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(54) **Use of biomarkers in monitoring a medication in a subject suffering from heart failure**

Verwendung von Biomarkern bei der Überwachung von Medikation in einem Patient mit Herzversagen

Utilisation de biomarqueurs pour le suivi d'une médication d'un sujet souffrant d'une insuffisance cardiaque

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Description

[0001] An aim of modem medicine is to provide personalized or individualized treatment regimens. Those are treatment regimens which take into account a patient's individual needs or risks. Personalized or individual treatment regimens shall be even taken into account for measures where it is required to decide on potential treatment regimens.

[0002] Heart failure (HF) is a major and growing public health problem. It is estimated that approximately 5 million patients in the USA have HF, more than 500 000 patients are diagnosed with HF for the first time each year, and more than 50.000 patients in the US die each year of HF as a primary cause. Heart failure (HF) is one of the main causes of morbidity and mortality in developed countries. Because of aging of the population and greater longevity of patients with cardiovascular disease incidence and prevalence of HF are increasing.

[0003] Identification of people at increased risk of developing HF, ischemic stroke, detrimental non-fatal stroke, myocardial ischemia/ myocardial infarction, arterial aneurysm, chronic kidney failure and finally heart failure and improved risk stratification in patients with early HF (stages A/B according to AHA/ACC classification) is important to initiate appropriate preventive treatment before non-reversible progression of HF or major complications occur.

[0004] Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood and to ensure the body's metabolic needs for supply with blood/oxygen. In such cases, the body tries to compensate lack of supply by structural changes of the myocardium (e.g. fibrosis, apoptosis, necrosis) aiming at maintaining the required supply. First structural changes to the myocardium are, in general, reversible changes but which, when untreated, turn to non reversible permanent changes which finally lead to chronic HF with the final stage of terminal HF.

[0005] HF is classified into various degrees of severity.

[0006] One classification is the so-called NYHA (New York Heart Association) classification. Heart failure patients are classified NYHA classes I, II, III and IV. A patient having heart failure has already experienced structural and functional changes to his pericardium, myocardium, coronary circulation or cardiac valves. He will not be able to fully restore his health, and is in need of a therapeutical treatment. Patients of NYHA Class I have no obvious symptoms of cardiovascular disease but already have objective evidence of functional impairment. Patients of NYHA class II have slight limitation of physical activity. Patients of NYHA class III show a marked limitation of physical activity. Patients of NYHA class IV are unable to carry out any physical activity without discomfort. They show symptoms of cardiac insufficiency at rest.

[0007] This functional classification is supplemented by the more recent classification by the American College of Cardiology and the American Heart Association (see J. Am. Coll. Cardiol. 2001;38;2101-2113, updated in 2005, see J. Am. Coll. Cardiol. 2005;46;e1-e82). 4 stages A, B, C and D are defined. Stages A and B are not HF but are considered to help identify patients early before developing "truly" HF. Stages A and B patients are best defined as those with risk factors for the development of HF. For example, patients with coronary artery disease, hypertension, or diabetes mellitus who do not yet demonstrate impaired left ventricular (LV) function, hypertrophy, or geometric chamber distortion would be considered stage A, whereas patients who are asymptomatic but demonstrate LV hypertrophy (LVH, a phenomenon in which the walls of the ventricles thicken) and/or impaired LV function would be designated as stage B. Stage C then denotes patients with current or past symptoms of HF associated with underlying structural heart disease (the bulk of patients with HF), and stage D designates patients with truly refractory HF.

[0008] Arterial hypertension places increased tension on the left ventricular myocardium that is manifested as stiffness and hypertrophy. Independently thereof, atherosclerosis develops within the coronary vessels as a consequence of hypertension. Subjects with hypertension have increased risk of detrimental non-fatal stroke. Antihypertensive medication may help to reduce the risk of detrimental non-fatal stroke. It is known that subjects suffering from diabetes mellitus are at an elevated risk of suffering from atherosclerosis. Subjects suffering from atherosclerosis are at an elevated risk of ischemic stroke. Antihypertensive medication may help to reduce the risk of ischemic stroke and ischemic heart disease.

[0009] Systolic dysfunction has been found to be associated with an increased risk to develop symptomatic systolic HF. Diastolic dysfunction is believed to be a precursor of diastolic HF. Early treatment of hypertension may improve diastolic function. A large number of individuals with left ventricular dysfunction, systolic as well as diastolic dysfunction, remain undiagnosed and untreated, although early therapy may improve outcome. Untreated hypertension is associated with an increased risk to develop heart failure, which is often is preceded by other cardiovascular and renal events: Hypertension or diabetes leading to ischemic stroke, detrimental non-fatal stroke, myocardial ischemia/ myocardial infarction, arterial aneurysm and finally heart failure, if the patient lives long enough. Persistent hypertension is a leading cause of chronic kidney failure. Early treatment of hypertension may help to prevent disease progression to a variety of cardiovascular as well as renal death risks.

[0010] In general, HF is diagnosed by e.g. echocardiography and Doppler sonography which, however, only permit to diagnose symptomatic later stages of HF. Individuals suffering from presymptomatic forms of HF cannot be diagnosed by these established methods. The poor diagnostics is one of the reasons that the survival rate for individuals diagnosed for HF is only 50% for 5 years.

[0011] According to the state of the art, it is currently recommended to treat patients at risk of heart failure with ACE

inhibitors and/or angiotensin receptor blockers. This includes patients classified into stages A and B according to the ACC/AHA guidelines.

[0012] Starting from stage C (which includes patients with structural heart disease having prior or current symptoms of heart disease) diuretics are recommended which include aldosterone antagonists in selected patients according to the ACC/AHA guidelines. Selected patients include those with moderate to severe heart failure and evidence of recent decompensation (see ACC/AHA guidelines).

[0013] It is appreciated that the effect of ACE inhibitors as well as of angiotensin receptor blockers is affected by functional polymorphisms (see McNamara, Heart Failure Clin 6 (2010), p 35-43, in particular Table 1). It has been shown that the prevalence of aldosterone escape on ACE inhibitors is greatest in the ACE DD genotype (Mc Namara et al, p. 39), supporting the rationale for the use of aldosterone antagonists.

[0014] Collagen formation in heart tissue is preceded by inflammation. It is known that inflammation is present in heart failure patients through activation of the renin-angiotension- aldosterone (RAAS) system, supporting the use of aldosterone antagonists in heart failure. Previously it has been shown that the aldosterone antagonist eplerone reduces collagen formation in heart failure patients as indicated by PIIINP levels (see G. Mak et al, JACC vol 54, no 18, 2009, p 1674-1682, in particular Figure 2). This is further supported by ongoing studies to test the use of aldosterone antagonists in NYHA class II patients (Mc Murray NEJM 362, 228 - 238, 2010, in particular p 236, "Areas of uncertainty").This is however consistent with a recent review indicating that aldosterone promotes collagen synthesis in the heart and promotes maladaptive cardiac remodelling (KIM Y.S., Current Treatment Options in Cardiovascular Medicine 11, 455 - 466, 2009, in particular p. 462, "ARAs").

[0015] WO 2009/138451 describes a method for diagnosing if a subject suffering from dilated cardiomyopathy is suffering from ischemic or non-ischemic dilated cardiomyopathy.

[0016] WO 2010/007041 describes a method for monitoring a subject suffering from heart failure.

[0017] WO 2009/047283 describes a method of diagnosing which medication is to be applied in the remodeling process of a subject after a myocardial infarction.

It was found that cardiac troponins and variants thereof, preferably troponin T or a variant thereof or troponin I or a variant thereof, in particular troponin T or a variant thereof, and GDF-15 or a variant thereof and, optionally, a natriuretic peptide selected from ANP type and BNP type natriuretic peptides and variants thereof, preferably BNP or a variant thereof or NT-proBNP or a variant thereof, in particular NT-proBNP or a variant thereof, give relevant information on the efficacy of treatment of the aforementioned subjects.

[0018] Accordingly, the present invention relates to method of monitoring a medication in a subject subjected to said medication, said medication being selected from ACE inhibitors, angiotension receptor blockers and aldosterone antagonists, said subject suffering from heart failure or stages preceding heart failure including risk factors for heart failure, the method comprising the steps of

a) measuring in a blood, serum or plasma sample obtained from the subject the concentrations of at least one cardiac troponin or a variant thereof and/or a natriuretic peptide or a variant thereof,
b) measuring in a blood, serum or plasma sample the concentration of GDF-15 or a variant thereof, and
c) monitoring the medication by comparing the thus determined concentrations with a reference amount,

wherein, if the concentrations of a cardiac troponin, in particular troponin T, and GDF-15 are measured, a ratio of the cardiac troponin and GDF-15 (cardiac Troponin/GDF-15) is formed, or
wherein, if the concentrations of a natriuretic peptide, in particular NT-proBNP, and GDF-15 are measured, a ratio of the natriuretic peptide and GDF-15 (natriuretic peptide/GDF-15) is formed.

[0019] Moreover, the present invention relates to a method of deciding on the adaptation of a medication selected from ACE inhibitors, angiotension receptor blockers and aldosterone antagonists in a subject subjected to said medication and suffering from heart failure or stages preceding heart failure including risk factors for heart failure, the method comprising the steps of

a) measuring in a blood, serum or plasma sample obtained from the subject the concentrations of at least one cardiac troponin or a variant thereof and/or a natriuretic peptide or a variant thereof,
b) measuring in a blood, serum or plasma sample the concentration of GDF-15 or a variant thereof, and
c) deciding on the adaptation of the medication by comparing the thus determined concentrations with a reference amount,

wherein, if the concentrations of a cardiac troponin, in particular troponin T, and GDF-15 are measured, a ratio of the cardiac troponin and GDF-15 (cardiac Troponin/GDF-15) is formed, or
wherein, if the concentrations of a natriuretic peptide, in particular NT-proBNP, and GDF-15 are measured, a ratio of the natriuretic peptide and GDF-15 (natriuretic peptide/GDF-15) is formed.

[0020] In an embodiment of the aforementioned methods, the medication is an ACE inhibitor.

[0021] In an embodiment of the aforementioned methods , a ratio of troponin T/GDF-15 of equal to or higher than about 0.01, preferably equal to higher than about 0.017, is indicative that the medication is appropriate and should not be changed, and/or a ratio troponin T/GDF-15 of lower than about 0.01, preferably lower than about 0.005 is indicative that the medication is not appropriate and should be adapted.

[0022] In an embodiment of the aforementioned methods, a ratio of NT-proBNP /GDF-15 of equal to or higher than about 0.8, preferably equal to or higher than about 1.9, is indicative that the medication is appropriate and should not be changed, and/or a ratio NT-proBNP /GDF-15 of lower than about 0.7, preferably lower than about 0.4 is indicative that the medication is not appropriate and should be adapted.

general definitions

[0023] Heart failure can be classified into a functional classification system according to the New York Heart Association (NYHA). Patients of NYHA Class I have no obvious symptoms of cardiovascular disease but already have objective evidence of functional impairment. Physical activity is not limited, and ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath). Patients of NYHA class II have slight limitation of physical activity. They are comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea. Patients of NYHA class III show a marked limitation of physical activity. They are comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea. Patients of NYHA class IV are unable to carry out any physical activity without discomfort. They show symptoms of cardiac insufficiency at rest. Heart failure, i.e., an impaired systolic and/or diastolic function of the heart, can be determined also by, for example, echocardiography, angiography, scintigraphy, or magnetic resonance imaging. This functional impairment can be accompanied by symptoms of heart failure as outlined above (NYHA class II-IV), although some patients may present without significant symptoms (NYHA I).

[0024] The present invention refers to the more recent ACC/AHA classification of heart failure, see introductory part, identifying 4 stages involved in the development of the HF syndrome. The first 2 stages (A and B) are clearly not HF but are an attempt to help healthcare providers identify patients early who are at risk for developing HF. Stages A and B patients are best defined as those with risk factors that clearly predispose toward the development of HF. Stage C then denotes patients with current or past symptoms of HF associated with underlying structural heart disease, and Stage D designates patients with truly refractory HF who might be eligible for specialized, advanced treatment strategies such as mechanical circulatory support, procedures to facilitate fluid removal, continuous inotropic infusions, or cardiac transplantation or other innovative or experimental surgical procedures, or for end-of-life care, such as hospice. This classification recognizes that there are established risk factors and structural prerequisites for the development of HF and that therapeutic interventions introduced even before the appearance of LV dysfunction or symptoms can reduce the population morbidity and mortality of HF.

[0025] The definition of the various stages is as follows (taken from the ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult, J. Am. Coll. Cardiol. 2001;38;2101-2113). The following includes a description of the stage and examples for pathophysiological states in individuals which would be classified in the respective stage.

Stage A:

[0026] Description: Patients at high risk of developing HF because of the presence of conditions that are strongly associated with the development of HF. Such patients have no identified structural or functional abnormalities of the pericardium, myocardium, coronary circulation or cardiac valves and have never shown signs or symptoms of HF.

