulty breathing) relates to a sensation of difficult or uncomfortable breathing or a feeling of not getting enough air in a subject. SoB may have many different causes, among them heart diseases such as heart attack, congestive heart failure, and pulmonary diseases (incl. pneumonia).

Acute coronary syndrome is an umbrella term used to cover any group of clinical symptoms compatible with acute myocardial ischemia. Acute myocardial ischemia is chest pain due to insufficient blood supply to the heart muscle that results from coronary artery disease (also called coronary heart disease). An acute coronary syndrome (ACS) is a set of signs and
symptoms, usually a combination of chest pain and other features, interpreted as being the result of abruptly decreased blood flow to the heart (cardiac ischemia); the most common cause for this is the disruption of atherosclerotic plaque in an epicardial coronary artery. The subtypes of acute coronary syndrome include unstable angina (UA, not associated with heart muscle damage), and two forms of myocardial infarction (heart attack), in which heart muscle is damaged. These types are named according to the appearance of the electrocardiogram (ECG/EKG) as non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI).

Arrhythmia is a term for any of a large and heterogeneous group of conditions in which there is abnormal electrical activity in the heart. The heart beat may be too fast or too slow, and may be regular or irregular. Some arrhythmias are life-threatening medical emergencies that can result in cardiac arrest and sudden death. Others cause symptoms such as an abnormal awareness of heart beat (palpitations), and may be merely annoying. These palpitations have also been known to be caused by atrial/ventricular fibrillation, wire faults, and other technical or mechanical issues in cardiac pacemakers/defibrillators. Still others may not be associated with any symptoms at all, but may predispose the patient to potentially life threatening stroke or embolism.

Asthma is a common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, airflow obstruction, and bronchospasm. Symptoms include wheezing, cough, chest tightness, and shortness of breath. Some individuals will have stable asthma for weeks or months and then suddenly develop an episode of acute asthma. Different asthmatic individuals react differently to various factors. However, most individuals can develop severe exacerbation of asthma from several triggering agents.

Bronchitis is inflammation of the mucous membranes of the bronchi, the airways that carry airflow from the trachea into the lungs. Bronchitis can be classified into two categories, acute and chronic, each of which has unique etiologies, pathologies, and therapies. Acute bronchitis is characterized by the development of a cough, with or without the production of sputum, mucus that is expectorated (coughed up) from the respiratory tract. Acute bronchitis often occurs during the course of an acute viral illness such as the common cold or influenza. Viruses cause about 90% of cases of acute bronchitis while bacteria account for less than 10%. Chronic bronchitis, a type of chronic obstructive pulmonary disease, is characterized by the presence of a productive cough that lasts for 3 months or more per year for at least 2
years. Chronic bronchitis most often develops due to recurrent injury to the airways caused by inhaled irritants. Cigarette smoking is the most common cause, followed by air pollution and occupational exposure to irritants, and cold air.

Chronic obstructive pulmonary disease (COPD) refers to chronic bronchitis and emphysema, a pair of two commonly co-existing diseases of the lungs in which the airways become nan-owed. This leads to a limitation of the flow of air to and from the lungs causing shortness of breath. In contrast to asthma, the limitation of airflow is poorly reversible and usually gets progressively worse over time. COPD is caused by noxious particles or gas, most commonly from tobacco smoking, which triggers an abnormal inflammatory response in the lung. The Inflammatory response in the larger airways is known as chronic bronchitis, which is diagnosed clinically when people regularly cough up sputum. In the alveoli, the inflammatory response causes destruction of the tissues of the lung, a process known as emphysema. The natural course of COPD is characterized by occasional sudden worsenings of symptoms called acute exacerbations, most of which are caused by infections or air pollution.

Pneumonia is an abnormal inflammatory condition of the lung. It is often characterized as including inflammation of the parenchyma of the lung (that is, the alveoli) and abnormal alveolar filling with fluid (consolidation and exudation). The alveoli are microscopic air-filled sacs in the lungs responsible for gas exchange. Pneumonia can result from a variety of causes, including infection with bacteria, viruses, fungi, or parasites, and chemical or physical injury to the lungs. Its cause may also be officially described as idiopathic—that is, unknown—when infectious causes have been excluded. Typical symptoms associated with pneumonia include cough, chest pain, fever, and difficulty in breathing. Diagnostic tools include x-rays and examination of the sputum. Treatment depends on the cause of pneumonia: bacterial pneumonia is treated with antibiotics. Pneumonia is a common illness which occurs in all age groups, and is a leading cause of death among the elderly and people who are chronically and terminally ill. Additionally, it is the leading cause of death in children under five years old worldwide.

Pulmonary embolism (PE) is a blockage of the main artery of the lung or one of its branches by a substance that has travelled from elsewhere in the body through the bloodstream (embolism). Usually this is due to embolism of a thrombus (blood clot) from the deep veins in the legs, a process termed venous thromboembolism. A small proportion is due to the embolization of air, fat or amniotic fluid. The obstruction of the blood flow through the lungs
and the resultant pressure on the right ventricle of the heart leads to the symptoms and signs of PE. The risk of PE is increased in various situations, such as cancer and prolonged bed rest. Symptoms of pulmonary embolism include difficulty breathing, chest pain on inspiration, and palpitations. Clinical signs include low blood oxygen saturation and cyanosis, rapid breathing, and a rapid heart rate. Severe cases of PE can lead to collapse, abnormally low blood pressure, and sudden death.

Pulmonary arterial hypertension (PAH) is a syndrome characterised by a progressive increase in pulmonary vascular resistance leading to right ventricular overload and eventually to right ventricular failure and premature death. Pulmonary Arterial Hypertension (PAH) is defined as a sustained elevation of mean pulmonary arterial pressure to more than 25 mmHg at rest or to more than 30 mmHg while exercising, with a normal pulmonary wedge pressure (< 15 mmHg). In most cases the earliest symptom is dyspnea on physical exertion. Other symptoms include syncope or near syncope, fatigue and peripheral oedema. Chest tightness and pain similar to angina may occur, particularly on physical exertion.

Stroke is defined as an acute focal neurological deficit resulting from a cerebrovascular disease. The two main types of stroke are ischemic and hemorrhagic, accounting for approximately 85% and 15%, respectively (Mickey 2003, The clinical practice of neurological and neurosurgical nursing (5th ed.). Philadelphia: Lippincott, Williams & Wilkins). When an ischemic stroke occurs, the blood supply to the brain is interrupted, and brain cells are deprived of glucose and oxygen. Approximately 45% of ischemic strokes are caused by small or large artery thrombus, 20% are embolic origin, and others have an unknown cause (Hickey 2003. The clinical practice of neurological and neurosurgical nursing (5th ed.). Philadelphia: Lippincott, Williams & Wilkins).

Transient ischemic attack (TIA) (also known as "mini-stroke") is a syndrome characterized by the sudden onset of discrete neurological symptoms that resolve completely within 24 hours. TIA may be reported by 0.5 – 8% of the elderly population (B"us et al., 1997, Stroke 28(4): 768-73). A patient representing with a TIA is at high risk of subsequent adverse events. The 90-day risk of stroke has been repotted to be greater than 10%. with the highest risk occurring within the first 2 days (Jons ton et al., 2003, Neurology- 60: 1429-34).

Myocardial infarction (MI) or acute myocardial infarction (AMI), commonly known as a heart attack, is the interruption of blood supply to part of the heart, causing some heart cells to die. This is most commonly due to occlusion (blockage) of a coronary artery following the
rupture of a vulnerable atherosclerotic plaque, which is an unstable collection of lipids (fatty acids) and white blood cells (especially macrophages) in the wall of an artery. The resulting ischemia (restriction in blood supply) and oxygen shortage, if left untreated for a sufficient period of time, can cause damage or death (infarction) of heart muscle tissue (myocardium).

On the basis of the ECG, a distinction is made between ST elevation MI (STEMI) or non-ST elevation MI (non-STEMI).

Diabetes mellitus type 2 or type 2 diabetes (formerly called non-insulin-dependent diabetes mellitus (NIDDM), or adult-onset diabetes) is a disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency.

Atherosclerosis (also known as arteriosclerotic vascular disease or ASVD) is the condition in which an artery wall thickens as the result of a build-up of fatty materials such as cholesterol. It is a syndrome affecting arterial blood vessels, a chronic inflammatory response in the walls of arteries, in large part due to the accumulation of macrophage white blood cells and promoted by low-density lipoproteins (plasma proteins that carry cholesterol and triglycerides) without adequate removal of fats and cholesterol from the macrophages by functional high density lipoproteins (HDL). It is commonly referred to as a hardening or furring of the arteries, it is caused by the formation of multiple plaques within the arteries.

In another particularly preferred embodiment, the disease is a post myocardial infarct condition, i.e. subjects having suffered a myocardial infarction.

Accordingly, the medication may, for example, be selected from the group consisting of anti-coagulant, thrombolytic drugs, platelet aggregation inhibitor, β-blocker, anti-oxidant, lipid lowering substance, diuretic. ACE (Angiotensin-Converting Enzyme) inhibitor, calcium channel blocker, endothelin-receptor antagonists, phosphodiesterase type 5 inhibitors, prostacyclin derivatives, soluble guanylate cyclase activators, hormone therapeutic agent, NO substituent, adenosine receptor blocker, cardiac glycoside, angiotensin-II antagonist, anti-diabetic drug, antiarrhythmic and antibiotic. Particularly preferred medications are ACE inhibitors, diuretics and β-blockers.

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channel blocker, hormone therapeutic agent, NO substituent, adenosine receptor blocker, cardiac glycoside, angiotensin-II antagonist, anti-diabetic drug, antiarrhythmic and antibiotic. Particularly preferred medications are ACE inhibitors, diuretics and β-blockers.

The medication may also be a combination of two or more drugs such as β-blocker/calcium channel blocker (*e.g.* Belnif®, *i.e.* active ingredients: metoprolol + nifedipin), angiotensin-II antagonist/diuretic (*e.g.* Blopress® - active ingredients: candesartan + hydrochlorothiazid).

The calcium channel blocker may for example be selected from the group consisting of dihydropyridine (*e.g.* Nicardipine), phenylalkylamine (*e.g.* Verapamil). Benzodiazepine (*e.g.* Diltiazem), Mibefradil and Fendiline.

The lipid lowering substance may for example be selected from the group consisting of statin (*e.g.* Lovastatin, Simvastatin, Pravastatin, Fluvastatin, Cerivastatin, Atorvastatin, Mevastatin, Pravastatin, Rosuvastatin), Fibrate (*e.g.* Bezafibrate, Fenofibrate. Elofibrate. Gemfibrozil), bile acid sequestrant (*e.g.* Cholestyramine. Colestipol) and nicotinic acid derivative (*e.g.* Acipimox, Xantinol nicotinate. Inositol nicotinate).

The anti-oxidant may for example be selected from the group consisting of vitamin A, vitamin C, Oxypurionol. Superoxide dismutase. and Probucol.

The ACE inhibitor may for example be selected from the group coconsisting of Captopril, Enalapril. Quanalapril. Peridoprii, Temocapril. Ramipril. Lisinopril.

The hormone therapeutic agent may for example be selected from the group consisting of β-Estradiol and Progesteron.

The NO substituent may for example be selected from the group consisting of organic nitrates (*e.g.* nitroglycerine), sydnonimine and L-arginine.

The anti-coagulant may for example be selected from the group consisting of a vitamin K antagonist (*e.g.* Phenprocoumon, Warfarin), a direct thrombin inhibitor (*e.g.* Lepirudin, Desirudin, Argatroban), Heparin.
The thrombolytic drug may for example be selected from the group consisting of tissue plasminogen activator (tPA), rt-PA, tenecteplase, anistreplase, streptokinase, and urokinase.

