Consensus document
Recommendations for the clinical use of cardiac natriuretic peptides

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Introduction

The discovery of the endocrine function of the heart, which contributes to the neurohormonal regulation of vasomotion and hydrosaline homeostasis, as well as the development of accurate and feasible assay methods allowed for the recognition of the pathophysiological and clinical value of cardiac natriuretic hormones (CNH) in the assessment of cardiovascular diseases, namely acute coronary syndromes (ACS) and heart failure.

In order to establish recommendations for the clinical use of CNH, a Consensus Committee, representative of the national clinical and laboratory expertise, has joined with the purpose to debate and focus on the following issues: selection of the study population, indications to CNH clinical use, administration protocols, and use of commercially available assays. Between April and October 2004 a Consensus Document of recommendations for the clinical use of cardiac natriuretic peptides has been completed, which has thereafter obtained the approval from the Italian Scientific Societies of Clinical Chemistry and Laboratory Medicine (Società Italiana di Biochimica Clinica e Biologia Molecolare Clinica-SiBioC, Società Italiana di Me-dicina di Laboratorio-SiMEL), Cardiology (Associazione Nazionale Medici Cardiologi Ospedalieri-ANMCO, Società Italiana di Cardiologia-SIC, Federazione Italiana di Cardiologia-FIC), and Emergency Medicine (Società Italiana di Medicina d'Emergenza-Urgenza-SiMEU).

These recommendations are based on the scientific evidence published in the literature, judged as the most significant by the Consensus experts, and reflect the present knowledge in a topic which day-by-day is enriched by novel methodological, pathophysiological, and clinical progress. This implies the necessity of a future re-evaluation and upgrade of the content of these recommendations. The strength of scientific data supporting each recommendation is characterized using the scoring criteria adopted by the European Society of Cardiology[1] and the American College of Cardiology/American Heart Association[2] (Table I). For each recommendation, the designations I, IIa, IIb and III describe the indications, and the upper case letters A through C describe the levels of evidence.

Table I. Classification of recommendations.

Summary of indications

I - Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.

II - Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

IIa - Weight of evidence/opinion is in favor of usefulness/efficacy.

IIb - Usefulness/efficacy is less well established by evidence/opinion.

III - Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.

Weight of evidence

A - Data derived from multiple randomized clinical trials that involved large patient populations.

B - Data derived from a limited number of randomized trials that involved small patient populations or from careful analysis of non-randomized studies or observational registries.

C - Expert consensus was the primary basis for the recommendation in the absence of clinical studies of good quality.

Acute coronary syndrome and heart failure: epidemiological and social relevance

ACS, ST-elevation myocardial infarction and non-ST-elevation ACS, including unstable angina and non-ST-elevation myocardial infarction, represent the main cause of death in western countries, holding a relevant social cost[3].

Congestive heart failure (CHF) is the most common diagnosis at discharge for patients > 65 years in western countries[4-6]. The relevance of CHF is huge: hundreds of thousands of new cases each year, millions of hospital admissions, hundreds of thousands of deaths for an estimated overall cost of more than 30 billion dollars in the United States[4]. In Italy, according to the diagnosis-related groups, CHF is the sixth cause of hospital admission (284 cases for 100 000 inhabitants) and first for length of hospitalization and therefore for social costs.

CHF is a progressive disease; many patients, elderly in particular, are diagnosed and treated when already in end-stage disease, which influences statistical data concerning mortality, as pointed out by the IN-CHF registry[7]. After first hospital admission, the 5-year survival rate is 30% for males aged between 67 and 74 years, 20% for males aged between 75 and 84 years, and 15% for males aged > 85 years[6].

Biochemistry and pathophysiology of cardiac natriuretic hormones

Biochemistry of cardiac natriuretic hormones

The presence of secretory granules in the atrial cells of mammals, including man, has been described since 1956[8,9], but the demonstration that the mammalian heart (including the human heart) produces some hormones is a recent finding[10]. The A-type or atrial natriuretic peptide (ANP) and, later, the B-type or brain natriuretic peptide (BNP, so-called because first isolated in the swine brain) were the first peptides being isolated and identified[11-15]. Recently the C-type natriuretic peptide (CNP) – mainly produced and secreted by endothelial cells and at the level of the central nervous system, and urodilatin – produced and secreted by renal cells (present only in urines, not in plasma), have been added to the same peptide family[11-15]. More recently, a new peptide, called "dendroaspis natriuretic peptide", has been identified in the plasma of mammals, although its origin and pathophysiological relevance have to be clarified yet[16].

All natriuretic hormonal peptides show the same structural conformation. Their peptide structure is characterized by a ring closed by a cysteine bridge. The amino acid frame of this ring is very similar throughout the variety of natriuretic peptides and is also preserved among the different animal species. Indeed, this is the molecular moiety that binds to the specific receptor; conversely, the lateral amino acid chains show a high degree of variability among the natriuretic peptides not only as for molecular length, but also for type of amino acid residues.

The cardiac natriuretic peptides, mainly ANP and BNP, are produced as prohormones and secreted by myocytes, as in the case of the BNP gene that produces a prohormone of 108 amino acids (proBNP); before being secreted, proteolytic enzymes split the prohormone into two peptides: the NH_2-terminal peptide fragment of 98 amino acids [named N-terminal $proBNP_{1-76}$ (NT-proBNP)] and the $proBNP_{77-108}$ (COOH-terminal peptide fragment), the active hormone (BNP).