[0027] Examples: Systemic hypertension; coronary artery disease; diabetes mellitus; history of cardiotoxic drug therapy or alcohol abuse; personal history of rheumatic fever; family history of cardiomyopathy.

Stage B:

[0028] Description: Patients who have developed structural heart disease that is strongly associated with the development of HF but who have never shown signs or symptoms of HF.

[0029] Examples: Left ventricular hypertrophy or fibrosis; left ventricular dilatation or hypocontractility; asymptomatic valvular heart disease; previous myocardial infarction.

Stage C:

[0030] Description: Patients who have current or prior symptoms of HF associated with underlying structural heart disease.

[0031] Examples: Dyspnea or fatigue due to left ventricular systolic dysfunction; asymptomatic patients who are undergoing treatment for prior symptoms of HF.

Stage D:

[0032] Description: Patients with advanced structural heart disease and marked symptoms of HF at rest despite maximal medical therapy and who require specialized interventions.
Examples: Patients who are frequently hospitalized for HF or cannot be safely discharged from the hospital; patients in the hospital awaiting heart transplantation; patients at home receiving continuous intravenous support for symptom relief or being supported with a mechanical circulatory assist device; patients in a hospice setting for the management of HF.

[0033] The ACC/AHA stages A, B, C and D specified beforehand are referred to in the context of the present invention as "stage A", "stage B", "stage C", and "stage D".

[0034] In the context of the methods of the present invention, functional and/or structural abnormalities of the heart preceding heart failure and/or preceding left ventricular hypertrophy shall be diagnosed. The term "abnormalities" as used herein, preferably, is intended to mean "at least one abnormality". Thus, one abnormality or more than one abnormality may be diagnosed in the context of the methods decribed herein.
The term "functional and/or structural abnormalities of the heart preceding heart failure" relates to several pathological states of the myocardium which are known in the art to typically occur prior to heart failure (i.e. they typically precede heart failure). Functional and/or structural abnormalities of the heart preceding heart failure, in the sense of the present invention, are generally symptomless functional and/or structural abnormalities of the heart preceding heart failure. Functional and/or structural abnormalities of the heart preceding heart failure may disappear after removing the underlying cause or by training exercise. Functional and/or structural abnormalities of the heart preceding heart failure, in particular symptomless functional and/or structural abnormalities of the heart preceding heart failure, may also develop into heart failure.
The term "functional and/or structural abnormalities of the heart preceding heart failure" as used in the present invention relates to functional and/or structural change and/or a functional and/or structural damage of the myocardium, epicardium, coronary circulation or valves, and is to be regarded as a functional abnormality of the heart and/or a structural abnormality of the heart. An example for a functional abnormality of the heart is an impaired pumping or filling capacity, often a systolic or a diastolic impairment. An example for a structural abnormality of the heart is a change in the geometry of the left ventricle. Often, the structural and/or functional heart abnormality/impairment is reversible when the underlying cause is remedied (e.g. when appropriately treated) without leaving permanent structural or functional damage to the myocardium typical for heart failure (i.e. an individual classified in stage B can enter back into stage A). An individual having functional and/or structural abnormalities of the heart preceding heart failure does not show signs of heart failure (thus the individual, preferably) is apparently healthy).

[0035] Heart failure is a condition that can result from any structural or functional cardiac disorder that impairs the ability of the heart to fill with or pump a sufficient amount of blood throughout the body. Heart failure is a chronic disease; it can, inter alia, occur either following an acute cardiovascular event (like myocardial infarction), or it can occur e.g. as a consequence of inflammatory or degenerative changes in myocardial tissue.
The term "heart failure" as used herein relates to an impaired systolic and/or diastolic function of the heart being accompanied by overt signs of heart failure as known to the person skilled in the art. Preferably, heart failure referred to herein is also chronic heart failure. Heart failure according to the present invention includes overt and/or advanced heart failure. In overt heart failure, the subject shows symptoms of heart failure as known to the person skilled in the art. The term "heart failure" as used herein refers to stages C and D of the ACC/AHA classification; in these stages, the subject shows typical symptoms of heart failure. i.e. the subject is not apparently healthy. The subject having heart failure and being classified into stage C or D has undergone permanent, non reversible structural and/or functional changes to his myocardium, and as a consequence of these changes, full health restoration is not possible. A subject having attained stage C or even D of the ACC/AHA classification cannot go back to stage B or even A.

[0036] Risk factors for heart failure are known to the person skilled in the art and include the following: hypertension; age, systolic and diastolic hypertension; coronary artery disease (CAD); subclinical organ damage, e.g. of the heart, brain, kidneys, blood vessels; obesity, preferably obesity defined as body mass index BMI < 25kg/m^2; adipositas; metabolic syndrome; diabetes mellitus type 1 or type 2, in particular type 2 diabetes mellitus; type 1 diabetes with microalbuminuria, cigarette smoking; history of revascularization; history of cardiotoxic drug therapy or alcohol abuse; dyslipidemia; total cholesterol, total cholesterol/HDL-cholesterol ratio, personal history of rheumatic fever; family history of cardiomyopathy.

[0037] It is to be understood that the above list is not exhaustive. A more exhaustive citation of risk factors is found in the 2007 Guidelines for the Management of Arterial Hypertension, European Heart Journal (2007) 28, 1462-1536 which is incorporated herein in its entirety in respect to the risk factors, in particular tables 1, 2 and 3 and figure 1.

[0038] Individual risk factors comprise the risk of CVD and of developing fatal atherosclerotic events, which is calculated

using the SCORE system available from the European Society of Hypertension (European Society of Hypertension Scientific Newsletter 2010, 11, No 48). According to the recommended scoring system of the ESC of Hypertension based on the number and levels of risk factors different risk groups are formed (low, low-moderate ...) and accordingly therapy is adapted.

An individual suffering from one or more of the risk factors as specified beforehand and not having symptoms of heart failure (apparently healthy) will in general and preferably be classified into ACC/AHA stage A in case no functional and/or structural abnormalities of the heart preceding heart failure is diagnosed in the individual.

[0039] It is important to note that the criteria are not ambiguous and the classification of an individual may vary depending on the physician carrying out examination. The first criterium for the classification of an individual in stage A (and also in stages B, C and D) of the ACC/AHA classification is the description of the patient (see the above definition of the ACC/AHA classification, as taken from the original publication of the Guidelines). The examples for risk factors/pathophysiological state of each stage cannot be exhaustive, as becomes clear from an inspection of the original publications. This means that, in the context of the present invention, an individual will in general and preferably be classified into stage A of the ACC/AHA classification even in case the risk factors which the individual bears are not explicitly cited in the guidelines.

[0040] In an embodiment of the present invention, the individual bearing risk factors of developing heart failure is an individual which has been classified into ACC/AHA stage A prior to carrying out the methods according to the present invention. The individual classified in stage A may have experienced physiological changes towards pathophysiological states belonging to ACC/AHA stage B (i.e. functional and/or structural abnormalities of the heart preceding heart failure). In the context of the present invention, this state is referred to as "early stage of functional and/or structural abnormalities of the heart preceding heart failure" (early stage B) and is different from a "late stages of functional and/or structural abnormalities of the heart preceding heart failure" (late stage B). Preferably, the individual does not show obvious symptoms of heart failure. It is even more preferred if the individual does not show left ventricular hypertrophy (i.e. the individual is apparently healthy).

The terms "individual", "subject" and "patient" may be used interchangeably herein and relate to an animal, preferably a mammal, and, more preferably, a human.

The term "cardiac Troponin" refers to all Troponin isoforms expressed in cells of the heart and, preferably, the subendocardial cells. These isoforms are well characterized in the art as described, e.g., in Anderson 1995, Circulation Research, vol. 76, no. 4: 681-686 and Ferrieres 1998, Clinical Chemistry, 44: 487-493. Preferably, cardiac Troponin refers to Troponin T and/or Troponin I, and, most preferably, to Troponin T. It is to be understood that isoforms of Troponins may be determined in the method of the present invention together, i.e. simultaneously or sequentially, or individually, i.e. without determining the other isoform at all. Amino acid sequences for human Troponin T and human Troponin I are disclosed in Anderson, loc cit and Ferrieres 1998, Clinical Chemistry, 44: 487-493.

[0041] The term "cardiac Troponin" encompasses also variants of the aforementioned specific Troponins, i.e., preferably, of Troponin I, and more preferably, of Troponin T. Such variants have at least the same essential biological and immunological properties as the specific cardiac Troponins. In particular, they share the same essential biological and immunological properties if they are detectable by the same specific assays referred to in this specification, e.g., by ELISA Assays using polyclonal or monoclonal antibodies specifically recognizing the said cardiac Troponins. Moreover, it is to be understood that a variant as referred to in accordance with the present invention shall have an amino acid sequence which differs due to at least one amino acid substitution, deletion and/or addition wherein the amino acid sequence of the variant is still, preferably, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 92%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% identical with the amino sequence of the specific Troponin. Variants may be allelic variants or any other species specific homologs, paralogs, or orthologs. Moreover, the variants referred to herein include fragments of the specific cardiac Troponins or the aforementioned types of variants as long as these fragments have the essential immunological and biological properties as referred to above. Preferably, the cardiac troponin variants have immunological properties (i.e. epitope composition) comparable to those of human troponin T or troponin I. Thus, the variants shall be recognizable by the aforementioned means or ligands used for determination of the concentration of the cardiac troponins. Thus, the variants shall be recognizable by the aforementioned means or ligands used for determination of the concentration of the cardiac troponins. Such fragments may be, e.g., degradation products of the Troponins. Further included are variants which differ due to posttranslational modifications such as phosphorylation or myristylation. Preferably the biological property of troponin I and its variant is the ability to inhibit actomyosin ATPase or to inhibit angiogenesis in vivo and in vitro, which may e.g. be detected based on the assay described by Moses et al. 1999 PNAS USA 96 (6): 2645-2650). Preferably the biological property of troponin T and its variant is the ability to form a complex with troponin C and I, to bind calcium ions or to bind to tropomyosin, preferably if present as a complex of troponin C, I and T or a complex formed by troponin C, troponin I and a variant of troponin T. It is known that low concentrations of circulating cardiac troponin may be detected in subjects at various conditions, but further studies are required to understand their respective role and rate (Masson et al., Curr Heart Fail Rep (2010) 7:15-21).

[0042] The term "Growth-Differentiation Factor-15" or "GDF-15" relates to a polypeptide being a member of the transforming growth factor (TGF)-β cytokine superfamily. The terms polypeptide, peptide and protein are used interchangeable throughout this specification. GDF-15 was originally cloned as macrophage-inhibitory cytokine-1 and later also identified as placental transforming growth factor-β, placental bone morphogenetic protein, non-steroidal anti-inflammatory drug-activated gene-1, and prostate-derived factor (Bootcov loc cit; Hromas, 1997 Biochim Biophys Acta 1354:40-44; Lawton 1997, Gene 203:17-26; Yokoyama-Kobayashi 1997, J Biochem (Tokyo), 122:622-626; Paralkar 1998, J Biol Chem 273:13760-13767). Similar to other TGF-β-related cytokines, GDF-15 is synthesized as an inactive precursor protein, which undergoes disulfide-linked homodimerization. Upon proteolytic cleavage of the N-terminal pro-peptide, GDF-15 is secreted as a ~28 kDa dimeric protein (Bauskin 2000, Embo J 19:2212-2220). Amino acid sequences for GDF-15 are disclosed in WO99/06445, WO00/70051, WO2005/113585, Bottner 1999, Gene 237: 105-111, Bootcov loc. cit, Tan loc. cit., Baek 2001, Mol Pharmacol 59: 901-908, Hromas loc cit, Paralkar loc cit, Morrish 1996, Placenta 17:431-441 or Yokoyama-Kobayashi loc cit.. GDF-15 as used herein encompasses also variants of the aforementioned specific GDF-15 polypeptides. Such variants have at least the same essential biological and immunological properties as the specific GDF-15 polypeptides. In particular, they share the same essential biological and immunological properties if they are detectable by the same specific assays referred to in this specification, e.g., by ELISA assays using polyclonal or monoclonal antibodies specifically recognizing the said GDF-15 polypeptides. A preferred assay is described in the accompanying Examples. Moreover, it is to be understood that a variant as referred to in accordance with the present invention shall have an amino acid sequence which differs due to at least one amino acid substitution, deletion and/or addition wherein the amino acid sequence of the variant is still, preferably, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 92%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% identical with the amino sequence of the specific GDF-15 polypeptides, preferably with the amino acid sequence of human GDF-15, more preferably over the entire length of the specific GDF-15, e.g. of human GDF-15. The degree of identity between two amino acid sequences can be determined by algorithms well known in the art. Preferably, the degree of identity is to be determined by comparing two optimally aligned sequences over a comparison window, where the fragment of amino acid sequence in the comparison window may comprise additions or deletions (e.g., gaps or overhangs) as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment. The percentage is calculated by determining the number of positions at which the identical amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity. Optimal alignment of sequences for comparison may be conducted by the local homology algorithm of Smith and Waterman Add. APL. Math. 2:482 (1981), by the homology alignment algorithm of Needleman and Wunsch J. Mol. Biol. 48:443 (1970), by the search for similarity method of Pearson and Lipman Proc. Natl. Acad. Sci. (USA) 85: 2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, PASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by visual inspection. Given that two sequences have been identified for comparison, GAP and BESTFIT are preferably employed to determine their optimal alignment and, thus, the degree of identity. Preferably, the default values of 5.00 for gap weight and 0.30 for gap weight length are used. Variants referred to above may be allelic variants or any other species specific homologs, paralogs, or orthologs. Moreover, the variants referred to herein include fragments of the specific GDF-15 polypeptides or the aforementioned types of variants as long as these fragments have the essential immunological and biological properties as referred to above. Such fragments may be, e.g., degradation products of the GDF-15 polypeptides. Further included are variants which differ due to post-translational modifications such as phosphorylation or myristylation.