The platelet aggregation inhibitor may for example be selected from the group consisting of Ticlopidin, Clopidogrel, Acetylsalicylic Acid.

The cardiac glycoside may for example be selected from the group consisting of Digoxin, Digitoxin, Deslanoside, Ouabain and Proscillaridin.

The diuretic may for example be selected from the group consisting of a loop diuretic (e.g. Furosemide), a benzothiadiazide diuretic (e.g. Metolazone), a potassium sparing diuretic (e.g. Spironolactone) and an osmotic diuretic (e.g. Mannitol).

The angiotensin-II antagonist may for example be selected from the group consisting of Candesartan, Eprosartan, Irbesartan, Telmisartan, Losartan, Valsartan and Olmesartan.

The β-blocker may for example be selected from the group consisting of a non-selective β-blocker (e.g. Nadolol, Penbutolol), a β1-selective agent (e.g. Bisoprolol, Metoprolol), and a α1/β-adrenergic antagonist (e.g. Carvedilol, Celiprolol).

The endothelin-receptor antagonists may for example be selected from the group consisting of a selective endothelin receptor type A antagonist (e.g. sitaxentan, ambrisentan, atrasentan, BQ-123), a selective endothelin receptor B antagonist (e.g. sarafotoxin B), and a endothelin receptor A/B antagonist (e.g. bosentan, tezosentan).

The phosphodiesterase type 5 inhibitors may for example be selected from the group consisting of sildenafil, sildenafil citrate, avanafil, lodenafil, mirodenafil, tadalafil, vardenafil, udenafil.

The prostacyclin derivatives may for example be selected from the group consisting of epoprostenol, treprostinil, iloprost, beraprost.

The soluble guanylate cyclase activators may for example be selected from the group consisting of cinaciguat, riociguat.
The antiarrhythmic may for example be selected from the group consisting of Chinidin, class I antiarrhythmics (e.g. Disopyramide, Lidocaine, Propafenone), class II antiarrhythmics (e.g. Metoprolol), class III antiarrhythmics (e.g. Amiodarone, Sotalol), class IV antiarrhythmics (e.g. Verapamil, Diltiazem).

The antibiotic may for example be selected from the group consisting of a Penicillin (e.g. Flucloxacillin, Amoxicillin, Ampicillin, Mezlocillin), a Cephalosporins (e.g. Cefazolin, Cefuroxim, Cefotaxim, Cefaclor, Cefalexin), a β-Lactamase Inhibitor (e.g. Sulbactam, Tazobactam), a Tetracycline (e.g. Doxycyclin, Minocyclin, Tetracyclin, Oxytetracyclin), an Aminoglycoside (e.g. Gentamicin, Neomycin, Streptomycin), a Makrolid-Antibiotic (e.g. Azithromycin, Clarithromycin, Erythromycin, Roxithromycin, Spiramycin, Clindamycin), a Lincosamide (e.g. Lincomycin), a Gyrase inhibitor (e.g. Ciprofloxacin, Ofloxac, Norfloxacin), Sulfonamides, Tr methoprin, a Glycopeptide Antibiotic (e.g. Vancomycin), a polypeptide antibiotic (e.g. Colistin, Polymyxin), an Amphenicolc (e.g. Chloramphenicol).

The anti-diabetic drug may for example be selected from the group consisting of insulins, alpha-glucosidase inhibitors, Biguanid derivatives (e.g. Metformin). Sulfonylurea derivatives (e.g. Glibenclamid, Tolbutamid) Pioglitazone, Repaglinid, Nateglinid. and Rosiglitazone maleat.

In one particularly preferred embodiment of the method according to the present invention the disease is ischemic stroke, the hormone precursor fragment to be determined is MR-proADM or a fragment thereof having a length of at least 12 amino acids and wherein the medication is statine. In this case the patients are preferably stratified into said categories using the following thresholds:

(i) responder to a medication for treatment of said disease: > 0.9 pmol/L MR-proADM
(ii) non-responder to a medication for treatment of said disease not showing an unfavourable effect after having received said medication: 0.5 - 0.9 pmol/L MR-proADM.
(iii) subjects showing an unfavourable effect after having received said medication: < 0.5 pmol/L MR-proADM.
In another particularly preferred embodiment of the method according to the present invention the disease is ischemic stroke, the hormone precursor fragment to be determined is MR-proADM or a fragment thereof having a length of at least 12 amino acids and wherein the medication is clopidogrel.

In yet another particularly preferred embodiment of the method according to the present invention the disease is ischemic stroke, the hormone precursor fragment to be determined is CT-proAVP or a fragment thereof having a length of at least 12 amino acids and wherein the medication is acetylsalicylic acid.

In yet another particularly preferred embodiment of the method according to the present invention the disease is ischemic stroke, the hormone precursor fragment to be determined is CT-proAVP or a fragment thereof having a length of at least 12 amino acids and wherein the medication is diuretics. In this case the patients are preferably stratified into said categories using the following thresholds:

(i) responder to a medication for treatment of said disease or non-responder to a medication for treatment of said disease not showing an unfavourable effect after having received said medication: < 4 pmol/L CT-proAVP.

(ii) subjects showing an unfavourable effect after having received said medication: > 4 pmol/L CT-proAVP.

In yet another particularly preferred embodiment of the method according to the present invention the disease is myocardial infarction, the hormone precursor fragment to be determined is MR-proADM or a fragment thereof having a length of at least 12 amino acids and wherein the medication is a diuretic. In this case the patients are preferably stratified into said categories using the following thresholds:

(i) responder to a medication for treatment of said disease or non-responder to a medication for treatment of said disease not showing an unfavourable effect after having received said medication: > 0.5 pmol/L MR-proADM.

(ii) subjects showing an unfavourable effect after having received said medication: < 0.5 pmol/L MR-proADM.

In yet another particularly preferred embodiment of the method according to the present invention the disease is post-myocardial infarction condition, the hormone precursor fragment
to be determined is CT-proAVP or a fragment thereof having a length of at least 12 amino acids and wherein the medication is an ACE inhibitor/adenosine receptor blocker (ARB). In this case the patients are preferably stratified into said categories using the following thresholds:

(i) responder to a medication for treatment of said disease: > 19 pmol/L CT-proAVP

(ii) non-responder to a medication for treatment of said disease not showing an unfavourable effect after having received said medication: 3.6 – 19 pmol/L CT-proAVP.

(iii) subjects showing an unfavourable effect after having received said medication: < 3.6 pmol/L CT-proAVP.

The threshold values cited herein above are to be understood as values for very particular, illustrative embodiments.

The unfavourable effect herein may e.g. be death or major adverse cardiac event (MACE). The outcome in terms of an unfavourable effect may be at a given time after entry of the patients into treatment, e.g. after admission in the emergency department. The outcome may be after several days, several weeks, several months or several years, e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 weeks or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 months after admission.

The bodily fluid is preferably selected from the group of blood, serum, plasma, cerebrospinal fluid, urine, saliva, sputum, and pleural effusions. More preferably the sample is selected from whole blood, plasma or serum, most preferably the sample is plasma.

The present invention also pertains to the use of an assay for the determination of the concentration of a vasoactive hormone or fragments thereof or precursors or fragments thereof having a length of at least 12 amino acid residues in a sample derived from a bodily fluid of a subject for the stratification of a subject having an acute or a chronic disease, into either of the categories:

(i) responder to a medication for treatment of said disease.

(ii) non-responder to a medication for treatment of said disease not showing an unfavourable effect after having received said medication;

(iii) subjects showing an unfavourable effect after having received said medication.
(iv) wherein said disease effects endothelial function/dysfunction.

In the context of the present invention also combinations of two or more vasoactive hormone levels or fragments thereof or precursors or fragments thereof having a length of at least 12 amino acid residues can be employed. Furthermore, some subjects according to the present invention may also receive a combination of two or more medications. Also these subjects may be stratified in the context of the present invention.

The invention also relates to the use of an antibody or a functional fragment thereof specific for a vasoactive hormone or fragments thereof or precursors or fragments thereof having a length of at least 12 amino acid residues selected from the group of Adrenomedullin (ADM), Atrial Natriuretic Peptide (ANP), Brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), Endothelin-1, Endothelin-2, Endothelin-3, Arginin-Vasopressin (AVP), Dendroaspis natriuretic peptide (DNP), Urodilatin, Angiotensin II, Urocortin, Urocortin-2 (Stresscopin-related peptide), Urocortin-3 (Stresscopin), Urotensin-II, Urotensin II-related protein (URP), Neuropeptide Y (NPY). Vasoactive intestinal peptide (VIP). Calcitonin gene-related peptide I (CGRP I), Calcitonin gene-related peptide II (CGRP II), Bradykinin, Relaxin, Apelin, Neurotensin, Substance P, and Neurokinin A (Substance K), Endolym A, Endokinin A/B, Endokinin C, Methionin-Enkephalin, Leucin-Enkephalin in a method for the stratification of a subject having an acute or a chronic disease, into either of the categories:

(i) responder to a medication for treatment of said disease,
(ii) non-responder to a medication for treatment of said disease not showing an unfavourable effect after having received said medication;
(iii) subjects showing an unfavourable effect after having received said medication,

wherein said disease effects endothelial function/dysfunction.

Suitable threshold levels for the stratification of subjects into different groups (categories) have to be determined for each particular combination of vasoactive hormone or fragments thereof or precursors or fragments thereof, medication and disease. This can e.g. be done by grouping a reference population of patients according to their level of vasoactive hormone into certain quantiles, e.g. tertiles, quartiles. quintiles or even according to suitable percentiles. For each of the quantiles or groups above and below certain percentiles, hazard ratios can be calculated comparing the risk for an adverse outcome, i.e. an "unfavourable
effect”, e.g. in terms of survival rate, between those patients who have received a certain medication and those who did not. In such a scenario, a hazard ratio (HR) above 1 indicates a higher risk for an adverse outcome for the patients who have received a treatment than for patients who did not. A HR below 1 indicates beneficial effects of a certain treatment in the group of patients. A HR around 1 (e.g. +1/-0.1) indicates no elevated risk but also no benefit from medication for the particular group of patients. By comparison of the HR between certain quantiles of patients with each other and with the HR of the overall population of patients, it is possible to identify those quantiles of patients who have an elevated risk and those who benefit from medication and thereby stratify subjects according to the present invention.

In a preferred embodiment of the method according to the present invention, at least two threshold levels of a vasoactive hormone or fragments thereof or precursors or fragments thereof having a length of at least 12 amino acids, have be determined to stratify said subjects into one of the following categories:

(i) responder to a medication for treatment of said disease;
(ii) non-responder to a medication for treatment of said disease not showing an unfavourable effect after having received said medication;
(iii) subjects showing an unfavourable effect after having received said medication.

In some cases unfavourable effects will affect patients with high levels (e.g. in the fifth quintile) of vasoactive hormones or fragments thereof or precursors or fragments thereof, while in other cases only patients with low levels of vasoactive hormones or fragments thereof or precursors or fragments thereof will be affected (e.g. in the first quintile). This depends on the particular medication, hormone and disease. However, with the above explanations, a skilled person is able to identify those groups of patients for which the medication has an unfavourable effect, those groups that do neither benefit nor suffer from the medication and those groups that benefit from the medication. Exemplarily, some combinations of hormone precursor fragments and medications are listed for several diseases in the appended examples.

In the appended examples, such an analysis of patients groups is demonstrated for patients from various clinical studies that have been treated with a variety of different drugs and for which the levels of various, vasoactive hormone precursor fragments has been measured.
However, the present invention is not limited to those combinations of medications, diseases and vasoactive hormones or fragments thereof or precursors or fragments thereof demonstrated in the examples, but provides for a more general method.

Determining (or measuring or detecting) the level of a vasoactive peptide hormone or fragment thereof or precursor or fragment thereof (also termed "marker peptide") herein may be performed using a detection method and/or a diagnostic assay as explained below.