[0043] The expression "comparing the concentration ... to the concentration as established in a control sample" is merely used to further illustrate what is obvious to the skilled artisan anyway. The control sample may be an internal or an external control sample. In one embodiment an internal control sample is used, i.e. the marker level(s) is(are) assessed in the test sample as well as in one or more other sample(s) taken from the same subject to determine if there are any changes in the level(s) of said marker(s). In another embodiment an external control sample is used. For an external control sample the presence or concentration of a marker in a sample derived from the individual is compared to its presence or concentration in an individual known to suffer from, or known to be at risk of, a given condition; or an individual known to be free of a given condition, i.e., "normal individual". Depending on the intended diagnostic use an appropriate control sample is chosen and a control or reference value for the marker established therein. It will be appreciated by the skilled artisan that such control sample in one embodiment is obtained from a reference population that is age-matched and free of confounding diseases. As also clear to the skilled artisan, the absolute marker values established in a control sample will be dependent on the assay used. Preferably samples from 100 well- characterized individuals from the appropriate reference population are used to establish a control (reference) value. Also preferred the reference population may be chosen to consist of 20, 30, 50, 200, 500 or 1000 individuals. Healthy individuals represent a preferred reference population for establishing a control value.

[0044] The term "deciding" as used herein means assessing as to whether a certain medication or treatment should

be administered to a subject having undergone the test according to the present invention.

[0045] Determining the concentration of a cardiac troponin or a variant thereof and, as the case may be, GDF-15 or a variant thereof, or any other peptide or polypeptide referred to in this specification relates to measuring the concentration or concentration, preferably semi-quantitatively or quantitatively. Measuring can be done directly or indirectly. Direct measuring relates to measuring the concentration or concentration of the peptide or polypeptide based on a signal which is obtained from the peptide or polypeptide itself and the intensity of which directly correlates with the number of molecules of the peptide present in the sample. Such a signal - sometimes referred to herein as intensity signal -may be obtained, e.g., by measuring an intensity value of a specific physical or chemical property of the peptide or polypeptide. Indirect measuring includes measuring of a signal obtained from a secondary component (i.e. a component not being the peptide or polypeptide itself) or a biological read out system, e.g., measurable cellular responses, ligands, labels, or enzymatic reaction products.

[0046] There are provided methods of therapy monitoring and therapy adaptation in a subject receiving administration of a medicament selected from ACE inhibitors, angiotensin receptor blockers and aldosterone antagonists, or any combination of the aforecited documents and, as the case may be, in addition to any further medicament or combination of medicaments known for the treatment of the hereinafter cited diseases. The method of the present invention, in particular, permits to decide on the administration of aldosterone antagonists, optionally in addition to ACE inhibitors and angiotensin receptor blockers.

[0047] In one embodiment, the subject has heart failure, in particular the subject is classified into stage C of the ACC/AHA system. In a further embodiment, the individual suffers from structural and/or functional abnormalities of the heart preceding heart failure.

[0048] It was found by the present inventors that cardiac troponins and variants thereof, preferably troponin T or a variant thereof or troponin I or a variant thereof, in particular troponin T or a variant thereof, and GDF-15 or a variant thereof and, optionally, a natriuretic peptide selected from ANP type and BNP type natriuretic peptides and variants thereof, preferably BNP or a variant thereof or NT-proBNP or a variant thereof, in particular NT-proBNP or a variant thereof, give relevant information on the efficacy of treatment of the aforementioned subjects. On the one hand, these subjects are those having heart failure, in particular being classified into stage C of the ACC/AHA system. On the other hand, the subjects have risk factors of suffering from heart failure and are, preferably, classified into stage A of the ACC/AHA classification, or suffer from structural and/or functional abnormalities of the heart preceding heart failure and are, preferably, classified into stage B of the ACC/AHA classification.

[0049] In particular, the amounts of GDF-15, NT-proBNP and Troponin T were determined in 97 patients with overt heart failure. All patients were on beta blocker as well as on ACE inhibitor therapy, 59 patients were on aldosterone antagonists, 38 did not receive aldosterone antagonists After the determination of the amounts of the aforementioned markers, the ratio of NT-pro BNP and GDF 15 and the ratio of Troponin T and GDF-15 was formed. Interestingly, it was found that the ratios in the group of aldosterone antagonist group were higher than in the group of patients not treated with aldosterone antagonists. Therefore, the determination of the GDF-15 in combination with a natriuretic peptide or a cardiac Troponin shall allow for making decisions on the therapy adaption in patients treated with an ACE inhibitor, an angiotensin receptor antagonist, or aldosterone antagonists (or combinations thereof). In particular, said determination shall allow for making decisions on the therapy adaption in patients treated with an ACE inhibitor. The aformentioned medicaments, in particular ACE inhibitors, sometimes become less effective resulting in an increased level of inflammation. In this case, a therapy adaptation with aldosterone antagonists as described herein below would be useful since aldosterone antagonists allow for reducing the level of inflammation. The methods described herein below allow for identifying subjects which may benefit from a therapy adaptation.

[0050] While ACE inhibitors and angiotension receptor blockers (ARBs) have been shown to be effective in large randomized trials there is currently no method available to diagnose the effectiveness of these drugs in the individual patient. This is in contrast to the application of these drugs in patients with kidney disease where the decrease of urinary albumin can be used to verify treatment success. Thus the method described offers for the first time a method for the diagnosis of treatment failure and provides guidance for improved treatment using aldosterone inhibitors or in the future drugs that inhibit synthesis of aldosterone.

[0051] In one embodiment of the invention, a medication which has been initiated in a subject according to the invention is monitored (i.e. it is assessed whether the medication is effective).

[0052] In a further embodiment of the invention, a decision on the adaptation of the medication is made, preferably in accordance with the results of the monitoring of the medication. In a particular preferred embodiment, it is decided if administration of an aldosterone antagonists is appropriate. It may also be conceived to administrate one or more aldosterone synthetase inhibitors, see Roumen L. et al J Medical Chemistry 2010, 53 1712 -25.

[0053] The present invention therefore furthermore provides a method of monitoring a medication which has been initiated in a subject suffering from heart failure or preceding heart failure including risk factors for heart failure, based on the comparison of the concentrations of at least on cardiac troponin or a variant thereof, and optionally of one or more other markers of heart failure, to the concentration of this or these marker(s) in a control sample.

[0054] The method of the invention may comprise the following steps: a) measuring in a sample obtained from the subject the concentration of at least one cardiac troponin or a variant thereof; b) measuring in a sample the concentration of GDF-15 or a variant thereof, c) monitoring the medication by comparing the thus determined concentrations with a reference amount, e.g. in a control sample.

[0055] Preferably, monitoring is carried out by comparing the determined concentrations with a reference amount.

[0056] Accordingly, the present invention provides a method of monitoring a medication to which a subject suffering from heart failure or stages preceding heart failure including risk factors for heart failure is subjected, said medication being selected from ACE inhibitors, angiotension receptor blockers and aldosterone antagonists the method comprising the steps of

a) measuring in a blood, serum or plasma sample obtained from the subject the concentration of at least one cardiac troponin or a variant thereof and/or a natriuretic peptide or a variant thereof,
b) measuring in a blood, serum or plasma the concentration of GDF-15 or a variant thereof,
c) monitoring the medication by comparing the thus determined concentrations with a reference amount,

wherein, if the concentrations of a cardiac troponin, in particular troponin T, and GDF-15 are measured, a ratio of the cardiac troponin and GDF-15 (cardiac Troponin/GDF-15) is formed, or
wherein, if the concentrations of a natriuretic peptide, in particular NT-proBNP, and GDF-15 are measured, a ratio of the natriuretic peptide and GDF-15 (natriuretic peptide/GDF-15) is formed.

[0057] The present invention furthermore provides a method of decision on the adaptation of a medication which has been initiated in a subject suffering from heart failure or stages preceding heart failure including risk factors for heart failure, based on the comparison of the concentrations of at least on cardiac troponin or a variant thereof, and optionally of one or more other markers of heart failure, to the concentration of this or these marker(s) in a control sample.

[0058] The method of the invention may comprise the following steps: a) repeatedly measuring in a sample obtained from the subject the concentrations of at least one cardiac troponin or a variant thereof; b) repeatedly measuring in a sample the concentration of GDF-15 or a variant thereof, c) deciding on the adaptation of the medication by comparing the thus determined concentrations with a reference amount.

[0059] Preferably, the decision on adaptation is carried out by comparing the determined concentrations with a reference amount.

[0060] The present invention therefore also provides a method of deciding on the adaptation of a medication selected from ACE inhibitors, angiotension receptor blockers and aldosterone antagonists in a subject subjected to said medication and suffering from heart failure or stages preceding heart failure including risk factors for heart failure, the method comprising the steps of

a) measuring in a blood, serum or plasma sample obtained from the subject the concentrations of at least one cardiac troponin or a variant thereof and/or a natriuretic peptide or a variant thereof,
b) measuring in a blood, serum or plasma sample the concentration of GDF-15 or a variant thereof, and
c) deciding on the adaptation of the medication by comparing the thus determined concentrations with a reference amount,

wherein, if the concentrations of a cardiac troponin, in particular troponin T, and GDF-15 are measured, a ratio of the cardiac troponin and GDF-15 (cardiac Troponin/GDF-15) is formed, or
wherein, if the concentrations of a natriuretic peptide, in particular NT-proBNP, and GDF-15 are measured, a ratio of the natriuretic peptide and GDF-15 (natriuretic peptide/GDF-15) is formed.

[0061] In a preferred embodiment of the present invention, the determination of the cardiac troponin and, optionally, the one or more other markers of heart failure is carried out repeatedly, i.e. at least 2 times, and preferably within a given time interval or time intervals.

[0062] A definition of the term "subject" has been given elsewhere herein. The definition applies accordingly. Preferably, the subject in the context of the method of deciding on the adaptation of a medication and the subject in the context of the method of monitoring a medication (both methods based on the determination of the amount of GDF-15 in combination with a natriuretic peptide and a cardiac Troponin), preferably, shall not have exhibited and acute coronary syndrome within at least 2 weeks, or, more preferably, within at least 4 week before the sample for carrying out the method has been obtained. Also preferably, the subject does not suffer from acute inflammation, in particular from the systemic inflammatory response syndrome (SIRS), at the time at which the sample for carrying out the method has been obtained.

[0063] The medication is selected from ACE inhibitors, angiotension receptor blockers and aldosterone antagonists. In particular, the medication is an ACE inhibitor.

[0064] Examples for these classes of drugs are the following:

ACE inhibitors: Enalapril, Captopril, Ramipril, Trandolapril; preferably Enalapril
angiotensin receptor blockers: Losartan, Valsartan, Irbesartan, Candesartan, Telmisartan, Eprosartan; preferably Losartan
aldosterone antagonists: Eplerenone, Spironolactone, Canrenone, Mexrenone, Prorenone, preferably, Spironolactone, more preferably, Eplerenone.

[0065] As described above the recommendation of ACE inhibitors in stages A and B suggests the need for antiinflammatory treatment, however because of polymorphisms this appears not to be effective in all cases. Aldosterone antagonists are considered to be useful also in patients belonging to stages A und B of the ACC/AHA classification, preferably in cases where ACE inhibitors and angiotensin receptor blockers are not effective.

[0066] Lack of effectiveness of ACE inhibitors and angiotensin receptor blockers can be identified by the present method of the invention. This applies, on the one hand, for subjects not suffering from heart failure, but having risk factors of developing heart failure, preferably subjects classified in stage A; on the other hand, the method applies to subjects suffering from functional and/or structural abnormalities of the heart preceding heart failure, preferably subjects classified in stage B. The method of the present invention also lends itself for subjects having non reversible structural damage of the heart (i.e. heart failure), preferably subjects classified in stage C.

[0067] In the context of the present invention, effectiveness of treatment with a medicament from the group ACE inhibitors, angiotensin receptor blockers and aldosterone antagonists is assessed by the concentrations of a cardiac troponin and variants thereof, preferably troponin T or a variant thereof or troponin I or a variant thereof, in particular troponin T or a variant thereof, in connection with the concentrations of GDF-15 or a variant thereof. In a further embodiment, effectiveness of treatment is assessed by the concentrations of a natriuretic peptide, preferably BNP or NT-proBNP, in particular NT-proBNP, in connection with the concentrations of GDF-15.

[0068] As clear from the foregoing, increased concentrations of a cardiac troponin in a subject indicate that the subject either suffers from functional and/or structural abnormalities of the heart preceding heart failure, or is already suffering from heart failure. Increased concentrations of a cardiac troponin may also indicate that the subject suffers from coronary artery disease; as known to the person skilled in the art, here the concentrations of a cardiac troponin may be increased in respect to healthy individuals.

[0069] Increased concentrations of a natriuretic peptide in a subject indicate that the subject either suffers from functional and/or structural abnormalities of the heart preceding heart failure, or is already suffering from heart failure. Increased concentrations of a natriuretic peptide may also indicate that the subject suffers from coronary artery disease; as known to the person skilled in the art, here the concentrations of a natriuretic peptide may be increased in respect to healthy individuals.

[0070] It is also clear from the foregoing that an increased concentration of GDF-15 in a subject is not only indicative of heart failure, but also indicates inflammatory processes occuring in the myocardium of the individual. Accordingly, if the concentration of GDF-15 is not increased or only slightly increased in respect to healthy individuals, this is indicative for no or a low number of inflammatory processes occuring in the myocardium. On the contrary, increased or highly increased concentrations of GDF-15 or a variant thereof in a subject show the occurance of inflammatory processes in the individual's myocardium.

[0071] The person skilled in the art is able to conclude the information necessary for the therapy monitoring and/or therapy adaptation from the respective values of the cardiac troponin or a variant thereof and concentrations of GDF-15 and variants thereof. For example, a only slightly increased concentration (in respect to healthy individuals) of a cardiac troponin or a variant thereof, preferably troponin I or a variant thereof or troponin I or a variant thereof, in particular troponin T or a variant thereof, in connection with an increased or even highly increased concentration of GDF-15 or a variant thereof indicates that the subject does not suffer from heart failure, but that a considerable number of inflammatory processes are ongoing in his myocardium, pointing to the danger of development of heart failure and that medication is not effective, with an adaptation being recommended (for an explanation of the therapy adaptation, please see elsewhere herein). Accordingly, an increased level (or highly increased level) of GDF-15 in combination with a slightly increased level of a cardiac troponin indicates that the therapy, in particular the therapy with an ACE inhibitor, shall be adapted.

[0072] On the other hand, a highly increased concentration (in espect to healthy individuals) of a cardiac troponin, preferably troponin I or troponin I, in particular troponin T or a variant thereof, in connection with an only slightly increased concentration of GDF-15 or a variant thereof indicates that the subject suffers from heart failure, but that inflammatory processes are moderate and that medication is effective and an adaptation is not necessary. Accordingly, a highly increased level of a cardiac Troponin in combination with a slightly increased level of GDF-15 indicates that the therapy, in particular the therapy with an ACE inhibitor, that an adaption of the therapy is not necessary, and, thus, that the therapy can be continued.

[0073] The person skilled in the art is aware that various intermediate constellations of the concentrations of the above-cited markers exist, indicating various degrees of efficacy of medicament administration.

[0074] In a preferred embodiment of the instant embodiment of the present invention, the ratio cardiac troponin /GDF

15 is formed, with the cardiac troponin being preferably troponin T or troponin I, in particular troponin T. By this, often a more profound information in respect to the treatment of the respective subject can be obtained. In general, a high ratio cardiac troponin/GDF-15 is often indicative of an appropriate medication suppressing inflammatory processes. Accordingly, a high ratio of the amount of a cardiac troponin to the amount of GDF-15, preferably, indicates that no adaption of the therapy is necessary, and, thus, that the therapy can be continued. Accordingly, a low ratio of the amount of a cardiac troponin to the amount of GDF-15 indicates that the therapy shall be adapted.

[0075] In a preferred embodiment of the aforementioned method the ratio of the amount of a cardiac troponin to the amount of GDF-15 is formed, and compared to a reference ratio of the amount of a cardiac troponin to the amount of GDF-15. Preferably, the reference ratio is derived from a subject for whom no therapy adaptation is necessary, or from a subject for whom the therapy shall be adapted (and, thus, from a subject who will benefit from therapy adaptation).

[0076] Preferably, an increased ratio of the amount of a cardiac troponin to the amount of GDF-15 in the sample from the subject to be tested as compared to the reference ratio indicates that no adaption of the therapy is necessary, and, thus, that the therapy can be continued (and thus, that the therapy shall not be changed), whereas a decreased ratio of the amount of a cardiac troponin to the amount of GDF-15 in the sample from the subject to be tested as compared to the reference ratio indicates that the therapy shall be adapted. Preferred reference ratios are mentioned herein below.

[0077] In an even more preferred embodiment of the present invention, the above mentioned ratio cardiac troponin /GDF 15 is used in connection with the individual concentrations

[0078] In general, a ratio troponin T/GDF-15 of ≥ (equal to or higher than) about 0.01, preferably about 0.017, is indicative that the medication is appropriate and should not be changed. On the contrary, a ratio troponin T/GDF-15 of < (lower than) about 0.01, preferably about 0.005 is indicative that the medication is not appropriate and should be adapted.

[0079] In a further embodiment of the present invention, the ratio natriuretic peptide/GDF-15 is formed. The natriuretic peptide is preferably a BNP type or an ANP type natriuretic peptide, even more preferably BNP or NT-proBNP, in particular NT-proBNP.

[0080] In further preferred embodiment embodiment of the aforementioned method the ratio of the amount of a natriuretic peptide to the amount of GDF-15 is formed, and compared to a reference ratio of the amount of a natriuretic peptide to the amount of GDF-15. Preferably, the reference ratio is derived from a subject for which no therapy adaptation is necessary, or from a subject for which the therapy shall be adapted (and, thus, a subject who will benefit from therapy adaptation).

[0081] Preferably, an increased ratio of the amount of a natriuretic peptide to the amount of GDF-15 in the sample from the subject to be tested as compared to the reference ratio indicates that no an adaption of the therapy is necessary, and, thus, that the therapy can be continued (and thus, shall not be changed), whereas a decreased ratio of the amount of a natriuretic peptide to the amount of GDF-15 in the sample from the subject to be tested as compared to the reference ratio indicates that the therapy shall be adapted. Preferred reference ratios are mentioned herein below.

[0082] In general, a ratio NT-proBNP /GDF-15 of ≥ (equal to or higher than) about 0.8, preferably about 1.9, is indicative that the medication is appropriate and should not be changed. On the contrary, a ratio NT-proBNP /GDF-15 of < (lower than) about 0.7, preferably about 0.4 is indicative that the medication is not appropriate and should be adapted.

[0083] In the context of the method of monitoring a medication in a subject subjected to said medication and suffering from heart failure or stages preceding heart failure including risk factors for heart failure, preferably, the following applies:

[0084] Preferably, the ratio cardiac troponin /GDF 15 is formed, with the cardiac troponin being preferably troponin T or troponin I, in particular troponin T. By this, often a more profound information in respect to the treatment of the respective subject can be obtained. In general, a high ratio cardiac troponin/GDF-15 is often indicative of an appropriate medication suppressing inflammatory processes. Accordingly, a high ratio of the amount of a cardiac troponin to the amount of GDF-15, preferably, indicates that the therapy is appropriate, and, thus, that the therapy can be continued. Accordingly, a low ratio of the amount of a cardiac troponin to the amount of GDF-15 indicates that the therapy is not appropriate.

[0085] In preferred embodiment embodiment of the aforementioned method the ratio of the amount of a cardiac troponin to the amount of GDF-15 is formed, and compared to a reference ratio of the amount of a cardiac troponin to the amount of GDF-15. Preferably, the reference ratio is derived from a subject for whom the therapy is appropriate, or from a subject for whom the therapy is not appropriate.

[0086] Preferably, an increased ratio of the amount of a cardiac troponin to the amount of GDF-15 in the sample from the subject to be tested as compared to the reference ratio indicates that the therapy is appropriate (and thus, that therapy shall not be changed), whereas a decreased ratio of the amount of a cardiac troponin to the amount of GDF-15 in the sample from the subject to be tested as compared to the reference ratio indicates that the therapy is not appropriate. Preferred reference ratios are mentioned herein below.

[0087] In an even more preferred embodiment of the present invention, the above mentioned ratio cardiac troponin /GDF 15 is used in connection with the individual concentrations

[0088] In general, a ratio troponin T/GDF-15 of equal to or higher than about 0.01, preferably about 0.017, is indicative that the medication is appropriate. On the contrary, a ratio troponin T/GDF-15 of < (lower than) about 0.01, preferably

about 0.005 is indicative that the medication is not appropriate.

[0089] In a further embodiment of the present invention, the ratio natriuretic peptide/GDF-15 is formed. The natriuretic peptide is preferably a BNP type or an ANP type natriuretic peptide, even more preferably BNP or NT-proBNP, in particular NT-proBNP.

[0090] In further preferred embodiment embodiment of the aforementioned method the ratio of the amount of a natriuretic peptide to the amount of GDF-15 is formed, and compared to a reference ratio of the amount of a natriuretic peptide to the amount of GDF-15. Preferably, the reference ratio is derived from a subject for whom the therapy is appropriate, or from a subject for whom the therapy is not appropriate.

[0091] Preferably, an increased ratio of the amount of a natriuretic peptide to the amount of GDF-15 in the sample from the subject to be tested as compared to the reference ratio indicates that the therapy is appropriate, whereas a decreased ratio of the amount of a natriuretic peptide to the amount of GDF-15 in the sample from the subject to be tested as compared to the reference ratio indicates that the therapy is not appropriate. Preferred reference ratios are mentioned herein below.

[0092] In general, a ratio NT-proBNP /GDF-15 of equal to or higher than about 0.8, preferably about 1.9, is indicative that the medication is appropriate. On the contrary, a ratio NT-proBNP /GDF-15 of < (lower than) about 0.7, preferably about 0.4 is indicative that the medication is not appropriate.

[0093] It is to be understood that the subjects of the present invention (suffering from either heart failure, preferably being classified stage C of the ACC/AHA classification; or having risk factors for heart failure or suffering from functional and/or structural abnormalities of the heart preceding heart failure, preferably being classified stage A or B of the ACC/AHA classification) already receive medication for the treatment of the aforementioned states, in general a medication selected from ACE inhibitors, angiotensin receptor blockers and aldosterone antagonists. In an even more preferred embodiment, the subject does not receive administration of an aldosterone antagonist.

[0094] In the decision on the adaptation of the medication, a preferred embodiment is the decision on the administration of an aldosterone antagonist, or the decision on the augmentation of the concentration of the aldosterone antagonist, or the decision on the administration of a different or a further aldosterone antagonist.

[0095] Accordingly, the therapy adaptation, preferably, is selected from i) the administration of an aldosterone antagonist, ii) the augmentation of the concentration (in particular the dosage) of the aldosterone antagonist, and iii) the administration of a different or a further aldosterone antagonist. Preferably, i) is recommended if the subject did not receive aldosterone antagonists prior to carrying out the method (i.e. before the sample has been obtained). Preferably, ii) or iii) is recommended if the subject did receive aldosterone antagonists prior to carrying out the method (i.e. before the sample has been obtained).

[0096] In case the concentrations of GDF-15 or a variant thereof in the individual show that inflammatory processes are predominant, in particular in consideration of the concentrations of a cardiac troponin in the individual showing heart failure or stages preceding heart failure, the medication should be adapted. Preferably, administration of an aldosterone antagonist should be initiated.

[0097] In case the concentrations of a cardiac troponin or a variant thereof in the individual show that the individual suffers from heart failure and stages preceding heart failure, in particular in consideration of the concentrations of GDF-15 or a variant thereof in the individual showing inflammatory processes or not, the medication should be adapted if the GDF-15 concentration shows that inflammatory processes are predominant, and the medication should not be adapted if GDF-15 concentrations are not increased or only slightly increased in respect to healthy individuals, indicating that inflammatory processes are not existent or not predominant.

[0098] Collagen synthesis in the heart is believed to be a reason for diastolic dysfunction, as the left ventricle becomes stiffer as a consequence of collagen deposition between the cells. An impaired filling capacity results. Therefore, aldosterone antagonists appear to be in particular appropriate for treating individuals who are at risk of suffering from diastolic dysfunction, or who are about to develop diastolic dysfunction, or who suffer from diastolic dysfunction which may worsen.