As mentioned herein, an "assay" or "diagnostic assay" can be of any type applied in the field of diagnostics. Such an assay may be based on the binding of an analyte to be detected to one or more capture probes with a certain affinity. Concerning the interaction between capture molecules and target molecules or molecules of interest, the affinity constant is preferably greater than $10^8$ M$^{-1}$.

In the context of the present invention, "capture molecules" are molecules which may be used to bind target molecules or molecules of interest, i.e. analytes (i.e. in the context of the present invention the cardiovascular and/or vasoactive peptide(s)) from a sample. Capture molecules must thus be shaped adequately, both spatially and in terms of surface features, such as surface charge, hydrophobicity, hydrophilicity, presence or absence of lewis donors and/or acceptors, to specifically bind the target molecules or molecules of interest. Hereby, the binding may for instance be mediated by ionic, van-der-Waals, pi-pi, sigma-pi, hydrophobic or hydrogen bond interactions or a combination of two or more of the aforementioned interactions between the capture molecules and the target molecules or molecules of interest. In the context of the present invention, capture molecules may for instance be selected from the group comprising a nucleic acid molecule, a carbohydrate molecule, a RNA molecule, a protein, an antibody, a peptide or a glycoprotein. Preferably, the capture molecules are antibodies, including fragments thereof with sufficient affinity to a target or molecule of interest, and including recombinant antibodies or recombinant antibody fragments, as well as chemically and/or biochemically modified derivatives of said antibodies or fragments derived from the variant chain with a length of at least 12 amino acids thereof.

The preferred detection methods comprise immunoassays in various formats such as for instance radioimmunoassay (RIA), chemiluminescence- and fluorescence- immunoassays,
Enzyme-linked immunoassays (ELISA), Luminex-based bead arrays, protein microarray assays, and rapid test formats such as for instance immuno chromatographic strip tests.

The assays can be homogenous or heterogeneous assays, competitive and non-competitive assays. In a particularly preferred embodiment, the assay is in the form of a sandwich assay, which is a non-competitive immunoassay, wherein the molecule to be detected and/or quantified is bound to a first antibody and to a second antibody. The first antibody may be bound to a solid phase, e.g. a bead, a surface of a well or other container, a chip or a strip, and the second antibody is an antibody which is labeled, e.g. with a dye, with a radioisotope, or a reactive or catalytically active moiety. The amount of labeled antibody bound to the analyte is then measured by an appropriate method. The general composition and procedures involved with "sandwich assays" are well-established and known to the skilled person. (The Immunoassay Handbook, Ed. David Wild, Elsevier LTD, Oxford; 3rd Ed. (May 2005), ISBN-13: 978-0080445267: Hultschig C et al, Cuir Opin Chem Biol. 2006 Feb;10(1):4-10. PMID: 16376134), incoorporated herein by reference).

In a particularly preferred embodiment the assay comprises two capture molecules, preferably antibodies which are both present as dispersions in a liquid reaction mixture, wherein a first labeling component is attached to the first capture molecule, wherein said first labeling component is part of a labeling system based on fluorescence- or chemiluminescence-quenching or amplification, and a second labeling component of said marking system is attached to the second capture molecule, so that upon binding of both capture molecules to the analyte a measurable signal is generated that allows for the detection of the formed sandwich complexes in the solution comprising the sample.

Even more preferred, said labeling system comprises rare earth cryptates or rare earth chelates in combination with a fluorescence dye or chemiluminescence dye, in particular a dye of the cyanine type.

In the context of the present invention, fluorescence based assays comprise the use of dyes, which may for instance be selected from the group comprising FAIVI (5-or 6-carboxyfluorescein), VIC₅ NED, Fluorescein, Fluoresceinisothiocyanate (FITC), IRD-700/800, Cyanine dyes, aucli as CY3. CY5. CY3.5, Cy7, Xanthen, 6-Carboxy-2,4,7,4,7-hexachlorofluorcscein (HEX), TET, 6-Carboxy-4\5  "-dichloro-2|7  "-
diraethodyfluorescein (JOE). N.N.N "-Tetramethyl- ò-carboxyrhodamine (TAMRA), 6-
Carboxy-X-rhodamine (ROX), 5-Carboxyrhodamine-6G (R6G5), 6-carboxyrhodamine-6G (RG6), Rhodamine, Rhodamine Green, Rhodaminc Red, Rhodamine 110, BODIPY dyes, such as BODIPY TMR, Oregon Green, Coumarines such as Unibelliferone, Benzimides, such as Hoechst 33258; Phenanthridines, such as Texas Red, Yakima Yellow, Alexa Fluor, PET, Ethidiumbromide, Acridinium dyes, Carbaol dyes, Phenoaxine dyes, Porphyrine dyes, Polymethin dyes, and the like.


The levels, i.e. the concentrations, of the one or more vasoactive hormones (or fragments thereof or precursors or fragments thereof) in the sample of the subject are used for the stratification of the subject into different risk groups for particular medications. For instance, concentrations of the vasoactive hormone (or fragments thereof or precursors or fragments thereof) above or in other cases below a certain threshold value is indicative for the risk of an unfavourable effect in the subject after having received said medication.

Survival analysis (Cox regression and hazard ratios) and Kaplan-Meier estimators may be used for the assessment or prediction of the risk (e.g. morbidity) of a certain medication for a patient with a vasoactive hormone level (or fragments thereof or precursors or fragments thereof) e.g. above or below a cut off.

Sequences

The amino acid sequence of the precursor peptide of Adrenomedullin (pre-pro-Adrenomedullin) is given in SEQ ID NO:1. Pro-Adrenomedullin relates to amino acid residues 22 to 185 of the sequence of pre-pro-Adrenomedullin. The amino acid sequence of pro-Adrenomedullin (pro-ADM) is given in SEQ ID NO:2. The pro-ADM N-terminal 20 peptide (PAMP) relates to amino acid residues 22-41 of pre-proADM. The amino acid
sequence of PAMP is given in SEQ ID NO:3. MR-pro-Adrenomedullin (MR-pro-ADM) relates to amino acid residues 45-92 of pre-pro-ADM. The amino acid sequence of MR-pro-ADM is provided in SEQ ID NO:4. The amino acid sequence of mature Adrenomedullin (ADM) is given in SEQ ID NO:5.

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<tr>
<th>SEQ ID NO:1 (amino acid sequence of pre-pro-ADM)</th>
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<tr>
<td>1 MKLVSLVALMY LGLSALGLGAD TARLDVASEF RKWKWNLALSR RGKRELRMSS</td>
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</tr>
<tr>
<td>51 SYPTGLADVK AGPAQTLIRP QDMKGAASRSP EDSSPDAARI RVKRYRQSMN</td>
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<tr>
<td>101 NFQGLRSFGC RFTGTCTVQKL AHQTYQFTDK DKNVAPRSK ISPQGYGRRR</td>
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<tr>
<td>151 RRSLPEAGPG RTLVSSKPQA HGAPPAPSGS APHFL</td>
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<tr>
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<tr>
<td>1 ARLDVASEFR KKWNKWALSR GKRRLMSSS YPTGLADVKA GPAQTLIRPQ</td>
<td></td>
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<tr>
<td>51 DMKGAASRSP DSSPDAARI VRKRYRQSMN FGQLRSGFCR FGTCTVQKLA</td>
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<tr>
<td>101 HQIYQFTDK KDNVAPRSK SPQGYGRRRR RSLPEAGPGR TLVS ZKPQAH</td>
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<tr>
<td>151 GAPAPPSSGA PHFL</td>
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<th>SEQ ID NO:3 (amino acid sequence of pro-ADM)</th>
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<tr>
<td>1 ARLDVASEFR KKWNKWALSR</td>
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<tr>
<th>SEQ ID NO:4 (amino acid sequence of MR-pro-ADM)</th>
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<tbody>
<tr>
<td>1 ELRMSSSYPT GLADVKAQ TLIRPDMDK GASRSPEFSS</td>
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<tr>
<th>SEQ ID NO:5 (amino acid sequence of ADM)</th>
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<tr>
<td>1 YRQSMNNFQG LRSFGCRTG CTVQKLHQA YQFTDKDKDN VAPRSKISPQ</td>
<td></td>
</tr>
<tr>
<td>51 GY</td>
<td></td>
</tr>
</tbody>
</table>

The amino acid sequence of the atrial natriuretic peptide (ANP) is given in SEQ ID NO:8. The sequence of the 153 amino acid pre-pro-AKP is shown in SEQ ID NO:6. Upon cleavage of an N-terminal signal peptide (25 amino acids) and the two C-terminal amino acids (127/128) proANP (SEQ ID NO:7) is released. ANP comprises residues 99-126 from the C-terminus of the precursor prohormone pro-ANP. This prohormone is cleaved into the mature 28 amino acid peptide ANP, also known as ANP (1-28) or α-ANP, and the amino terminal fragment ANP (1-98) (NT-proANP, SEQ ID NO:9). Mid-regional proANP (MR-proANP) is defined as NT-proANP or any fragments thereof comprising at least amino acid residues 53-90 (SEQ ID NO: 10) of proANP. The C-terminal two arginine residues (positions 152 and 153
in pre-pro-ANP, SEQ ID NO:6, are not present in another allele of the gene encoding pre-pro-ANP, thus pre-pro-ANP may comprise only residues 1 to 153. This of course is also true for the respective fragments of pre-pro-ANP, particularly pro-ANP.

SEQ ID NO: 6 (amino acid sequence of pre-pro-ANP):

1 MSSFSTTTVS FLLLAFLQQL GQTRANPMYN AVSNADMDF KNLDDHLEEK
51 MPLEDEWPP QVLSSEPNEEA GAALSPLPEV PPWTGEVSPA QRDGGALGRG
101 PWDSSDRSAL LKSKLARALT APRSLRRSSC FGGRMDRIGA QSGLGCNSFR
151 YRR

SEQ ID NO: 7 (amino acid sequence of pro-ANP):

1 NPMYNAVSNA DLMDFKNLLD HLEEKMLE D EWPPQVLSE PNEEAGAALS
51 PLPEVPPWTG EVSPAQRDGQ ALGRGPWDSS DRSALLKSL RALLTAPRSL
101 RRSSCFGGRM DRIGAQZGLG CNSFRY

SEQ ID NO: 8 (amino acid sequence of ANP):

1 SLRRSSCFGG RMDRIGAQSG LGCNSFRY

SEQ ID NO: 9 (amino acid sequence of NT-proANP):

1 NPMYNAVSNA DLMDFKNLLD HLEEKMLE D EWPPQVLSE PNEEAGAALS
51 PLPEVPPWTG EVSPAQRDGQ ALGRGPWDSS DRSALLKSL RALLTAPR

SEQ ID NO: 10 (amino acid sequence of amino acids 53-90 of proANP):