[0099] In the context of the present embodiment of the present invention, the terms "decreased" and "increased" refer to the average values in a healthy subject. These values are known to the person skilled in the art and are as follows: about 2.0 pg/mL, or about 3 pg/ml for troponin T (or 0.0 pg/mL taking into account the test's sensitivity of about 2.0); about 680 pg/ml, preferably about 580 pg/mL, in particular about 500 pg/mL for GDF-15; about 68 pg/ml, preferably about 37 pg/mL, in particular about 18 pg/mL for NT-proBNP.

[0100] As known to the person skilled in the art mean average values of NT-ProBNP in healthy subjects increase with age (e.g. 37 pg/mL at age 18-44, 72 pg/ml at age 55-64, 107 pg/ml at age 65-74, 211 pg/ml at age above 75). The person skilled in the art considers this when assessing whether the amount of natriuretic peptide is increased. Thus, whether an amount of a natriuretic peptide is increased, e.g. by at least 20% in respect to the amount in a sample from a healthy individual, can be determined by the skilled person without further ado.

[0101] The terms "decreased" or "increased" as used in the context of the present invention denote in case of GDF-15 an increase or decrease of at least 10 %, preferably at least 20 % in respect to healthy individuals; in case of troponin T and NT-proBNP, the terms "decreased" or "increased" as used in the context of the present invention denote an

increase or decrease of at least 20%, preferably at least 30 %, in respect to healthy individuals.

A healthy subject/individual, preferably, is a subject not bearing risk factors of heart failure, in particular a normotensive subject (see e.g. group 1 in Example 1). More preferably, said subject is a subject not bearing risk factors of heart failure and not having functional and structural abnormalities of the heart preceding heart failure and/or preceding left ventricular hypertrophy. Is is further preferred that the healthy subject is a subject bearing risk factors of heart failure, but not having functional and/or structural abnormalities preceding heart failure and/or preceding LVH (see e.g. group 2 in Example 1). Preferably, the subject bearing risk factors of heart failure, but not having functional and/or structural abnormalities preceding heart failure and/or preceding LVH is a stage A subject. Preferably, if the healthy subject bears risk factors of heart disease, the subject to be tested bears the same risk factors.

[0102] The term "natriuretic peptide" comprises Atrial Natriuretic Peptide (ANP)-type and Brain Natriuretic Peptide (BNP)-type peptides and variants thereof having the same predictive potential. Natriuretic peptides according to the present invention comprise ANP-type and BNP-type peptides and variants thereof (see e.g. Bonow, 1996, Circulation 93: 1946-1950). ANP-type peptides comprise pre-proANP, proANP, NT-proANP, and ANP. BNP-type peptides comprise pre-proBNP, proBNP, NT-proBNP, and BNP. The pre-pro peptide (134 amino acids in the case of pre-proBNP) comprises a short signal peptide, which is enzymatically cleaved off to release the pro peptide (108 amino acids in the case of proBNP). The pro peptide is further cleaved into an N-terminal pro peptide (NT-pro peptide, 76 amino acids in case of NT-proBNP) and the active hormone (32 amino acids in the case of BNP, 28 amino acids in the case of ANP). Preferably, natriuretic peptides according to the present invention are NT-proANP, ANP, and, more preferably, NT-proBNP, BNP, and variants thereof. ANP and BNP are the active hormones and have a shorter half-life than their respective inactive counterparts, NT-proANP and NT-proBNP. BNP is metabolized in the blood, whereas NT-proBNP circulates in the blood as an intact molecule and as such is eliminated renally. The in-vivo half-life of NT-proBNP is 120 min longer than that of BNP, which is 20 min (Smith 2000, J Endocrinol. 167: 239-46.). Preanalytics are more robust with NT-proBNP allowing easy transportation of the sample to a central laboratory (Mueller 2004, Clin Chem Lab Med 42: 942-4.). Blood samples can be stored at room temperature for several days or may be mailed or shipped without recovery loss. In contrast, storage of BNP for 48 hours at room temperature or at 4° Celsius leads to a concentration loss of at least 20 % (Mueller loc.cit.; Wu 2004, Clin Chem 50: 867-73.). Therefore, depending on the time-course or properties of interest, either measurement of the active or the inactive forms of the natriuretic peptide can be advantageous. The most preferred natriuretic peptides according to the present invention are NT-proBNP or variants thereof. As briefly discussed above, the human NT-proBNP, as referred to in accordance with the present invention, is a polypeptide comprising, preferably, 76 amino acids in length corresponding to the N-terminal portion of the human NT-proBNP molecule. The structure of the human BNP and NT-proBNP has been described already in detail in the prior art, e.g., WO 02/089657, WO 02/083913 or Bonow loc. cit. Preferably, human NT-proBNP as used herein is human NT-proBNP as disclosed in EP 0 648 228 B1. The NT-proBNP referred to in accordance with the present invention further encompasses allelic and other variants of said specific sequence for human NT-proBNP discussed above. Specifically, envisaged are variant polypeptides which are on the amino acid level preferably, at least 50%, 60%, 70%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% identical to human NT-proBNP, preferably over the entire length of human NT-proBNP. The degree of identity between two amino acid sequences can be determined by algorithms well known in the art. Preferably, the degree of identity is to be determined by comparing two optimally aligned sequences over a comparison window, where the fragment of amino acid sequence in the comparison window may comprise additions or deletions (e.g., gaps or overhangs) as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment. The percentage is calculated by determining the number of positions at which the identical amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity. Optimal alignment of sequences for comparison may be conducted by the local homology algorithm of Smith and Waterman Add. APL. Math. 2:482 (1981), by the homology alignment algorithm of Needleman and Wunsch J. Mol. Biol. 48:443 (1970), by the search for similarity method of Pearson and Lipman Proc. Natl. Acad. Sci. (USA) 85: 2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, PASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by visual inspection. Given that two sequences have been identified for comparison, GAP and BESTFIT are preferably employed to determine their optimal alignment and, thus, the degree of identity. Preferably, the default values of 5.00 for gap weight and 0.30 for gap weight length are used. Variants referred to above may be allelic variants or any other species specific homologs, paralogs, or orthologs. Substantially similar and also envisaged are proteolytic degradation products which are still recognized by the diagnostic means or by ligands directed against the respective full-length peptide. Also encompassed are variant polypeptides having amino acid deletions, substitutions, and/or additions compared to the amino acid sequence of human NT-proBNP as long as the said polypeptides have NT-proBNP properties. NT-proBNP properties as referred to herein are immunological and/or biological properties. Preferably, the NT-proBNP variants have immunological properties (i.e. epitope composition) comparable to those of human NT-proBNP. Thus, the variants shall be recognizable by the aforementioned means or ligands used for determination of the amount of the natriuretic peptides. Biological

and/or immunological NT-proBNP properties can be detected by the assay described in Karl et al. (Karl 1999, Scand J Clin Lab Invest 230:177-181), Yeo et al. (Yeo 2003, Clinica Chimica Acta 338:107-115). Variants also include posttranslationally modified peptides such as glycosylated peptides. Further, a variant in accordance with the present invention is also a peptide or polypeptide which has been modified after collection of the sample, for example by covalent or non-covalent attachment of a label, particularly a radioactive or fluorescent label, to the peptide.

[0103] It is to be understood that the subjects which are in the context of the present embodiment of the invention (namely methods of therapy monitoring and therapy adaptation in a subject receiving administration of a medicament selected from ACE inhibitors, angiotensin receptor blockers and aldosterone antagonists) should not suffer from diseases which affect the concentrations of the markers cited in respect to individuals not suffering from the cardiac abnormalities or diseases which are the subject-matter of the present invention. Accordingly, the subject should be clinically healthy except for heart failure/functional and/or structural abnormalities of the heart preceding heart failure, and for risk factor of suffering from heart failure. Furthermore, the subject should not suffer from diabetes mellitus, should not have liver disease, should not be pregnant and should not suffer from malignancies.

[0104] The person skilled in the art is aware that the concentrations cited in the present application for the cardiac troponins (troponin T or a variant thereof and troponin I or a variant thereof), NT-proBNP or a variant thereof and - to a lesser extent - for GDF-15 or a variant thereof may not apply for patients suffering from impaired renal function, preferably patients suffering from renal failure, in particular patients suffering from chronic and end stage renal failure. In a preferred embodiment of the present invention, patients suffering from impaired renal function, preferably patients suffering from renal failure, in particular patients suffering from chronic and end stage renal failure are not comprised in (excluded from) the methods of the present invention. In another preferred embodiment, patients with renal hypertension are not comprised in (excluded from) the methods of the present invention.

[0105] Preferably, the "subject" as used herein excludes patients suffering from impaired renal function, preferably patients suffering from renal failure, in particular patients suffering from chronic and end stage renal failure, more preferably patients with renal hypertension, most preferably all of the patients suffering from one of the diseases and conditions mentioned in this sentence. In this context, "renal failure" is regarded as an impaired glomerular filtration rate (GFR) lying below the usual ranges of 60 to 120 ml/min, preferably below 60 ml/min. Chronic renal failure is a long-standing, progressive deterioration of renal function which often results in end stage renal failure. End stage renal failure is diagnosed when the GFR reaches a rate of up to about 30 ml/min. GFR is determined by the creatinine clearance, which is known to the person skilled in the art. Subjects with impaired renal function show higher levels of troponin I and troponin T than those cited above, due to an impaired clearance of the peptide. The levels vary with the severity of the renal impairment.

[0106] The severity of renal impairment is divided into various grades, as displayed below.

0: ≥ 90 ml/min

1: ≥ 90 ml/min with microalbuminuria

2: ≥ 60 - < 90 ml/min

3: ≥ 30 - < 60 ml/min

4: ≥ 15 - < 30 ml/min

5: < 15 ml/min

(Source: National Kidney Foundation, as published in: Am J. Kidney Dis 39 suppl 1, 2002; Clinical Practice Guidelines for chronic kidney disease).

[0107] The subject as set forth herein shall be, preferably, about to leave stage A and about to enter stage B (or shall have entered early stage B). Accordingly, the subject, preferably, shall have no history of myocardial infarction, in particular shall have no history of known myocardial infarction. Thus, the term "subject" as used herein, preferably, excludes a subject having a history of known myocardial infarction.

[0108] A subject who has no history of known myocardial infarction (MI), preferably, did not suffer from myocardial infarction (in particular from diagnosed myocardial infarction) in the past, i.e. before the sample to be tested has been obtained. The term "myocardial infarction" is well known in the art. As used herein, the term, preferably, includes ST-elevation MI (STEMI) and non-ST-elevated MI (NSTEMI).

[0109] Also preferably, the term "subject" as used herein, preferably, excludes a subject who suffers from coronary artery disease. Thus, the subject to be tested shall not suffer from coronary artery disease. This applies, in particular, to the methods of diagnosing, methods of differentiating, methods of monitoring a medication, and methods of predicting

as set forth herein.

[0110] The term "coronary artery disease" (CAD, frequently also called coronary heart disease (CHD) is known to the person skilled in the art. The term, preferably, refers to a condition in which at least one of the major coronary arteries is narrowed, whereby stenosis of more than 50 % should occur per vessel. A subject not suffering from CAD, has less than 50% stenosis (and thus less than 50% occlusion) of the major coronary arteries. How to assess the degree of occlusion of a coronary artery is well known in the art, preferably, the degree is assessed by coronary angiography.

[0111] The term "sample" refers to samples of blood, plasma or serum.

[0112] In accordance with the present invention, determining the concentration of a peptide or polypeptide can be achieved by all known means for determining the concentration of a peptide in a sample (the terms "concentration", "level" and "amount" are, preferably used interchangeably herein). Said means comprise immunoassay devices and methods which may utilize labeled molecules in various sandwich, competition, or other assay formats. Said assays will develop a signal which is indicative for the presence or absence of the peptide or polypeptide. Moreover, the signal strength can, preferably, be correlated directly or indirectly (e.g. reverse-proportional) to the concentration of polypeptide present in a sample. Further suitable methods comprise measuring a physical or chemical property specific for the peptide or polypeptide such as its precise molecular mass or NMR spectrum. Said methods comprise, preferably, biosensors, optical devices coupled to immunoassays, biochips, analytical devices such as mass- spectrometers, NMR-analyzers, or chromatography devices. Further, methods include micro-plate ELISA-based methods, fully-automated or robotic immunoassays (available for example on Elecsys™ analyzers), CBA (an enzymatic Cobalt Binding Assay, available for example on Roche-Hitachi™ analyzers), and latex agglutination assays (available for example on Roche-Hitachi™ analyzers).

[0113] Preferably, determining the concentration of a peptide or polypeptide comprises the steps of (a) contacting a cell capable of eliciting a cellular response the intensity of which is indicative of the concentration of the peptide or polypeptide with the said peptide or polypeptide for an adequate period of time, (b) measuring the cellular response. For measuring cellular responses, the sample or processed sample is, preferably, added to a cell culture and an internal or external cellular response is measured. The cellular response may include the measurable expression of a reporter gene or the secretion of a substance, e.g. a peptide, polypeptide, or a small molecule. The expression or substance shall generate an intensity signal which correlates to the concentration of the peptide or polypeptide.