1 PEVPPWTGEV SPAQRDGGAL GRGPWDSSDR SALLKSL

The sequence of the 164 amino acid precursor peptide of Vasopressin (pre-pro-Vasopressin) is given in SEQ ID NO: 11. Pro-Vasopressin relates to the amino acid residues 29 to 164 of the sequence of pre-pro-Vasopressin. The amino acid sequence of pro-Vasopressin is given in SEQ ID NO: 12. Pro-Vasopressin is cleaved into mature Vasopressin, Neurophysin II and C-terminal proVasopressin (CT-proAVP or Copeptin). Vasopressin relates to the amino acid residues 20 to 28 of pre-pro-Vasopressin. The amino acid sequence of Vasopressin is shown in SEQ ID NO: 13. Copeptin relates to amino acid residues 126 to 164 of pre-pro-Vasopressin. The amino acid sequence of Copeptin is provided in SEQ ID NO: 14. Neurophysin II comprises the amino acid residues 32 to 124 of pre-pro-Vasopressin and its sequence is shown in SEQ ID NO: 15.
The sequence of the 212 amino acid precursor peptide of Endothelin-1 (pre-pro-Endothelin-1) is given in SEQ ID NO: 16. Pro-ET-1 relates to the amino acid residues 18 to 212 of the sequence of pre-pro-ET-1. The amino acid sequence of pro-ET-1 is given in SEQ ID NO: 17. Pro-ET-1 is cleaved into mature ET-1, big-ET-1 and C-terminal proET-1 (CT-proET-1). ET-I relates to the amino acid residues 53 to 73 of pre-pro-ET-1. The amino acid sequence of ET-I is shown in SEQ ID NO: 18. CT-proET-1 relates to amino acid residues 168 to 212 of pre-pro-ET-1. The amino acid sequence of CT-proET-I is provided in SEQ ID NO: 19. Big-ET-1 comprises the amino acid residues 53 to 90 of pre-pro-ET-1 and its sequence is shown in SEQ ID NO: 20.
The sequence of the 134 amino acid precursor peptide of brain natriuretic peptide (pre-pro-BNP) is given in SEQ ID NO:21. Pro-BNP relates to amino acid residues 27 to 134 of pre-pro-BNP. The sequence of pro-BNP is shown in SEQ ID NO:22. Pro-BNP is cleaved into N-terminal pro-BNP (NT-pro-BNP) and mature BNP. NT-pro-BNP comprises the amino acid residues 27 to 102 and its sequence is shown in SEQ ID NO:23. The SEQ ID NO:24 shows the sequence of BNP comprising the amino acid residues 103 to 134 of the pre-pro-BNP peptide.
SEQ ID NO: 23 (amino acid sequence of NT-pro-BNP):

```
1 HPLGSPGSAS DLETSGLQEQ RNHLQGKLSE LQVEQTSLEP LQΞSPRPTGV
51 WKSREVATEG IRGHRKMVL YTLRAPR
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SEQ ID NO: 24 (amino acid sequence of BNP):

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1 SPKMVQGSGC FGRKMDRISS SSGLGCKVLR RH
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Description of drawings

Figures 1 to 8 illustrate the survival rate for patients suffering from shortness of breath (SOB), acute coronary syndrome, acute heart failure (AHF), arrhythmia, asthma exacerbation, bronchitis, chest pain, influenza, chronic obstructive pulmonary disease (COPD), pneumonia and pulmonary embolism from the “Biomarkers in the Assessment of Congestive Heart failure study” (“BACH”).

Fig. 1: Marker MR-proADM and medicament ACE-Inhibitor; solid line means no medication, dashed line means medication; A: overall population (n=974), n=506 without medication (deaths=64), n=441 with medication (deaths=42); B: 1st MR-proADM quintiie (0.03 - 0.657 nmol/L; n=188). n=135 without medication (deaths=2), n=53 with medication (deaths=2); C: 2nd to 4th MR-proADM quinties (0.658 - 1.89 nmol/L; n=570), n=271 without medication (deaths=31). n=299 with medication (deaths=23); D: 5th MR-proADM quintiie (1.90 - 14.6 nmol/L; n=189), n=100 without medication (deaths=31), n=89 with medication (deaths=17).

Fig. 2: Marker MR-proAMP and medicament Statin; solid line means no medication, dashed line means medication; A: overall population (n=330), n=887 without medication (deaths=57), n=443 with medication (deaths=22); B: 1st MR-proANP quintiie (3.9 - 54.6 pmol/L; n=259), n=234 without medication (deaths=1). n=25 with medication (deaths=1 ); C: 2nd to 4th MR-proANP quinties (54.7 - 431 pmol/L; n=805), n=501 without medication (deaths=28), n=304 with medication (deaths=8); D: 5th MR-proADM quintiie (431.1 - 2510 pmol/L; n=266), n=152 without medication (deaths=28), n=144 with medication (deaths=13).
Fig. 3: Marker CT-proAVP and medicament Diuretic; solid line means no medication, dashed line means medication; A: overall population (n=943), n=588 without medication (deaths=59), n=355 with medication (deaths=47); B: 1st CT-proAVP quintile (0.71 - 5.44 pmol/L; n=188), n=159 without medication (deaths=8), n=29 with medication (deaths=2); C: 2nd to 4th CT-proAVP quintiles (5.45 - 43.2 pmol/L; n=566), n=354 without medication (deaths=26), n=212 with medication (deaths=19); D: 5th CT-proAVP quintile (43.3 - 1050 pmol/L; n=189), n=75 without medication (deaths=25), n=1 14 with medication (deaths=26).

Fig. 4: Marker BNP and medicament Calcium-Channel Blocker; solid line means no medication, dashed line means medication; A: overall population (n=892), n=666 without medication (deaths=59). n=226 with medication (deaths=11); B: 1st BNP quintile (3 - 65 pg/mL; n=183), n=152 without medication (deaths=4), n=31 with medication (deaths=2); C: 2nd to 4th BNP quintiles (65 - 904 pg/mL; n=537), n=378 without medication (deaths=27), n=159 with medication (deaths=8); D: 5th BNP quintile (904 - 7850 pg/mL: n=172), n=136 without medication (deaths=28), n=36 with medication (deaths=2).

Fig. 5: Marker CT-proET-1 and medicament Beta-Blocker; solid line means no medication, dashed line means medication; A: overall population (n=895), n=432 without medication (deaths=39), n=463 with medication (deaths=31); B: 1st CT-proET-1 quintile (6.92 - 67 pmol/L; n=184), n=121 without medication (deaths=Q) s n=63 with medication (deaths=1); C: 2nd to 4th CT-proET-1 quintiles (67 - 182 pmol/L; n=542), n=249 without medication (deaths=21), n=293 with medication (deaths=18); D: 5th CT-proET-1 quintile (182 - 709 pmol/L; n=169), n=62 without medication (deaths=18), n=107 with medication (deaths=12).

Fig. 6: Marker NT-proBNP and medicament Warfarin; solid line means no medication, dashed line means medication; A: overall population (n=875), n=651 without medication (deaths=53), n=224 with medication (deaths=5); B: 1st NT-proBNP quintile (3 - 280 pg/mL; n=174), n=159 without medication (deaths=4), n=15 with medication (deaths=1); C: 2nd to 4th NT-proBNP quintiles (280 - 7080 pg/mL; n=553), n=374 without medication (deaths=26), n=161 with medication (deaths=7); D: 5th NT-proBNP quintile (7080 - 112000 pg/mL; n=166), n=1 18 without medication (deaths=23), n=48 with medication (deaths=7).

Fig. 7: Marker combination MR-proADM and CT-proET-1 and medicament ACE-Inhibitor; solid line means no medication, dashed line means medication; A: overall population
(n=i330), n=739 without medication (deaths=51), n=591 with medication (deaths=-28); B: I\textsuperscript{st} quintile with both biomarkers below the median (n=560; median MR-proADM concentration 0.875 nmol/L, median CT-proET-1 concentration 88.2 pmol/L). n=396 without medication (deaths=6), n=164 with medication (deaths=3); C: 2\textsuperscript{nd} to 4\textsuperscript{th} quintile with either MR-proADM or CT-proET-1 above the respective median (n=167), n=89 without medication (deaths=6), n=78 with medication (deaths=5); D: 5\textsuperscript{th} quintile with both biomarkers above the respective median (n=603), n=254 without medication (deaths=39), n=349 with medication (deaths=20).

Fig. 8: Marker CT-proET-1 and medicament combination ACE-Inhibitor and Beta-Blocker; solid line means no medication, dashed line means medication; A: overall population (n=607), n=344 without medication (deaths=43), n=263 with medication (deaths=27); B: I\textsuperscript{st} CT-proET-1 quintile (6.9 – 67 pmol/L, n=137), n=101 without medication (deaths=1), n=36 with medication (deaths=2); C: 2\textsuperscript{nd} to 4\textsuperscript{th} CT-proET-1 quintile (67 – 182 pmol/L, n=353), n=194 without medication (deaths=26), n=159 with medication (deaths=1); D: 5\textsuperscript{th} CT-proET-1 quintile (182 - 709 pmol/L, n=17), n=49 without medication (deaths=16), n=68 with medication (deaths=14).

Figures 9 to 13 illustrate the survival rate for patients suffering from ischemic stroke, hemorrhagic stroke or transient ischemic attack from the "Copeptin to guide disease severity and Management. Osmostatus and Stress" ("COSMOS").

Fig. 9: Marker CT-proAVP and Medicament Diuretic; solid line means no medication, dashed line means medication; A: overall population (n=418), n=279 without medication (deaths=13), n=139 with medication (deaths=24); B: I\textsuperscript{st} CT-proAVP quintile (0.9 – 3.93 pmol/L, n=87), n=67 without medication (deaths=1), n=20 with medication (deaths=0); C: 2\textsuperscript{nd} to 4\textsuperscript{th} CT-proAVP quintiles (3.93 - 32.9 pmol/L, n=247), n=70 without medication (deaths=6), n=77 with medication (deaths=8); D: 5\textsuperscript{th} CT-proAVP quintile (32.9 - 778 pmol/L, n=84), n=42 without medication (deaths=6), n=42 with medication (deaths=16).

Fig. 10: Marker CT-proET-1 and Medicament Statin; solid line means no medication, dashed line means medication; A: overall population (n=415), n=310 without medication (deaths=26), n=105 with medication (deaths=9); B: I\textsuperscript{st} CT-proET-1 quintile (1 - 51.4 pmol/L, n=85), n=75 without medication (deaths=3), n=10 with medication (deaths=2); C: 2\textsuperscript{nd} to 4\textsuperscript{th} CT-proET-1 quintiles (51.4 - 93.1 pmol/L, n=252), n=178 without medication (deaths=10),
n=74 with medication (deaths=4); D: 5\textsuperscript{th} CT-proET-1 quintile (93.1 - 571 pmoI/L; n=78),
n=57 without medication (deaths=13), n=21 with medication (deaths=3).

Fig. 11: Marker MR-proADM and Medicament Statin; solid line means no medication,
dashed line means medication; A: overall population (n=417), n=312 without medication
(deaths=26), n=105 with medication (deaths=9); B: 1\textsuperscript{st} MR-proADM quintile (0.05 - 0.47
nmol/L; n=93), n=80 without medication (deaths=3), n=13 with medication (deaths=2); C: 2\textsuperscript{nd}
to 4\textsuperscript{th} MR-proADM quintiles (0.47 - 0.91 nmol/L; n=245), n=176 without medication
(deaths=8), n=69 with medication (deaths=5); D: 5\textsuperscript{th} MR-proADM quintile (0.91 – 5.49
nmol/L; n=79), n=56 without medication (deaths=15). n=23 with medication (deaths=2).

Fig. 12: Marker MR-proANP and Medicament Acetylsalicylic Acid; solid line means no
medication, dashed line means medication; A: overall population (n=449), n=240 without
medication (deaths=22), n=209 with medication (deaths=20); B: 1\textsuperscript{st} MR-proANP quintile
(22.3 - 69.5 pmoI/L; n=91), n=40 without medication (deaths=0), n=51 with medication
(deaths=0); C: 2\textsuperscript{nd} to 4\textsuperscript{th} MR-proANP quintiles (69.5 – 250 pmol/L; n=272). n=148 without
medication (deaths=12), n=124 with medication (deaths=6); D: 5\textsuperscript{th} MR-proANP quintile (250
– 1540 pmol/L; n=86). n=52 without medication (deaths=10), n=34 with medication
(deaths=14).

Fig. 13: Marker combination MR-proADM and CT-proET-1 and Antihypertensive
Medication; solid line means no medication, dashed line means medication; A: overall
population (n=432), n=164 without medication (deaths=8), n=268 with medication
(deaths=30); B: 1\textsuperscript{st} quintile with both biomarkers below the median (n=176; median MR-
proADM concentration 0.67 nmol/L, median CT-proET-1 concentration 69.1 pmol/L), n=101
without medication (deaths=1), n=75 with medication (deaths=4); C: 2\textsuperscript{nd} to 4\textsuperscript{th} quintile with
either MR-proADM or CT-proET-1 above the respective median (n=89). n=32 without
medication (deaths=1), n=61 with medication (deaths=8); D: 5\textsuperscript{th} quintile with both biomarkers
above the respective median (n=163), n=34 without medication (deaths=6), n=132 with
medication (deaths=18).

Figures 14 to 21 illustrate the survival rate for patients suffering from myocardial infarction
from the “Leicester Acute Myocardial Infarction Peptide Study” (“LAMP”). Figures 22 to 34
illustrate the rate of major cardiac events for patients suffering from acute myocardial
infarction from "LAMP-Study ".

Fig. 14: Marker MR-proADM and Medicament Diuretic; solid line means no medication,
dashed line means medication; A: overall population (n=1464), n=869 without medication
(deaths=56), n=291 with medication (deaths=24); B: 1st MR-proADM quintile (0.04 - 0.47
mmol/L; n=229). n=2Q9 without medication (deaths=5), n=2G with medication (deaths=3); C:
2nd to 4th MR-proADM quintiles (0.47 - 1.18 nmol/L; n=700), n=542 without medication
(deaths=1S), n=158 with medication (deaths=7); D: 5th MR-proADM quintile (1.18 – 6.75
nmol/L; n=23 l), n=1 18 without medication (deaths=36), n=1 13 with medication (deaths=14).

Fig. 15: Marker MR-proANP and Medicament Diuretic; solid line means no medication,
dashed line means medication; A: overall population (n=1464), n=990 without medication
(deaths=55). n=474 with medication (deaths=37); B: 1st MR-proANP quintile (4.9 - 65
pmol/L; n=300), n=250 without medication (deaths=1 ), n=50 with medication (deaths^); C:
2nd to 4th MR-proANP quintiles (65 - 264 pmol/L; n=871), n=612 without medication
(deaths=21), n=259 with medication (deaths=14); D: 5th MR-proANP quintile (264 - 1630
pmol/L; n=293), n=128 without medication (deaths=33). n=1 65 with medication (deaths=21).

Fig. 16: Marker CT-proAVP and Medicament Nitr a te; solid line means no medication, dashed
line means medication; A: overall population (n=1,161), n=667 without medication
(deaths=58), n=494 with medication (deaths=23); B: 1st CT-proAVP quintile (0.3 1 - 4.6
pmol/L; n=23 l), n=1 62 without medication (deaths=1), n=69 with medication (deaths=2); C:
2nd to 4th CT-proAVP quintiles (4.6 - 42.1 pmol/L; n=698), n=380 without medication
(deaths=1 9), π= 318 with medication (deaths=1 l); D: 5th CT-proAVP quintile (42.1 - 1040
pmol/L; n=232), n=125 without medication (deaths=38), n=107 with medication (deaths=10).

Fig. 17: Marker CT-proET-1 and Medicament Calcium Channel Blocker; solid line means no
medication, dashed line means medication; A: overall population (n=1459), n=1207 without
medication (deaths=77), n=252 with medication (deaths=1 6); B: 1st CT-proET-1 quintile (4.6
- 56.6 pmol/L; n=295), n=252 without medication (deaths=6), n=43 with medication
(deaths=2); C: 2nd to 4th CT-proET-1 quintiles (56.6 - 118 pmol/L; n=877), n=723 without
medication (deaths=23), n=154 with medication (deaths=--?); D: 5th CT-proET-1 quintile (118
- 671 pmol/L; n=287), n=232 without medication (deaths=48), n=55 with medication (deaths=7).

Fig. 18: Marker NT-proBNP and Medicament Calcium Channel Blocker; solid line means no medication, dashed line means medication; A: overall population (n=1174), n=1026 without medication (deaths=78), n=148 with medication (deaths=7); B: 1st NT-proBNP quintile (0.3 - 204 pg/mL; n=223), n=200 without medication (deaths=3), n=23 with medication (deaths=1); C: 2nd to 4th NT-proBNP quintiles (204 - 3160 pg/mL; n=713), n=618 without medication (deaths=34), n=95 with medication (deaths=4); D: 5th NT-proBNP quintile (3160 - 11800 pg/mL; n=238), n=208 without medication (deaths=41), n=30 with medication (deaths=2).

Fig. 19: Marker CT-proAVF and combination of medicaments Nitrate and Diuretic; solid line means no medication, dashed line means medication: A: overall population (n=647), n=51 without medication (deaths=43), n=136 with medication (deaths=10); B: 1st CT-proAVP quintile (0.31 - 4.6 pmol/L; n=159), n=141 without medication (deaths=2), n=18 with medication (deaths=2); C: 2nd to 4th CT-proAVP quintiles (4.6 - 42.1 pmol/L; n=364), n=285 without medication (deaths=13), n=79 with medication (deaths=3); D: 5th CT-proAVP quintile (42.1 - 1040 pmol/L; n=124), n=85 without medication (deaths=29), n=39 with medication (deaths=5).

Fig. 20: Marker combination CT-proAVP and MR-proADM and Medicament Diuretic; solid line means no medication, dashed line means medication: A: overall population (n=161), n=870 without medication (deaths=56), n=291 with medication (deaths=24); B: 1st quintile with both biomarkers below the median (n=362, median CT-proAVP concentration 10.75 pmol/L, median MR-proADM concentration 0.72 nmoL/L), n=326 without medication (deaths=2), n=36 with medication (deaths=1); C: 2nd to 4th quintile with either CT-proAVP or MR-proADM above the respective median (n=437), n=343 without medication (deaths=15), n=94 with medication (deaths=7); D: 5th quintile with both biomarkers above the respective median (n=362), n=201 without medication (deaths=39), n=161 with medication (deaths=16).

Fig. 21: Marker combination CT-proAVP and MR-proANP and combination of medicaments Nitrate and Diuretic; solid line means no medication, dashed line means medication; A: overall population (n=646), n=511 without medication (deaths=43), n=135 with medication (deaths=10); B: 1st quintile with both biomarkers below the median (n=239, median CT-proAVP concentration 10.75 pmol/L, median MR-proANP concentration 117 pmol/L), n=223
without medication (deaths=3), n=16 with medication (deaths=1); C: 2nd to 4th quintile with either CT-proAVP or MR-proANP above the respective median (n=210), n=161 without medication (deaths=6), n=49 with medication (deaths=2); D: 5th quintile with both biomarkers above the respective median (n=197), n=127 without medication (deaths~34), n=70 with medication (deaths=7).

Fig. 22: Marker MR-proADM and Medicament Diuretic; solid line means no medication, dashed line means medication; A: overall population (n=1160), n=869 without medication (MACE=15), n=291 with medication (MACE=67); B: 1st MR-proADM quintile (0.04 - 0.47 nmol/L; n=229), n=209 without medication (MACE=10), n=20 with medication (MACE=6); C: 2nd to 4th MR-proADM quintiles (0.47 - 1.18 nmol/L; π=700), n=542 without medication (MACE=81), n=158 with medication (MACE=28); D: 5th MR-proADM quintile (1.18 - 6.75 nmol/L; n=231), n=18 without medication (MACE=49), n=113 with medication (MACE=33).

Fig. 23: Marker MR-proANP and Medicament Calcium Channel Blocker; solid line means no medication, dashed line means medication; A: overall population (n=1160), n=1015 without medication (MACE=16), n=145 with medication (MACE=21); B: 1st MR-proANP quintile (14.5 - 59.6 pmol/L; n=230), n=215 without medication (MACE=1), n=15 with medication (MACE=72), n=98 with medication (MACE=14); D: 5th MR-proANP quintile (283 - 1650 pmol/L; n=232), n=200 without medication (MACE=85), n=32 with medication (MACE=6).

Fig. 24: Marker CT-proAVP and Medicament ACE Inhibitor; solid line means no medication, dashed line means medication; A: overall population (n=1463), n=399 without medication (MACE=74), n=1064 with medication (MACE=128); B: 1st CT-proAVP quintile (0.3 – 3.6 pmol/L; n=293), n=75 without medication (MACE=3), n=218 with medication (MACE=20); C: 2nd to 4th CT-proAVP quintiles (3.6 - 18.7 pmol/L; n=880), n=226 without medication (MACE=25), n=654 with medication (MACE=66); D: 5th CT-proAVP quintile (18.7 - 441 pmol/L; n=290), n=98 without medication (MACE=46); n=192 with medication (MACE=42).

Fig. 25: Marker CT-proET-1 and Medicament Calcium Channel Blocker; solid line means no medication, dashed line means medication; A: overall population (n=1459), n=1207 without medication (deaths=3), n=16 with medication (deaths=1); C: 2nd to 4th quintile with either CT-proAVP or MR-proANP above the respective median (n=210), n=161 without medication (deaths=6), n=49 with medication (deaths=2); D: 5th quintile with both biomarkers above the respective median (n=197), n=127 without medication (deaths~34), n=70 with medication (deaths=7).
medication (MACE=164), n=252 with medication (MACE=38); B: 1\textsuperscript{st} CT-proET-1 quintile (4.6 - 56.6 pmol/L; n=295), n=252 without medication (MACE=9), n=43 with medication (MACE=S); C: 2\textsuperscript{nd} b 4\textsuperscript{th} CT-proET-1 quintiles (56.6 - 118 pmol/L; n=877), n=723 without medication (MACE=75). n=154 with medication (MACE=I 6); D: 5\textsuperscript{th} CT-proET-1 quintile (118 - 671 pmol/L; n=287), n=232 without medication (MACE=8Q). n=55 with medication (MACE=14).

Fig. 26: Marker NT-proBNP and Medicament Beta Blocker; solid line means no medication, dashed line means medication; A: overall population (n=1 174), n=234 without medication (MACE=64), n=940 with medication (MACE=I 28); B: 1\textsuperscript{st} NT-proBNP quintile (0.3 - 204 pg/mL; n=224), n=31 without medication (MACE=I), n=193 with medication (MACE=H): C: 2\textsuperscript{nd} to 4\textsuperscript{th} NT-proBNP quintiles (204 - 3160 pg/mL; n=712). n=123 without medication (MACE=25). n=589 with medication (MACE=71); D: 5\textsuperscript{th} NT-proBNP quintile (31 60 - 11 800 pg/mL; n=238). n=80 without medication (MACE=38), n=158 with medication (MACE=43).

Fig. 27: Marker MR-proADM and combination of medicaments Nitrate and Diuretic; solid line means no medication, dashed line means medication; A: overall population (n=647), n=51 1 without medication (MACE=80), n=136 with medication (MACE=37): B: 1\textsuperscript{st} MR-proADM quintile (0.035 0.47 nmol/L; n=13). n=104 without medication (MACE=3), n=9 with medication (MACE=3): C: 2\textsuperscript{nd} to 4\textsuperscript{th} MR-proADM quintiles (0.47 - 1.18 nmol/L; n=406), n=333 without medication (MACE=37), n=73 with medication (MACE=H); D: 5\textsuperscript{th} MR-proADM quintile (1.18 - 6.75 nmol/L; n=128), n=74 without medication (MACE=35), n=54 with medication (MACE=20).

Fig. 28: Marker MR-proANP and combination of medicaments Nitrate and Diuretic; solid line means no medication, dashed line means medication; A: overall population (n=788), n=592 without medication (MACE=76), n=196 with medication (MACE=47): B: 1\textsuperscript{st} MR-proANP quintile (4.9 - 65 pmol/L; n=1 72), n=154 without medication (MACE=3), n=1 8 with medication (MACE=2); C: 2\textsuperscript{nd} to 4\textsuperscript{th} MR-proANP quintiles (65 - 264 pmol/L; n=455). n=357 without medication (MACE=41), n=98 with medication (MACE=20); D: 5\textsuperscript{th} MR-proANP quintile (264 - 1630 pmol/L; n=161), n=81 without medication (MACE=32), n=80 with medication (MACE=25).
Fig. 29: Marker CT-proAVP and combination of medicaments Nitrate and Thrombolytic Drug; solid line means no medication, dashed line means medication; A: overall population (n=788), n=559 without medication (MACE=72), n=229 with medication (MACE=30); B: 1st CT-proAVP quintile (0.3 – 3.6 pmol/L; n=178), n=127 without medication (MACE=4), n=51 with medication (MACE=6); C: 2nd to 4th CT-proAVP quintiles (3.6 - 18.7 pmol/L; n=475), n=328 without medication (MACE=33), n=147 with medication (MACE=17); D: 5th CT-proAVP quintile (18.7 – 441 pmol/L; n=135), n=104 without medication (MACE=35), n=31 with medication (MACE=7).

Fig. 30: Marker CT-proET-1 and combination of medicaments Nitrate and Diuretic; solid line means no medication, dashed line means medication; A: overall population (n=339), n=238 without medication (MACE=35), n=56 with medication (MACE=I 2); B: 1st CT-proET-1 quintile (3.7 - 65.4 pmol/L; n=80), n=75 without medication (MACE=3), n=5 with medication (3VIACE=1); C: 2nd to 4th CT-proET-1 quintiles (65.4 - 136 pmol/L; n=200), n=170 without medication (MACE=14), n=30 with medication (MACE=4); D: 5th CT-proET-1 quintile (136 – 468 pmol/L; n=59), n=38 without medication (MACE=I 8), n=21 with medication (MACE=7).

Fig. 31: Marker NT-proBNP and combination of medicaments Beta Blocker and Dirutec; solid line means no medication, dashed line means medication; A: overall population (n=371), n=154 without medication (MACE=41), n=217 with medication (MACE=49); B: 1st NT-proBNP quintile (0.3 - 204 pg/mL; n=50), n=28 without medication (MACE=I), n=22 with medication (MACE=2); C: 2nd to 4th NT-proBNP quintiles (204 – 3160 pg/mL; n=202), n=81 without medication (MACE=15), n=121 with medication (MACE=26); D: 5th NT-proBNP quintile (3160 – 11800 pg/mL; n=119), n=45 without medication (MACE=25), n=74 with medication (MACE=21 )