[0114] Also preferably, determining the concentration of a peptide or polypeptide comprises the step of measuring a specific intensity signal obtainable from the peptide or polypeptide in the sample. As described above, such a signal may be the signal intensity observed at an m/z variable specific for the peptide or polypeptide observed in mass spectra or a NMR spectrum specific for the peptide or polypeptide.

[0115] Determining the concentration of a peptide or polypeptide may, preferably, comprises the steps of (a) contacting the peptide with a specific ligand, (b) (optionally) removing non-bound ligand, (c) measuring the concentration of bound ligand. The bound ligand will generate an intensity signal. Binding according to the present invention includes both covalent and non-covalent binding. A ligand according to the present invention can be any compound, e.g., a peptide, polypeptide, nucleic acid, or small molecule, binding to the peptide or polypeptide described herein. Preferred ligands include antibodies, nucleic acids, peptides or polypeptides such as receptors or binding partners for the peptide or polypeptide and fragments thereof comprising the binding domains for the peptides, and aptamers, e.g. nucleic acid or peptide aptamers. Methods to prepare such ligands are well-known in the art. For example, identification and production of suitable antibodies or aptamers is also offered by commercial suppliers. The person skilled in the art is familiar with methods to develop derivatives of such ligands with higher affinity or specificity. For example, random mutations can be introduced into the nucleic acids, peptides or polypeptides. These derivatives can then be tested for binding according to screening procedures known in the art, e.g. phage display. Antibodies as referred to herein include both polyclonal and monoclonal antibodies, as well as fragments thereof, such as Fv, Fab and $F(ab)_2$ fragments that are capable of binding antigen or hapten. The present invention also includes single chain antibodies and humanized hybrid antibodies wherein amino acid sequences of a non-human donor antibody exhibiting a desired antigen-specificity are combined with sequences of a human acceptor antibody. The donor sequences will usually include at least the antigen-binding amino acid residues of the donor but may comprise other structurally and/or functionally relevant amino acid residues of the donor antibody as well. Such hybrids can be prepared by several methods well known in the art. Preferably, the ligand or agent binds specifically to the peptide or polypeptide. Specific binding according to the present invention means that the ligand or agent should not bind substantially to ("cross-react" with) another peptide, polypeptide or substance present in the sample to be analyzed. Preferably, the specifically bound peptide or polypeptide should be bound with at least 3 times higher, more preferably at least 10 times higher and even more preferably at least 50 times higher affinity than any other relevant peptide or polypeptide. Non-specific binding may be tolerable, if it can still be distinguished and measured unequivocally, e.g. according to its size on a Western Blot, or by its relatively higher abundance in the sample. Binding of the ligand can be measured by any method known in the art. Preferably, said method is semi-quantitative or quantitative. Suitable methods are described in the following.

[0116] First, binding of a ligand may be measured directly, e.g. by NMR or surface plasmon resonance.

[0117] Second, if the ligand also serves as a substrate of an enzymatic activity of the peptide or polypeptide of interest, an enzymatic reaction product may be measured (e.g. the concentration of a protease can be measured by measuring the concentration of cleaved substrate, e.g. on a Western Blot). Alternatively, the ligand may exhibit enzymatic properties itself and the "ligand/peptide or polypeptide" complex or the ligand which was bound by the peptide or polypeptide, respectively, may be contacted with a suitable substrate allowing detection by the generation of an intensity signal. For measurement of enzymatic reaction products, preferably the concentration of substrate is saturating. The substrate may also be labeled with a detectable label prior to the reaction. Preferably, the sample is contacted with the substrate for an adequate period of time. An adequate period of time refers to the time necessary for a detectable, preferably measurable, concentration of product to be produced. Instead of measuring the concentration of product, the time necessary for appearance of a given (e.g. detectable) concentration of product can be measured.

[0118] Third, the ligand may be coupled covalently or non-covalently to a label allowing detection and measurement of the ligand. Labeling may be done by direct or indirect methods. Direct labeling involves coupling of the label directly (covalently or non-covalently) to the ligand. Indirect labeling involves binding (covalently or non-covalently) of a secondary ligand to the first ligand. The secondary ligand should specifically bind to the first ligand. Said secondary ligand may be coupled with a suitable label and/or be the target (receptor) of tertiary ligand binding to the secondary ligand. The use of secondary, tertiary or even higher order ligands is often used to increase the signal. Suitable secondary and higher order ligands may include antibodies, secondary antibodies, and the well-known streptavidin-biotin system (Vector Laboratories, Inc.). The ligand or substrate may also be "tagged" with one or more tags as known in the art. Such tags may then be targets for higher order ligands. Suitable tags include biotin, digoxygenin, His-Tag, Glutathion-S-Transferase, FLAG, GFP, myc-tag, influenza A virus haemagglutinin (HA), maltose binding protein, and the like. In the case of a peptide or polypeptide, the tag is preferably at the N-terminus and/or C-terminus. Suitable labels are any labels detectable by an appropriate detection method. Typical labels include gold particles, latex beads, acridan ester, luminol, ruthenium, enzymatically active labels, radioactive labels, magnetic labels ("e.g. magnetic beads", including paramagnetic and superparamagnetic labels), and fluorescent labels. Enzymatically active labels include e.g. horseradish peroxidase, alkaline phosphatase, beta-Galactosidase, Luciferase, and derivatives thereof. Suitable substrates for detection include di-amino-benzidine (DAB), 3,3'-5,5'-tetramethylbenzidine, NBT-BCIP (4-nitro blue tetrazolium chloride and 5-bromo-4-chloro-3-indolyl-phosphate, available as ready-made stock solution from Roche Diagnostics), CDP-Star™ (Amersham Biosciences), ECF™ (Amersham Biosciences). A suitable enzyme-substrate combination may result in a colored reaction product, fluorescence or chemoluminescence, which can be measured according to methods known in the art (e.g. using a light-sensitive film or a suitable camera system). As for measuring the enzymatic reaction, the criteria given above apply analogously. Typical fluorescent labels include fluorescent proteins (such as GFP and its derivatives), Cy3, Cy5, Texas Red, Fluorescein, and the Alexa dyes (e.g. Alexa 568). Further fluorescent labels are available e.g. from Molecular Probes (Oregon). Also the use of quantum dots as fluorescent labels is contemplated. Typical radioactive labels include ^{35}S, ^{125}I, ^{32}P, ^{33}P and the like. A radioactive label can be detected by any method known and appropriate, e.g. a light-sensitive film or a phosphor imager. Suitable measurement methods according the present invention also include precipitation (particularly immunoprecipitation), electrochemiluminescence (electro-generated chemiluminescence), RIA (radioimmunoassay), ELISA (enzyme-linked immunosorbent assay), sandwich enzyme immune tests, electrochemiluminescence sandwich immunoassays (ECLIA), dissociation-enhanced lanthanide fluoro immuno assay (DELFIA), scintillation proximity assay (SPA), turbidimetry, nephelometry, latex-enhanced turbidimetry or nephelometry, or solid phase immune tests. Further methods known in the art (such as gel electrophoresis, 2D gel electrophoresis, SDS polyacrylamid gel electrophoresis (SDS-PAGE), Western Blotting, and mass spectrometry), can be used alone or in combination with labeling or other detection methods as described above.

[0119] The concentration of a peptide or polypeptide may be, also preferably, determined as follows: (a) contacting a solid support comprising a ligand for the peptide or polypeptide as specified above with a sample comprising the peptide or polypeptide and (b) measuring the concentration peptide or polypeptide which is bound to the support. The ligand, preferably chosen from the group consisting of nucleic acids, peptides, polypeptides, antibodies and aptamers, is preferably present on a solid support in immobilized form. Materials for manufacturing solid supports are well known in the art and include, inter alia, commercially available column materials, polystyrene beads, latex beads, magnetic beads, colloid metal particles, glass and/or silicon chips and surfaces, nitrocellulose strips, membranes, sheets, duracytes, wells and walls of reaction trays, plastic tubes etc. The ligand or agent may be bound to many different carriers. Examples of well-known carriers include glass, polystyrene, polyvinyl chloride, polypropylene, polyethylene, polycarbonate, dextran, nylon, amyloses, natural and modified celluloses, polyacrylamides, agaroses, and magnetite. The nature of the carrier can be either soluble or insoluble for the purposes of the invention. Suitable methods for fixing/immobilizing said ligand are well known and include, but are not limited to ionic, hydrophobic, covalent interactions and the like. It is also contemplated to use "suspension arrays" as arrays according to the present invention (Nolan 2002, Trends Biotechnol. 20(1):9-12). In such suspension arrays, the carrier, e.g. a microbead or microsphere, is present in suspension. The array consists of different microbeads or microspheres, possibly labeled, carrying different ligands. Methods of producing such arrays, for example based on solid-phase chemistry and photo-labile protective groups, are generally known (US

5,744,305).

[0120] The term "concentration" as used herein encompasses the absolute concentration of a polypeptide or peptide, the relative concentration or concentration of the said polypeptide or peptide as well as any value or parameter which correlates thereto or can be derived therefrom. Such values or parameters comprise intensity signal values from all specific physical or chemical properties obtained from the said peptides by direct measurements, e.g., intensity values in mass spectra or NMR spectra. Moreover, encompassed are all values or parameters which are obtained by indirect measurements specified elsewhere in this description, e.g., response levels determined from biological read out systems in response to the peptides or intensity signals obtained from specifically bound ligands. It is to be understood that values correlating to the aforementioned concentrations or parameters can also be obtained by all standard mathematical operations.

[0121] The following Examples shall merely illustrate the invention. They shall not be construed, whatsoever, to limit the scope of the invention.

Examples

Methods

[0122] Troponin T was determined using Roche's electrochemiluminescence ELISA sandwich test Elecsys Troponin T hs (high sensitive) STAT (Short Turn Around Time) assay. The test employs two monoclonal antibodies specifically directed against human cardiac troponin T. The antibodies recognize two epitopes (amino acid position 125-131 and 136-147) located in the central part of the cardiac troponin T protein, which consists of 288 amino acids. The hs-TnT assay allows a measurement of troponin T levels in the range of 3 to 10000 pg/mL.

[0123] NT-proBNP was determined using Roche's electrochemiluminescence ELISA sandwich test Elecsys proBNP II STAT (Short Turn Around Time) assay. The test employs two monoclonal antibodies which recognize epitopes located in the N-terminal part (1-76) of proBNP (1-108).

[0124] To determine the concentration of GDF-15 in serum and plasma samples, an Elecsys prototype test was employed, using a polyclonal, GDF-15 affinity chromatography-purified, goat anti-human GDF-15 IgG antibody from R&D Systems (AF957). In each experiment, a standard curve was generated with recombinant human GDF-15 from R&D Systems (957-GD/CF). The results with new batches or recombinant GDF-15 protein were tested in standard plasma samples and any deviation above 10% was corrected by introducing an adjustment factor for this assay. GDF-15 measurements in serum and plasma samples from the same patient yielded virtually identical results after correction for eventual dilution factors. The detection limit of the assay was 200 pg/ml.

Example 1:

[0125] Troponin T, NT-proBNP and GDF-15 were determined in the below-described collective of individuals. A total of 97 patients with overt heart failure were included into the study, mean age 60.9 years, 52 males, 45 females, LVEF below 50%, who had a normal kidney function as documented by normal creatinine levels. All patients were on beta blocker as well as on ACE inhibitor therapy, 59 patients were on aldosterone antagonists, 38 did not receive aldosterone antagonists. Patients were treated in the study according to guidelines (see above). None of the patients suffered from diabetes mellitus or metabolic syndrome, in addition none of the patients suffered from liver disease or malignancies.

[0126] 38 patients receiving no aldosterone (all Class C) had the following characteristics:

Table 1: Marker concentrations in 38 patients receiving no aldosterone

Percentile	NT-pro BNP (pg/mL)	Troponin T (pg/mL)	GDF-15 (pg/mL)	LVEF (%)	NYHA class	ratio NT-pro BNP/GDF 15	ratio Troponin T/GDF 15
25	157	1.7	663	57	1.0	0.196	0.002
50	464	6.6	1161	45	1.5	0.401	0.005
75	1195	18.1	2228	28.5	2.5	0.682	0.011

[0127] Patients receiving aldosterone antagonists (all class C) has the following characteristics:

Table 2: Marker concentrations in patients receiving aldosterone antagonists

Percentile	NT-pro BNP (pg/mL)	Troponin T (pg/mL)	GDF-15 (pg/mL)	LVEF (%)	NYHA class	ratio NT-pro BNP/GDF 15	ratio Troponin T/GDF 15
25	475	7.3	915	35	1.0	0.254	0.004
50	1194	15.3	1535	28	2.0	0.800	0.009
75	2072	24.0	2493	20	3.0	1.898	0.017

[0128] Patients who received aldosterone antagonists had more severe heart failure than those who did not receive aldosterone antagonists. When ratios were formed it became however clear that GDF 15 was lower relative to NT-pro BNP and GDF 15 in the aldosterone antagonist group indicating that GDF 15 was a valuable marker for the use and monitoring of aldosterone antagonists.