Fig. 32: Marker combination MR-proADM and MR-proANP and Medicament Calcium Channel Blocker; solid line means no medication, dashed line means medication; A: overall population (n=1116), n=1015 without medication (MACE=1 62), n=146 with medication (MACE=22); B: 3rd quintile with both biomarkers below the median (n=429, median MR-proADM concentration 0.72 nmol/L. median MR-proANP concentration 117 pmol/L), n=383 without medication (MACE=1 9), n=46 with medication (MACE=1 5); C: 2nd to 4th quintile with either MR-proADM or MR-proANP above the respective median (n=303), n=271 without
medication (MACE<36), n=32 with medication (MACE=4); D: 5th quintile with both biomarkers above the respective median (n=429), n=361 without medication (MACE=107), n=68 with medication (MACE=D).

Fig. 33: Marker combination MR-proADM and CT-proAVP and Medicament ACE Inhibitor; solid line means no medication, dashed line means medication; A: overall population (n=1 163), n=209 without medication (MACE=60), n=954 with medication (MACE=124); B: 1st quintile with both biomarkers below the median (n=362, median MR-proADM concentration 0.72 nmol/L, median CT-proAVP concentration 10.75 pmol/L), n=57 without medication (MACE=2). n=305 with medication (MACE=18); C: 2nd to 4th quintile with either MR-proADM or CT-proAVP above the respective median (n=439). n=66 without medication (MACE=80), n=373 with medication (MACE=46); D: 5th quintile with both biomarkers above the respective median (n=362). n=86 without medication (MACE=42), n=276 with medication (MACE=OQ).

Fig. 34: Marker combination MR-proADM and MR-proANP and combination of medicaments Beta Blocker and Diuretic; solid line means no medication, dashed line means medication; A: overall population (n=365), n=151 without medication (MACE=40), n=214 with medication (MACE=48); B: 1st quintile with both biomarkers below the median (n=75, median MR-proADM concentration 0.72 nmol/L, median MR-proANP concentration 117 pmol/L), n=45 without medication (MACE=1), n=30 with medication (MACE=4): C: 2nd to 4th quintile with either MR-proADM or MR-proANP above the respective median (n=89), n=36 without medication (MACE=9). n=53 with medication (MACE=0); D: 5th quintile with both biomarkers above the respective median (n=201). n=70 without medication (MACE=30), n=131 with medication (MACE=31).
Example

Example 1: Measurement of Biomarkers


For MR-proANP detection, 14 µl of patients serum were incubated for 14 min. The measuring range was 0-1 000 pmol/L, the limit of detection 2.1 pmol/L. and the limit of quantitation 4.5 pmol/L. The intra assay CV was 1.2 % and the inter laboratory CV 5.4 %.

This assay uses the same antibody pair as the reference assay (Morgenthaler et al. 2004. Clin Chem 50:234-6), and the correlation between the two assay systems was r=0.99.

For MR-proADM detection, 26 µl serum was incubated for 29 min. The measuring range was 0-1 00 nmol/L, the limit of detection and limit of quantification were 0.05 and 0.23 nmol/L, respectively. The intra assay CV was 1.9 % and the inter laboratory CV was 9.8 %.

This assay uses the same antibody pair as described in detail elsewhere (Morgenthaler et al. 2005. Clin Chem 51: 1823-9), and the correlation between the two assay systems was r=0.99.

CT-proAVP (Copeptin) levels were measured with a chemiluminescence sandwich immunoassay with a lower detection limit of 1.7 pmol/L (Morgenthaler et al. 2006. Clin Chem 52:112-9). In 359 healthy individuals (153 men and 206 women), median CT-proAVP levels were 4.2 pmol/L ranging from 1.0-13.8 pmol/L. The inter laboratory CV was <20% and the intra assay CV was <10% for samples > 2.25 pmol/L.

CT-proET-1 levels were measured with a chemiluminescence sandwich immunoassay with a lower detection limit of 0.4 pmol/L (Papassotiriau et al. 2006. Clin Chem 52: 1144-51). In 326 healthy individuals (150 male and 176 female) CT-proET-1 values followed a
Gaussian distribution with a mean (SD) of 44.3 (10.6) pmol/L and a range of 10.5-77.4 pmol/L. The intra assay imprecision (CV) was < 5% and the inter laboratory CV was < 10%.

BNP was measured with Triage two-site immunoassay reagents (Biosite, San Diego, CA) formatted for Becknian Coulter instrumentation (Brea, CA). Performance in the laboratory included a limit of quantitation of 5.0 ng/L, within run imprecision (CV) of 1.5% and total imprecision (CV) of 3.0%.

NTproBNP was measured by electrochemiluminescence on the ElecSys 2010 analyzer (Roche Diagnostics, Indianapolis, IN). Performance in the laboratory included a limit of quantitation of 10.0 ng/L, within run imprecision (CV) of 1.5% and total imprecision (CV) of 3.0%.

Example 2: Clinical Studies

The present invention is based on patients and samples from the following clinical studies:

jlpost_stroke patients [COSMOS study]

Study setting, Inclusion/ exclusion criteria

The study was set at the emergency and neurological and neurosurgical clinic of the University Hospital of Basel. All consecutive patients who are admitted to the emergency department with an ischemic or hemorrhagic stroke or transient ischemic attack (TIA) according to the World Health Organization criteria with symptom onset within the last 3 days were included into the study. Patients without an informed consent were excluded.

Baseline data collection

Access to data of all eligible patients that are not included into this study is important to avoid a selection bias. Thus, we will collect baseline data and information on inclusion and exclusion criteria in all eligible patients irrespective whether they are or are not included into the study. This will allow the comparison of baseline data of eligible patients who consented to participate with those who did not. Baseline data collection in patients will be collected by the investigators and contain:

a) age
b) gender
c) BMI
d) **Medical history items**: actual history that preceded the hospitalization; ABCD score (Rothwell et al. 2005. *A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack*. Lancet 366: 29-36) in patients with transient ischemic attack; family history; relevant co-morbidities also assessed by the charlson index (Goldstein et al. 2004. *Charlson Index comorbidity adjustment for ischemic stroke outcome studies. Stroke 35: 1941-5*) (i.e. hypertension, previous stroke, previous TIA, ischemic heart disease, atrial fibrillation, diabetes mellitus, renal and liver dysfunction, congestive heart failure, dyslipidemia: comorbidities with the risk of hyponatremia (severe hypothyroidism, glucocorticoid insufficiency, neoplasm, HIV infection); smoking history (pack-years) and status (pack per day); current medication; alcohol consumption (glass and grams per day); time from onset of symptoms to admission.

e) **Place of residence**: i.e. independent living, defined as living at home or in an old people’s home with or without support of the family circle and/or professional care (the family circle consists of the spouse and/or other important persons who live together with the patient; dependent living, defined as nursing home long-stay department, other hospital.

f) **Clinical items**: physical examination including neurological status. NIHSS (to assess the severity of stroke) and Glasgow Coma scale (GCS; Adams et al. 1999. *Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST)*. Neurology 53: 126-31), blood pressure, pulse rate, weight.

volume status (including skin turgor, jugular venous distension, auscultation, if available flow sheet of fluid intake and loss), body temperature; in neurosurgical patients intracerebral pressure if performed within the routine clinical management.

g) **Clinical symptoms** of hyponatremia will be evaluated on admission and in case of sodium imbalance in neurological patients. In patients undergoing intracranial surgery we will evaluate clinical symptoms daily. Specifically we will monitor the presence of headache, anorexia, nausea, vomiting, muscle cramps and aches, seizures, confusion, apathetic or lethargic development.

h) **Routine/Standard laboratory tests**: routine blood sampling including: hematocrit, blood urea nitrogen, bicarbonate, total protein, albumin, uric acid serum and urine electrolytes, urine and serum osmolality, creatinine, lipids, TSH, fT4, T3, and basal Cortisol. All blood sampling will be done before any food intake, or smoking, if feasible. Alternatively, influencing factors will be monitored.

i) **Imaging**: Computer tomography or MRI of the neurocranium (T1, T2, diffusion-weighted image sequence, with or without contrast), if indicated magnetic resonance angiography or
conventional cerebral angiography. We will record the time-points of contrast agent application.

Stroke patients will also be classified on the basis of the vascular territory of the ischemic lesion as follows: total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), lacunar circulation syndrome (LACS), posterior circulation syndrome (POCS).

j) Further investigations: Stroke patients will have neurosonography, echocardiography, standard 12-leaf electrocardiography and 24-hour electrocardiography and then will be classified by etiology of strokes according to Trial of Org 10172 in acute Treatment (TOAST) stroke subtype classification, which differs between large artery atherosclerosis, cardioembolism, small-artery occlusion, other etiology, and undetermined etiology.

Informed consent statement

The study will be approved by the ethics committee of Basel (Ethikkommission beider Basel).

It is important to note that this is an exploratory and observational study; the only study related intervention will be the asseveration of 7.5 ml of plasma obtained during the routinely performed blood sampling. Therefore, patients are required to provide written informed consent that they agree for the use of their data for scientific purposes. In patients, in which “informed consent” is not feasible due to sequela of the acute CMS lesion (the latter a prerequisite for inclusion), patients’ next to kin can sign an assent form to state the presumptive will of the patient. In case, next of kin are not readily available, a treating physician - who must not be involved in the study - have to certify that there are no objections for inclusion in the study from his point of view. Only after these informed consent procedures the patient can be included in the study.

Management of participants throughout the trial
Step 1. All eligible patients in the emergency department or the neurological ward will be included into the study.

Step 2. All baseline data will be collected.

Step 3. During hospitalization we Clinical items including weight, blood pressure, pulse rate, volume status and body temperature will be assessed by chart review until discharge.

- Fluid treatment and drugs.
- Potential symptoms of hyponatremia, i.e. headache, nausea, vomiting, muscle cramps and aches, anorexia, impaired consciousness, seizure.
- Routinely performed laboratory tests (chemogramm, plasma glucose, serum osmolality, urine osmolality, sodium in urine, hematocrit) will be sampled at the time-points when blood sampling is routinely done on the wards.


The future place of residence (i.e. dependent vs. independent living) will be assessed.

Step 5. In patients with ischemic stroke a telephone follow-up regarding morbidity and mortality (as assessed by the Barthel Index and Ranking Scale) will be obtained after 3 months. An unfavorable outcome will be defined as a Barthel Index <85 or modified Ranking scale of 3 to 6.

Study population:

The study involved 983 consecutive patients with acute myocardial infarction (AMI) admitted to the Coronary Care Unit of Leicester Royal Infirmary. Acute myocardial infarction was diagnosed if a patient had a plasma creatinine kinase-MB elevation greater than twice normal or a cardiac Troponin I level >0.1 ng/ml with at least 1 of the following: chest pain lasting >20min or diagnostic serial electrocardiographic changes consisting of new pathological Q waves or ST-segment and T-wave changes. Acute myocardial infarction was subcategorized into ST-segment elevation myocardial infarction (STEMI) or non-ST-segment myocardial infarction (NSTEMI).

The study complied with the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from all patients.

Exclusion criteria were known malignancy, or surgery in the previous month. The estimated glomerular filtration rate (eGFR) was calculated from the simplified formula derived from the MDRD (Modification of Diet in Renal Disease) study, recently validated in patients with HF (Smilde et al. 2006. Drawbacks and prognostic value of formulas estimating renal function in patients with chronic heart failure and systolic dysfunction. Ciculation 114: 1572-80).
Plasma samples:
Blood samples were drawn on 1 occasion 3 to 5 days after the onset of chest pain. After 15 min bed rest, 20 ml blood was collected into tubes containing ethylenediaminetetraacetic acid (EDTA) and aprotinin. All plasma samples were stored at -70°C until assayed in a blinded fashion in a single batch. In a subgroup of 132 patients from the original 983-patient cohort, blood sampling was performed daily for 5 days from admission to discharge.

Echocardiography:

Study Population
This study was approved by the institutional review boards (IRB) of the respective enrolling institutions. A total of 1,641 patients from fifteen centers were enrolled from March, 2007 to February, 2008. These centers included 8 from the United States, 6 from Europe and 1 from New Zealand. To be eligible for the trial patients had to report shortness of breath as the primary complaint upon presentation to the emergency department. Patients under 18 years of age or unable to provide consent were excluded from the trial. Patients determined to be experiencing an acute myocardial infarction were also excluded.

For each patient enrolled in the study, physicians assigned to the emergency department who were blinded to the results of ANP, ADM and other investigational markers, assessed the probability that the patient had acute heart failure or pneumonia via two separate Likert scale questionnaires. The physician assigned a value of 0 to 100 percent clinical certainty.
Confirmation of Diagnosis

To determine the actual diagnosis, two cardiologists reviewed all medical records pertaining to the patient and independently classified the diagnosis as dyspnea due to congestive heart failure, pneumonia or due to other underlying disease. Both cardiologists were blinded to each other, the investigational markers, as well as the emergency physician’s preliminary diagnosis. They did have access to the emergency department case report forms that included chest radiographic data, radionuclide angiography, echocardiography, medical history, catheterization data and the hospital course for patients who were admitted to the hospital. In the event of diagnostic disagreement among the cardiology reviewers they were asked to meet to come to a common conclusion. In the event they were unable to come to a common conclusion, a third party cardiology adjudicator was assigned by the endpoints committee and asked to review the data and determine which diagnosis was the most accurate.

In order to come to a conclusion of pneumonia, a pneumonia criterion modified from Fine et al. 1990 and Leroy et al. 1995 had to be fulfilled. Further, all diagnosis of pneumonia had to be verified by an endpoints committee pulmonologist assigned to the case.

Measurement of markers used for two endpoints

The markers were measured at the assigned core lab at the University of Maryland Medical Center. MR-proANP and MR-proADM were detected using novel fully automated sandwich immunoassay systems on the B.R.A.H.M.S KRYPTOR (B.R.A.H.M.S AG, Hennigsdorf/Berlin, Germany) (Caruhal et al. 2009. Clin Biochem 42:725-8). This random access analyzer employs the sensitive Time Resolved Amplified Cryptate Emission (‘TRECE) technology, based on a non-radioactive-transfer between 2 fluorophores, europium cryptate and XL665.


For MR-proANP detection, 14μL of patients scrupt were incubated for 14 min. The measuring range was 0-1 0000 pmol/L, the limit of detection 2.1 pmol/L. and the limit of quantitation 4.5 pmol/L. The intra assay CV was 1.2 % and the inter laboratory CV 5.4 %.
This assay uses the same antibody pair as the reference assay (Morgenthaler et al. 2004, Clin Chem 50: 234-6), and the correlation between the two assay systems was r=0.99.

For MR-proADM detection, 26 µl serum was incubated for 29 min. The measuring range was 0-100 nmol/L. the limit of detection and limit of quantification were 0.05 and 0.23 nmol/L, respectively. The intra assay CV was 1.9 % and the inter laboratory CV was 9.8 %. This assay uses the same antibody pair as described in detail elsewhere (Morgenthaler et al. 2005. Clin Chem 51: 1823-9), and the correlation between the two assay systems was r=0.99.

Analysis of data for all studies:

Survival rates, i.e. the proportion of patients surviving at a given time after entry into the studies, are plotted in the appended figures over time for different combinations of a particular vasoactive hormone with a particular medication. The patients have been stratified into quintiles according to their respective hormone levels. Data for patients having received the particular medication are plotted separately from patients that did not receive a medication. For some cases, two or more quintiles have been pooled were appropriate. Hazard ratios (HR) have been calculated for various combinations of particular vasoactive hormones with particular medications, HR have also been calculated for particular quintiles and/or pooled quintiles and compared to overall HR for each combination.

Table 1 lists the results for the patients from the BACH study (patients suffering from shortness of breath (SOB), acute coronary syndrome, acute heart failure (AHF), arrhythmia, asthma exacerbation, bronchitis, chest pain, influenza, chronic obstructive pulmonary disease (COPD), pneumonia and/or pulmonary embolism.). At low levels of vasoactive hormones, the administration of e.g. calcium-channel blockers, diuretics and statins has an unfavourable effect, while at higher levels the administration of these drugs has a positive effect. In contrast, at high levels of vasoactive hormones, the administration of e.g. antibiotics has an unfavourable effect, while at lower levels the administration of these drugs has a positive effect.

Table 2 lists the results for the patients from the COSMOS study (patients having suffered from ischemic or haemorrhagic stroke or TIA). At low levels of vasoactive hormones, the administration of statins, anti-coagulants and plavix has an unfavourable effect, while at higher levels the administration of these drugs has a positive effect. In contrast, at high levels
of vasoactive hormones, the administration of acetylsalicylic acid, thrombolytic drugs, diuretics and steroids has an unfavourable effect, while at lower levels the administration of these drugs has a positive effect.

Table 3 lists the results for the patients from the LAMP study (patients having suffered a myocardial infarction) in respect to death as the unfavourable effect (outcome). At low levels of vasoactive hormones, the administration of the medication (except for thrombolytic drugs when the hormone is proANP) has an unfavourable effect, while at higher levels the administration of the drugs has a positive effect.

Table 4 lists the results for the patients from the LAMP study (patients having suffered a myocardial infarction) in respect to MACE as the unfavourable effect (outcome). At low levels of vasoactive hormones, the administration of the medication (except for thrombolytic drugs when the hormone is proANP) has an unfavourable effect, while at higher levels the administration of the drugs has a positive effect.
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<th>Medicament (overall patient group)</th>
<th>Biomarker</th>
<th>HR in Marker-Quintile 1</th>
<th>Range</th>
<th>HR in Marker-Quintile 2-4</th>
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MR-proADM values in nmol/L, MR-proANP values in pmol/L, CT-proAVP values in pmol/L, BNP values in pg/mL, CT-proET-1 values in pmol/L, NT-proBNP values in pg/mL.

* Quintiles 1 to 4 are pooled
Table 2 Results COSMOS

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MR-proADM values in nmol/L, MR-proANP values in pmol/L, CT-proAVP values in pmol/L, CT-proET-1 values in pmol/L
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MR-proADM values in nmoi/L, MR-proANP values in pmoi/L, CT-proAVP values in pmol/L, CT-proET-1 values in pmol/L, NT-proBNP values pg/mL.
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MR-proADSl values in nmol/L, MR-proANP values in pmol/L, CT-proAVP values in pmol/L, CT-proET-1 values in pmol/L, NT-proBNP values in pg/mL
Claims

1. A method for the stratification of a subject having an acute or a chronic disease, wherein said disease effects endothelial function/dysfunction, comprising the steps of:
   (i) taking a sample of bodily fluid from said subject;
   (ii) determining in said sample of bodily fluid the concentration of a vasoactive hormone or fragments thereof or precursors or fragments thereof having a length of at least 12 amino acid residues;
   (iii) stratifying said subjects into one of the following categories:
      - responder to a medication for treatment of said disease,
      - non-responder to a medication for treatment of said disease not showing an unfavourable effect after having received said medication;
      - subjects showing an unfavourable effect after having received said medication.

2. A method for the stratification of a subject having an acute or a chronic disease, wherein said disease effects endothelial function/dysfunction, comprising the steps of:
   - taking a sample of bodily fluid from said subject;
   - determining in said sample of bodily fluid the concentration of a vasoactive hormone or fragments thereof or precursors or fragments thereof having a length of at least 12 amino acid residues;
   - stratifying said subjects into one of the following categories:
     (iii) responder or non-responder to a medication for treatment of said disease not showing an unfavourable effect after having received said medication;
     (iv) subjects showing an unfavourable effect after having received said medication.

3. A method for the stratification of a subject having an acute or a chronic disease, wherein said disease effects endothelial function/dysfunction, comprising the steps of:
   - taking a sample of bodily fluid from said subject;
- determining in said sample of bodily fluid the concentration of a vasoactive hormone or fragments thereof or precursors or fragments thereof having a length of at least 12 amino acid residues;
- attributing the concentration of the vasoactive hormone or fragments thereof or precursors or fragments thereof in the sample to a risk of the subject of experiencing an unfavourable effect after receiving a particular medication.

4. A method according to any of claims 1-3 for avoiding an unfavourable effect after receiving a particular medication.