[0129] As described above the recommendation of ACE inhibitors in stages A and B suggest the need for anti inflammatory treatment, however because of polymorphisms this appears not to be effective in all cases, thus low dose aldosterone antagonists are likely to be useful also in stages A und B heart failure. The ratios of NT-pro BNP/GDF 15 and Troponin T/GDF 15 give guidance as to the use of this drug. In all cases, in other words while ACE inhibitors and angiotension receptor blockers (ARBs) have been shown to be effective in large randomized trials there is currently no method available to diagnose the effectiveness of these drugs in the individual patient. This is in contrast to the application of these drugs in patients with kidney disease where the decrease of urinary albumin can be used to verify treatment success. Thus the method described offers for the fist time a method for the diagnosis of treatment failure and provides guidance for improved treatment using aldosterone inhibitors or in the future drugs that inhibit synthesis of aldosterone.

Individual case studies

[0130] A 62 year old patient with stable established class C heart failure is currently on a combination of beta blockers and ACE inhibitors. GDF-15, NT-proBNP and Troponin T are determined in serum sample obtained from the patient. The NT-pro BNP/GDF 15 ratio is 0.39, and the Troponin T/GDF 15 ratio is 0.003. Because of inappropriate therapy he is started with spironolactone 25 mg/day. Three months later, the NT-pro BNP/GDF 15 ratio is 0.62 and Troponin T/GDF 15 ratio is 0.006. Because of the still inappropriate therapy, spironolactone is increased to 50 mg/day. Again 3 months later therapy is found appropriate with a NT-pro BNP/GDF 15 ratio of 0.9 and a troponin T/GDF 15 ratio of 0.012.

[0131] A 48 year old female patient with stable class C heart failure is on standard therapy with beta blockers and ACE inhibitors. GDF-15, NT-proBNP and Troponin T are determined in plasma sample obtained from the patient. The NT pro BNP/GDF 15 ratio is 0.95 and the Troponin T/GDF 15 ratio 0.011. The results indicate that the patient does not require therapy with an aldosterone antagonist. As the therapy has only been started 9 months ago, she is informed of the possibility of ACE inhibitor resistance and is advised to have a follow up visit in 12 months or when symptoms of heart failure develop.

[0132] A 68 year old male patient with stable heart failure class C is currently on a combination of beta blocker, ACE inhibitors and low dose aldosterone antagonists. The NT-pro BNP/GDF 15 ratio is 0.95 and the troponin T /GDF 15 ratio is 0.012. The patient is informed that therapy is adequate and to stay on current treatment schedule and to return to a follow up visit in 12 months or if symptoms worsen.

[0133] A 56 year old patient with stable type C heart failure is on a therapy with beta blockers, ACE inhibitors and 25 mg/day spironolactone, the NT-pro BNP/GDF 14 ratio is 1,7, the Troponin T /GDF 15 ratio is 0.02. The patient is advised that an attempt can be made to discontinue spironolactone for three months, as the effect of discontinuation is only recognised with significant delay, and then to decide on the necessity of spironolactone. Three months after discontinuation of spironolactone the NT-pro BNP/GDF 15 ratio is 0.9 and the troponin T/GDF 14 ratio is 0.013. The patient is informed that spironolactone can be discontinued.

Claims

1. A method of monitoring a medication in a subject subjected to said medication, said medication being selected from ACE inhibitors, angiotension receptor blockers and aldosterone antagonists, said subject suffering from heart failure or stages preceding heart failure including risk factors for heart failure, the method comprising the steps of

    a) measuring in a blood, serum or plasma sample obtained from the subject the concentrations of at least one

cardiac troponin or a variant thereof and/or a natriuretic peptide or a variant thereof,
b) measuring in a blood, serum or plasma sample the concentration of GDF-15 or a variant thereof, and
c) monitoring the medication by comparing the thus determined concentrations with a reference amount,

wherein, if the concentrations of a cardiac troponin, in particular troponin T, and GDF-15 are measured, a ratio of the cardiac troponin and GDF-15 (cardiac Troponin/GDF-15) is formed, or
wherein, if the concentrations of a natriuretic peptide, in particular NT-proBNP, and GDF-15 are measured, a ratio of the natriuretic peptide and GDF-15 (natriuretic peptide/GDF-15) is formed.

2. A method of deciding on the adaptation of a medication selected from ACE inhibitors, angiotension receptor blockers and aldosterone antagonists in a subject subjected to said medication and suffering from heart failure or stages preceding heart failure including risk factors for heart failure, the method comprising the steps of

a) measuring in a blood, serum or plasma sample obtained from the subject the concentrations of at least one cardiac troponin or a variant thereof and/or a natriuretic peptide or a variant thereof,
b) measuring in a blood, serum or plasma sample the concentration of GDF-15 or a variant thereof, and
c) deciding on the adaptation of the medication by comparing the thus determined concentrations with a reference amount,

wherein, if the concentrations of a cardiac troponin, in particular troponin T, and GDF-15 are measured, a ratio of the cardiac troponin and GDF-15 (cardiac Troponin/GDF-15) is formed, or
wherein, if the concentrations of a natriuretic peptide, in particular NT-proBNP, and GDF-15 are measured, a ratio of the natriuretic peptide and GDF-15 (natriuretic peptide/GDF-15) is formed.

3. The method according to claim 1 or 2, wherein the medication is an ACE inhibitor.

4. The method according to any one of claims 1 to 3, wherein a ratio of troponin T/GDF-15 of equal to or higher than about 0.01, preferably equal to or higher than about 0.017, is indicative that the medication is appropriate and should not be changed, and/or wherein a ratio troponin T/GDF-15 of lower than about 0.01, preferably lower than about 0.005 is indicative that the medication is not appropriate and should be adapted.

5. The method according to any one of claims 1 to 3, wherein a ratio of NT-proBNP /GDF-15 of equal to or higher than about 0.8, preferably equal to or higher than about 1.9, is indicative that the medication is appropriate and should not be changed, and/or wherein a ratio NT-proBNP /GDF-15 of lower than about 0.7, preferably lower than about 0.4 is indicative that the medication is not appropriate and should be adapted.

6. The method according to any of claims 2 to 5, wherein the adaptation is selected from i) the administration of an aldosterone antagonist, ii) the augmentation of the concentration of the aldosterone antagonist, and iii) the administration of a different or a further aldosterone antagonist.

Patentansprüche

1. Verfahren zum Überwachen eines Medikamentes in einem Individuum, das dem Medikament ausgesetzt wird, wobei das Medikament ausgewählt ist aus ACE-Hemmern, Angiotensin-Rezeptor-Blockern und Aldosteron-Antagonisten, wobei das Individuum an Herzversagen oder Stadien, die Herzversagen vorangehen, einschließlich Risikofaktoren für Herzversagen, leidet, wobei das Verfahren die folgenden Schritte umfasst

a) Messen der Konzentrationen mindestens eines kardialen Troponins oder einer Variante davon und/oder eines natriuretischen Peptids oder einer Variante davon in einer aus dem Individuum entnommenen Blut-, Serum- oder Plasmaprobe,
b) Messen der Konzentration von GDF-15 oder einer Variante davon in einer Blut-, Serum- oder Plasmaprobe, und
c) Überwachen des Medikaments durch Vergleichen der so ermittelten Konzentrationen mit einem Referenzwert,

wobei, wenn die Konzentrationen eines kardialen Troponins, insbesondere Troponin T, und GDF-15 gemessen werden, ein Verhältnis des kardialen Troponins und GDF-15 (kardiales Troponin/GDF-15) gebildet wird, oder
wobei, wenn die Konzentrationen eines natriuretischen Peptids, insbesondere NT-proBNP, und GDF-15 gemessen

werden, ein Verhältnis des natriuretischen Peptids und GDF-15 (natriuretisches Peptid/GDF-15) gebildet wird.

2. Verfahren zum Entscheiden bezüglich der Anpassung eines Medikaments, ausgewählt aus ACE-Hemmern, Angiotensin-Rezeptor-Blockern und Aldosteron-Antagonisten, in einem Individuum, das dem Medikament ausgesetzt wurde und an Herzversagen oder Stadien, die Herzversagen vorangehen, einschließlich Risikofaktoren für Herzversagen, leidet, wobei das Verfahren die folgenden Schritte umfasst

a) Messen der Konzentrationen mindestens eines kardialen Troponins oder einer Variante davon und/oder eines natriuretischen Peptids oder einer Variante davon in einer aus dem Individuum entnommenen Blut-, Serum- oder Plasmaprobe,
b) Messen der Konzentration von GDF-15 oder einer Variante davon in einer Blut-, Serum- oder Plasmaprobe, und
c) Entscheiden bezüglich der Anpassung des Medikaments, durch Vergleichen der so bestimmten Konzentrationen mit einem Referenzwert,

wobei, wenn die Konzentrationen eines kardialen Troponins, insbesondere Troponin T, und GDF-15 gemessen werden, ein Verhältnis des kardialen Troponins und GDF-15 (kardiale Troponin/GDF-15) gebildet wird, oder wobei, wenn die Konzentrationen eines natriuretischen Peptids, insbesondere NT-proBNP, und GDF-15 gemessen werden, ein Verhältnis des natriuretischen Peptids und GDF-15 (natriuretisches Peptid/GDF-15) gebildet wird, oder wobei, wenn die Konzentrationen eines natriuretischen Peptids, insbesondere NT-proBNP, und GDF-15 gemessen werden, ein Verhältnis des natriuretischen Peptids und GDF-15 (natriuretisches Peptid/GDF-15) gebildet wird.

3. Verfahren nach Anspruch 1 oder 2, wobei das Medikament ein ACE-Hemmer ist.

4. Verfahren nach einem der Ansprüche 1 bis 3, wobei ein Verhältnis von Troponin T/GDF-15 von gleich oder größer als etwa 0,01, vorzugsweise gleich oder größer als etwa 0,017, anzeigt, dass das Medikament geeignet ist, und nicht geändert werden sollte, und/oder wobei ein Verhältnis von Troponin T/GDF-15 von weniger als etwa 0,01, vorzugsweise weniger als etwa 0,005, anzeigt, dass das Medikament nicht geeignet ist und angepasst werden sollte.

5. Verfahren nach einem der Ansprüche 1 bis 3, wobei ein Verhältnis von NT-proBNP/GDF-15 von gleich oder größer als etwa 0,8, vorzugsweise gleich oder größer als etwa 1,9, anzeigt, dass das Medikament geeignet ist und nicht geändert werden sollte, und/oder wobei ein Verhältnis von NT-proBNP/GDF-15 von weniger als etwa 0,7, vorzugsweise weniger als etwa 0,4, anzeigt, dass das Medikament nicht geeignet ist und angepasst werden sollte.

6. Verfahren nach einem der Ansprüche 2 bis 5, wobei die Anpassung ausgewählt ist aus i) der Verabreichung eines Aldosteron-Antagonisten, ii) der Steigerung der Konzentration des Aldosteron-Antagonisten, und iii) der Verabreichung eines anderen oder eines weiteren Aldosteron-Antagonisten.

Revendications

1. Procédé de surveillance d'une médication chez un sujet soumis à ladite médication, ladite médication étant choisie parmi des inhibiteurs d'ACE, des antagonistes de récepteur d'angiotensine et des antagonistes d'aldostérone, ledit sujet souffrant d'insuffisance cardiaque ou de stades précédant une insuffisance cardiaque comprenant des facteurs de risque d'insuffisance cardiaque, le procédé comprenant les étapes de

a) mesure dans un échantillon de sang, de sérum ou de plasma obtenu à partir du sujet des concentrations d'au moins une troponine cardiaque ou un variant de celle-ci et/ou un peptide natriurétique ou un variant de celui-ci,
b) mesure dans un échantillon de sang, de sérum ou de plasma de la concentration de GDF-15 ou un variant de celui-ci, et
c) surveillance de la médication par comparaison des concentrations déterminées ainsi à une quantité de référence,

dans lequel, si les concentrations d'une troponine cardiaque, en particulier la troponine T, et GDF-15 sont mesurées, un rapport de la troponine cardiaque et de GDF-15 (troponine cardiaque/GDF-15) est formé, ou dans lequel, si les concentrations d'un peptide natriurétique, en particulier NT-proBNP, et GDF-15 sont mesurées, un rapport du peptide natriurétique et de GDF-15 (peptide natriurétique/GDF-15) est formé.