5. The method according to any of claims 1 to 4, wherein the vasoactive hormone is a peptide hormone selected from the group consisting of Adrenomedullin (ADM), Atrial Natriuretic Peptide (ANP), Brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), Endothelin-1, Endothelin-2, Endothelin-3, Arginin-Vasopressin (AVP), Dendroaspis natriuretic peptide (DNP), Urodilatin, Angiotensin II, Urocrtin, Urocrtin-2 (Stresscopin-related peptide), Urocrtin-3 (Stresscopin), Urotensin-I I, Urotensin II-related protein (URP), Neuropeptide Y (NPY), Vasoactive intestinal peptide (VIP), Calcitonin gene-related peptide I (CGRP I) and Calcitonin gene-related peptide II (CGRP II), Relaxin, Endokinin A or fragments thereof or precursors or fragments thereof having a length of at least 12 amino acid residues or is a hormone selected from the group consisting of Bradykinin, Apelin, Neurotensin, Substance P, Neurokinin A (Substance K), Endokinin A/B, Endokinin C, Methionin-Enkephalin, Leucin-Enkephalin or fragments thereof or precursors or fragments thereof having a length of at least 12 amino acid residues, or is a hormone selected from the group consisting of Serotonin, Prostaglandins and Thromboxane.

6. The method according to claim 5, wherein the precursor fragment of the vasoactive hormone adrenomedullin is Midregional pro-Adrenomedullin (MR-proADM) or a fragment thereof having a length of at least 12 amino acid residues.

7. The method according to claim 5, wherein the precursor fragment of the vasoactive hormone ANP is Midregional pro-Atrial natriuretic peptide (MR-proANP) or a fragment thereof having a length of at least 12 amino acid residues.
The method according to claim 5, wherein the precursor fragment of the vasoactive hormone endothelin-1 is C-terminal pro-Endothelin-1 (CT-proET-1) or a fragment thereof having a length of at least 12 amino acid residues.

The method according to claim 5, wherein the precursor fragment of the vasoactive hormone Arg-Vasopressin is C-terminal pro-AVP (Copeptin) or a fragment thereof having a length of at least 12 amino acid residues.

The method according to claims 1 to 9, wherein the disease is selected from the group consisting of: chronic heart failure, shortness of breath (SOB), acute coronary syndrome, acute heart failure (AHF), arrhythmia, asthma exacerbation, bronchitis, chest pain, influenza, chronic obstructive pulmonary disease (COPD), pneumonia and pulmonary embolism, pulmonary arterial hypertension (PAH), post stroke condition, post myocardial infarct condition, diabetes type II, cancer, atherosclerosis, infections, inflammatory diseases, and post surgery condition.

The method according to claims 1 to 10, wherein the medication is selected from the group consisting of anti-coagulant, thrombolytic drugs, platelet aggregation inhibitor, β-blocker, anti-oxidant, lipid lowering substance, diuretic, ACE inhibitor, calcium channel blocker, endothelin-receptor antagonists, phosphodiesterase type 5 inhibitors, prostacyclin derivatives, soluble guanylate cyclase activators, hormone therapeutic agent, NO substituent, adenosine receptor blocker, cardiac glycoside, angiotensin-II antagonist, anti-diabetic drug, antiarrhythmic and antibiotic.

The method according to claim 11, wherein the medication is selected from the group consisting of ACE inhibitors, diuretics and β-blockers.

The method according to claims 1 to 12, wherein the unfavourable effect is death or major adverse cardiac event (MACE).

The method according to any of the preceding claims, wherein the bodily fluid is selected from the group of blood, serum, plasma, cerebrospinal fluid, urine, saliva, sputum, and pleural effusions.
15. Use of an assay for the determination of the concentration of a vasoactive hormone or fragments thereof or precursors or fragments thereof having a length of at least 12 amino acid residues in a sample derived from a bodily fluid of a subject for the stratification of a subject having an acute or a chronic disease, into either of the categories:

- responder to a medication for treatment of said disease,
- non-responder to a medication for treatment of said disease not showing an unfavourable effect after having received said medication;
- subjects showing an unfavourable effect after having received said medication, wherein said disease effects endothelial function/dysfunction.

16. Use of an antibody or a functional fragment thereof specific for a vasoactive hormone or fragments thereof or precursors or fragments thereof having a length of at least 12 amino acid residues selected from the group of Adrenomedullin (ADM), Atrial Natriuretic Peptide (ANP), Brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), Endothelin-1, Endothelin-2, Endothelin-3, Arginin-Vasopressin (AVP), Dendroaspis natriuretic peptide (DNP), Urodilatin, Angiotensin II, Urocortin, Urocortin-2 (Stresscopin-related peptide), Urocortin-3 (Stresscopin), Urotensin-II, Urotensin II-related protein (URP), Neuropeptide Y (NPY), Vasoactive intestinal peptide (VIP), Calcitonin gene-related peptide I (CGRP I), Calcitonin gene-related peptide II (CGRP II), Endokinin A, Endokinin A/B, Endokinin C, Bradykinin, Relaxin, Apelin, Neotensin, Substance P, and Neurokinin A (Substance K), Methionin-Enkephalin, Leucin-Enkephalin, in a method for the stratification of a subject having an acute or a chronic disease, into either of the categories:

- responder to a medication for treatment of said disease,
- non-responder to a medication for treatment of said disease not showing an unfavourable effect after having received said medication;
- subjects showing an unfavourable effect after having received said medication, wherein said disease effects endothelial function/dysfunction.
Figures

Fig. 1

A

B

C

D

Prop. of patients surviving

Time (weeks)

100%

80%

60%

40%

20%

0%

0 2 4 6 8 10 12

Time (weeks)

100%

80%

60%

40%

20%

0%

0 2 4 6 8 10 12

Time (weeks)

100%

80%

60%

40%

20%

0%

0 2 4 6 8 10 12

Time (weeks)
Fig. 4

A

B

C

D

Prop. of patients surviving

Prop. of patients surviving

Prop. of patients surviving

Prop. of patients surviving

Time (weeks)

Time (weeks)

Time (weeks)

Time (weeks)
Fig. 5

A

Prop. of patients surviving

100%

80%

60%

40%

20%

0%

0 2 4 6 8 10 12

Time (weeks)

B

Prop. of patients surviving

100%

80%

60%

40%

20%

0%

0 2 4 6 8 10 12

Time (weeks)

C

Prop. of patients surviving

100%

80%

60%

40%

20%

0%

0 2 4 6 8 10 12

Time (weeks)

D

Prop. of patients surviving

100%

80%

60%

40%

20%

0%

0 2 4 6 8 10 12

Time (weeks)
Fig. 8

A

B

C

D

Prop. of patients surviving

100%
80%
60%
40%
20%
0%

Time (weeks)

0 2 4 6 8 10 12

100%
80%
60%
40%
20%
0%

Time (weeks)

0 2 4 6 8 10 12

100%
80%
60%
40%
20%
0%

Time (weeks)

0 2 4 6 8 10 12

100%
80%
60%
40%
20%
0%

Time (weeks)

0 2 4 6 8 10 12
Fig. 9

A

B

C

D

Prop. of patients surviving

Prop. of patients surviving

Prop. of patients surviving

Prop. of patients surviving

Time (months)

Time (months)

Time (months)

Time (months)
Fig. 10

A

B

C

D

Prop. of patients surviving

Prop. of patients surviving

Prop. of patients surviving

Prop. of patients surviving

Time (months)

Time (months)

Time (months)

Time (months)
Fig. 11

A

Prop. of patients surviving

100%
80%
60%
40%
20%
0%

0 1 2 3
Time (months)

B

Prop. of patients surviving

100%
80%
60%
40%
20%
0%

0 1 2 3
Time (months)

C

Prop. of patients surviving

100%
80%
60%
40%
20%
0%

0 1 2 3
Time (months)

D

Prop. of patients surviving

100%
80%
60%
40%
20%
0%

0 1 2 3
Time (months)
Fig. 12

A

Prop. of patients surviving

100%

80%

60%

40%

20%

0%

0 1 2 3

Time (months)

B

Prop. of patients surviving

100%

80%

60%

40%

20%

0%

0 1 2 3

Time (months)

C

Prop. of patients surviving

100%

80%

60%

40%

20%

0%

0 1 2 3

Time (months)

D

Prop. of patients surviving

100%

80%

60%

40%

20%

0%

0 1 2 3

Time (months)
Fig. 13
Fig. 14

A

B

C

D

Prop. of patients surviving

Prop. of patients surviving

Prop. of patients surviving

Prop. of patients surviving

Time (months)

Time (months)

Time (months)

Time (months)
Fig. 15

A

B

C

D

Prop. of patients surviving

Prop. of patients surviving

Prop. of patients surviving

Prop. of patients surviving

Time (months)

Time (months)

Time (months)

Time (months)
Fig. 19

A

B

C

D

Prop. of patients surviving vs. time (months)
Fig. 20

A

B

C

D

Prop. of patients surviving

100%

80%

60%

40%

20%

0%

Time (months)

0 1 2 3

100%

80%

60%

40%

20%

0%

Time (months)

0 1 2 3

100%

80%

60%

40%

20%

0%

Time (months)

0 1 2 3

100%

80%

60%

40%

20%

0%

Time (months)

0 1 2 3
Fig. 23

A

B

C

D

Prop. of patients surviving

100%

80%

60%

40%

20%

0%

0 1 2 3

Time (months)

Prop. of patients surviving

100%

80%

60%

40%

20%

0%

0 1 2 3

Time (months)

Prop. of patients surviving

100%

80%

60%

40%

20%

0%

0 1 2 3

Time (months)

Prop. of patients surviving

100%

80%

60%

40%

20%

0%

0 1 2 3

Time (months)
Fig. 24

A

B

C

D

Prop. of patients surviving

Time (months)

Prop. of patients surviving

Time (months)

Prop. of patients surviving

Time (months)

Prop. of patients surviving

Time (months)
Fig. 25

A

B

C

D

Prop. of patients surviving

Prop. of patients surviving

Prop. of patients surviving

Prop. of patients surviving

Time (months)

Time (months)

Time (months)

Time (months)
Fig. 26

A

B

C

D
Fig. 27

A

B

C

D
Fig. 28

A

B

C

D

Prop. of patients surviving

Prop. of patients surviving

Prop. of patients surviving

Prop. of patients surviving

0% 20% 40% 60% 80% 100%

0 1 2 3

Time (months)

0 1 2 3

Time (months)

0 1 2 3

Time (months)

0 1 2 3

Time (months)
Fig. 30

A

Prop. of patients surviving

100%
80%
60%
40%
20%
0%

Time (months)

B

Prop. of patients surviving

100%
80%
60%
40%
20%
0%

Time (months)

C

Prop. of patients surviving

100%
80%
60%
40%
20%
0%

Time (months)

D

Prop. of patients surviving

100%
80%
60%
40%
20%
0%

Time (months)
Fig. 31

A

B

C

D

Prop. of patients surviving

Prop. of patients surviving

Prop. of patients surviving

Prop. of patients surviving

Time (months)

Time (months)

Time (months)

Time (months)
Fig. 33

A

B

C

D

Proportion of patients surviving vs. time (months)

Proportion of patients surviving vs. time (months)
Fig. 34

A

B

C

D

Prop. of patients surviving

Prop. of patients surviving

Prop. of patients surviving

Prop. of patients surviving

Time (months)

Time (months)

Time (months)

Time (months)
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N33/50
ADDITIONAL.

According to International Patent Classification (IPC) or to both national classification and IPC.

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

Electronic data base consulted during the international search (name of data base and, where practical, search terms used).

EPO-Internal, WPI Data, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>DE 10 2006 060835 A1 (BRAHMS AG [DE]) 26 June 2008 (2008-06-26) claims 1-20</td>
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X Further documents are listed in the continuation of Box C

X See patent family annex

* Special category of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered to be solved by the prior art described in the document

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is taken alone

"S" document member of the same patent family

Date of the actual completion of the international search: 10 June 2010

Date of mailing of the international search report: 18/06/2010

Name and mailing address of the ISA/ European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040 Fax (+31-70) 340-3016

Author of the search report: Moreno de Vega, C

Form PCT/ISA/21G (second sheet) (April 2005)

page 1 of 2
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<td>KHAN SOHAIL Q ET AL: &quot;C-terminal provasopressin (copeptin) as a novel and prognostic marker in acute myocardial infarction Leicester acute myocardial infarction peptide (LAMP) study&quot; CIRCULATION, LIPPINCOTT WILLIAMS &amp; WILKINS, US LNKD- DOI:10.1161/CIRCULATIONAHA.106.685503, vol 115, no. 16, 1 April 2007 (2007-04-01), pages 2103-2110, XP002491227 ISSN: 0009-7322</td>
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