2. Procédé de décision de l'adaptation d'une médication choisie parmi des inhibiteurs d'ACE, des antagonistes de récepteur d'angiotensine et des antagonistes d'aldostérone chez un sujet soumis à ladite médication et souffrant d'insuffisance cardiaque ou de stades précédant une insuffisance cardiaque comprenant des facteurs de risque d'insuffisance cardiaque, le procédé comprenant les étapes de

a) mesure dans un échantillon de sang, de sérum ou de plasma obtenu à partir du sujet des concentrations d'au moins une troponine cardiaque ou un variant de celle-ci et/ou un peptide natriurétique ou un variant de celui-ci,
b) mesure dans un échantillon de sang, de sérum ou de plasma de la concentration de GDF-15 ou un variant de celui-ci, et
c) décision de l'adaptation de la médication par comparaison des concentrations déterminées ainsi à une quantité de référence,

dans lequel, si les concentrations d'une troponine cardiaque, en particulier la troponine T, et GDF-15 sont mesurées, un rapport de la troponine cardiaque et de GDF-15 (troponine cardiaque/GDF-15) est formé, ou dans lequel, si les concentrations d'un peptide natriurétique, en particulier NT-proBNP, et GDF-15 sont mesurées, un rapport du peptide natriurétique et de GDF-15 (peptide natriurétique/GDF-15) est formé.

3. Procédé selon la revendication 1 ou 2, dans lequel la médication est un inhibiteur d'ACE.

4. Procédé selon l'une quelconque des revendications 1 à 3, dans lequel un rapport de troponine T/GDF-15 égal ou supérieur à environ 0,01, de préférence égal ou supérieur à environ 0,017, est une indication que la médication est appropriée et ne doit pas être modifiée, et/ou dans lequel un rapport de troponine T/GDF-15 inférieur à environ 0,01, de préférence inférieur à environ 0,005 est une indication que la médication n'est pas appropriée et doit être adaptée.

5. Procédé selon l'une quelconque des revendications 1 à 3, dans lequel un rapport de NT-proBNP /GDF-15 égal à ou supérieur à environ 0,8, de préférence égal ou supérieur à environ 1,9, est une indication que la médication est appropriée et ne doit pas être modifiée, et/ou dans lequel un rapport NT-proBNP/GDF-15 inférieur à environ 0,7, de préférence inférieur à environ 0,4 est une indication que la médication n'est pas appropriée et doit être adaptée.

6. Procédé selon l'une quelconque des revendications 2 à 5, dans lequel l'adaptation est choisie parmi i) l'administration d'un antagoniste d'aldostérone, ii) l'augmentation de la concentration de l'antagoniste d'aldostérone, et iii) l'administration d'un antagoniste d'aldostérone différent ou supplémentaire.

Fig. 1

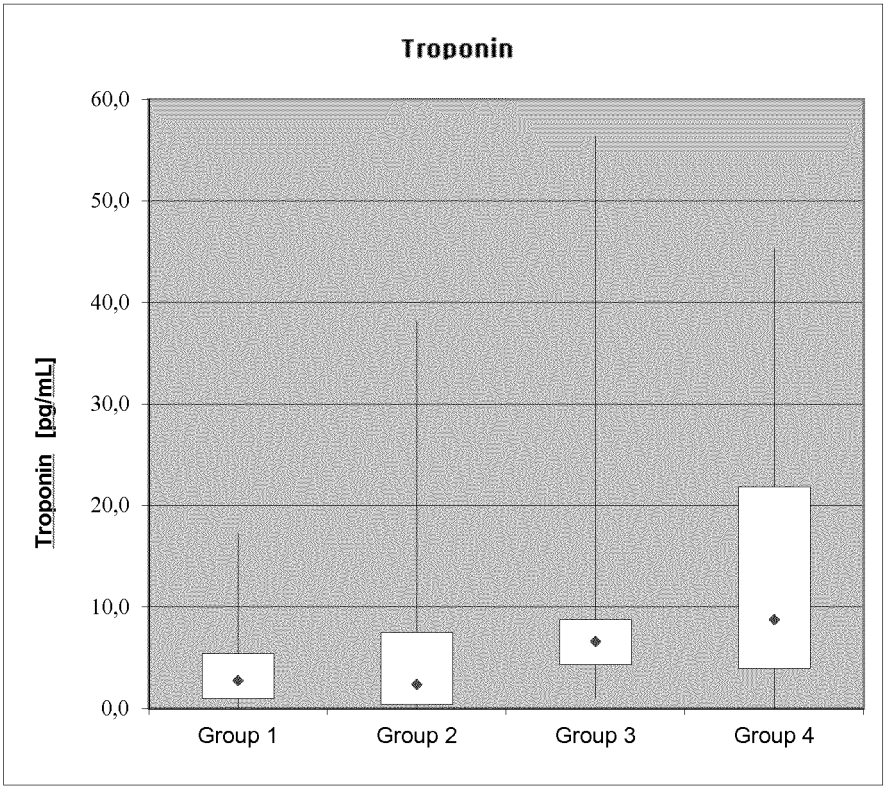

Troponin
Troponin [pg/mL]
60,0
50,0
40,0
30,0
20,0
10,0
0,0
Group 1
Group 2
Group 3
Group 4

Fig. 2

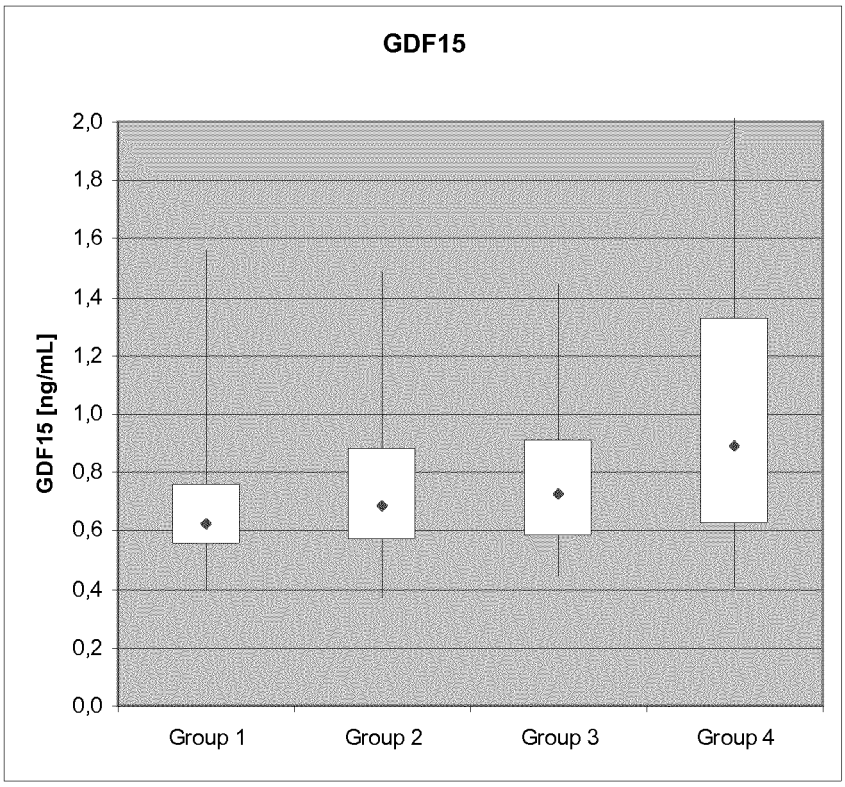

GDF15
GDF15 [ng/mL]
2,0
1,8
1,6
1,4
1,2
1,0
0,8
0,6
0,4
0,2
0,0
Group 1
Group 2
Group 3
Group 4

Fig. 3

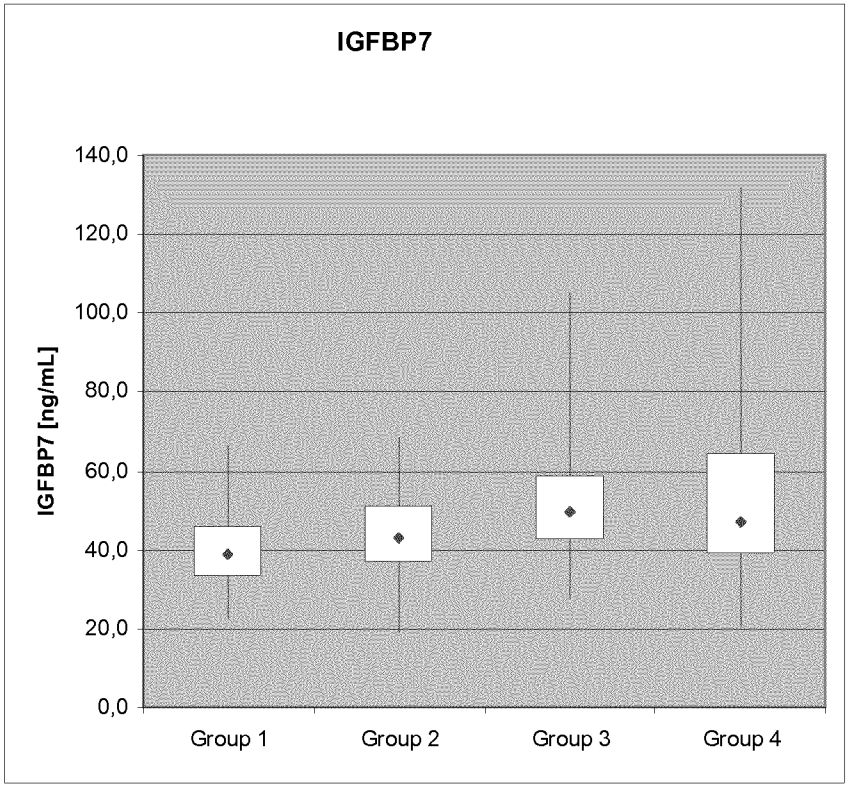
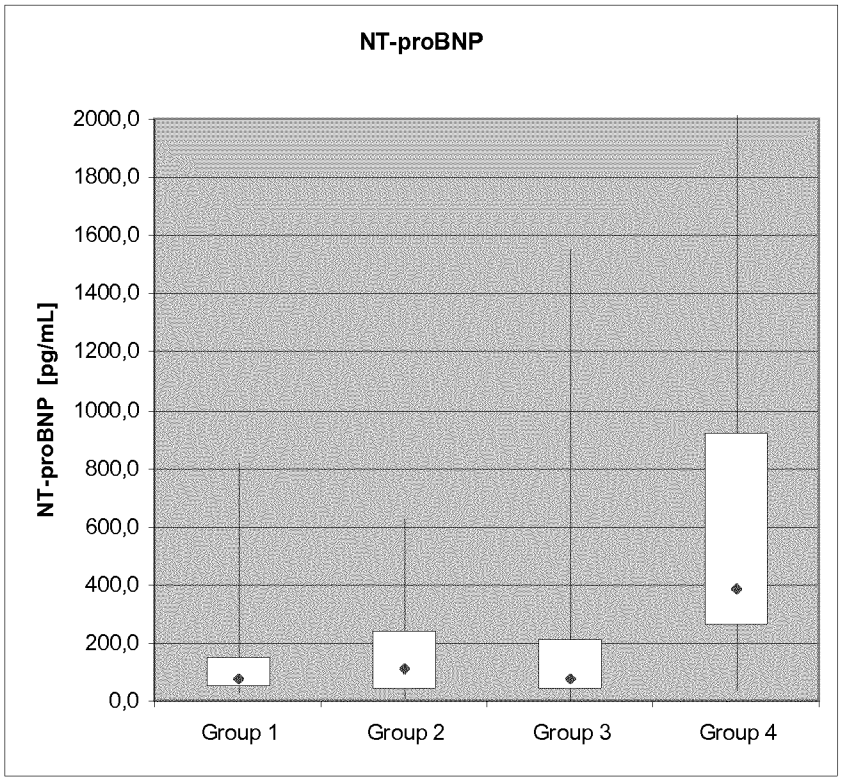

IGFBP7
IGFBP7 [ng/mL]
140,0
120,0
100,0
80,0
60,0
40,0
20,0
0,0
Group 1
Group 2
Group 3
Group 4

Fig. 4


NT-proBNP
NT-proBNP [pg/mL]
2000,0
1800,0
1600,0
1400,0
1200,0
1000,0
800,0
600,0
400,0
200,0
0,0
Group 1
Group 2
Group 3
Group 4

REFERENCES CITED IN THE DESCRIPTION

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专利名称(译)	使用生物标志物监测患有心力衰竭的受试者的药物		
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摘要(译)

本发明涉及一种监测接受所述药物治疗的受试者的药物的方法，所述药物选自ACE抑制剂，血管紧张素受体阻滞剂和醛固酮拮抗剂。还关注的是决定受试者中选自ACE抑制剂，血管紧张素受体阻滞剂和醛固酮拮抗剂的药物的适应性的方法。

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(54) Use of biomarkers in monitoring a medication in a subject suffering from heart failure

Verwendung von Biomarkern bei der Überwachung von Medikation in einem Patient mit Herzversagen

Utilisation de biomarqueurs pour le suivi d'une médication d'un sujet souffrant d'une insuffisance cardiaque

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