All these peptides (proBNP, NT-proBNP, and BNP) can be isolated in the plasma[17-21]. In patients with CHF, the plasma levels of the precursor proBNP tend to increase progressively with the increase of the derived peptides (BNP and NT-proBNP), according to the severity of the disease[17-19].

Regulation of cardiac natriuretic hormone synthesis and secretion

ANP and BNP are synthesized and secreted by atrial and ventricular myocytes, but it is currently believed that ANP is more concentrated at the atrial level, while BNP is more represented at the ventricular level. Moreover, stimulus for synthesis and secretion of the two different peptides may vary at the atrial and ventricular sites[11,12].

Differently from the atrial myocytes, ventricular myocytes do not show evident secretory granules at electron microscope in healthy adult subjects[11,12]. Conversely, recent observations have shown the presence of

secretory granules in patients with cardiomyopathy[22,23]. In addition, because the ventricular mass is relatively greater than the atrial one, a chronic stimulus produces a greater amount of hormonal molecules, particularly BNP (more than ANP). For example, in CHF the secretion rate of BNP and ANP molecules tends to be higher in relation to the severity of myocardial dysfunction and heart failure symptoms; hence while the value of this ratio (BNP/ANP) is < 1 in normal subjects, it is 3-5 in severe CHF (NYHA functional class III-IV)[13]. For this reason BNP assay holds a more sensitive and accurate diagnostic power than ANP in cardiac patients[24], which is also the reason why this document will devote greater attention to the clinical relevance of BNP and its related peptides (i.e. proBNP and NT-proBNP).

At the atrial level, wall stretching is the most important stimulus for synthesis and secretion of CNH[11,12]. Therefore, all conditions which increase venous return (i.e. physical exercise, supine position, water immersion) produce a rapid increase in ANP (more than BNP) levels.

On the other hand, ventricular wall distension, as well as hypertrophy and fibrosis, may induce cardiomyocyte hormonal production[11,12,24-26]. More recently some studies have suggested that also myocardial ischemia (and perhaps only hypoxia) may induce the synthesis/secretion of CNH (particularly BNP from ventricular cells)[27-29]. These results could explain the finding of increased BNP levels in patients with ACS without significant dilation of the ventricular chambers[27]. The possible presence of diastolic dysfunction and the significant relation between BNP and NT-proBNP plasma levels and mortality in patients with unstable angina and preserved ventricular systolic function support the hypothesis that myocardial ischemia might stimulate BNP synthesis and secretion also in the absence of necrosis[27-31].

Several experimental studies and clinical trials have demonstrated that CNH synthesis and secretion are tightly regulated with complex interchanges between the neurohormonal and immune system. In fact, norepinephrine, endothelin, and angiotensin II are considered the most powerful stimulators of CNH synthesis/secretion[11,12,31]; similarly glucocorticoids, sex steroid hormones, thyroid hormones, some growth factors and cytokines (like the tumor necrosis factor-α and interleukin-1 and interleukin-6) exert a stimulating role on the CNH system[11,12,32-40].

On the other hand, CNH exert an inhibitory action on the neurohormonal and immunological systems[11,12,30,41-45]. Numerous studies suggest that the CNH system not only has a powerful counter-regulative, diuretic, natriuretic and vasodilator effect with respect to the neurohormonal system, but it also shows a relevant inhibitory effect on myocardial and vascular remodeling and on post-angioplasty restenosis[46-50]. CNH have also an important effect on the microvascular system where they counteract endothelial dysfunction; here, we shall recall that endothelial cells produce CNP, a member of the natriuretic peptide family, which has mainly a paracrine action on the vessels[46,50].

B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide plasma levels: pathophysiological aspects

As already stated, the CNH system is not only influenced by hemodynamic changes leading to ventricular enlargement and/or an increase in ventricular wall stress, but also by neuroendocrine (sympathetic, renin-angiotensin-aldosterone, endothelins) and cytokine (with vasoconstrictor, sodium-retentive and hypertrophic effects) systems. In addition, the response of the CNH system to neuroendocrine and cytokine activation is not linear (probably log-shaped); thus, in the presence of small stresses, the hormone system responds with a much greater augmentation of BNP levels[13,51]. It is possible that small hemodynamic changes which are hardly detectable at standard instrumental evaluation, may produce significant changes in BNP levels.

Moreover, age and sex may also play a relevant role in the regulation of BNP levels (or NT-proBNP)[13,51,52]. It is well known, in fact, that during their fertile period women show higher values (almost 2-fold) than their male counterparts, but after the age of 50, these values increase in both sexes, so that a 60-year-old man may have doubled values of BNP levels than a 30-year-old man[13,51,52].

Nevertheless, elevated CNH levels may be found in some physiological (especially pregnancy and physical exercise) and pathological conditions and also in some therapeutic settings (steroid sex hormones, corticosteroids, thyroid hormones, sympathomimetic agents with beta-agonist activity, beta-blockers and digitalis)[13] (Table II). In some of these cases cardiac output is often within the normal range or rather slightly increased (for example physical exercise or hyperthyroidism). On the other hand, many diseases showing increased CNH levels may show the same symptoms of heart failure such as peripheral edema, dyspnea and fatigue (renal disease, hydroelectrolytic imbalance, hepatic cirrhosis, pulmonary disease). In these cases a real discordance may be highlighted between the results of cardiac instrumental examination (first echocardiography), clinical symptoms and BNP/NT-proBNP assay.

Analytical and pre-analytical issues of B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide measurements

Antigen characterization

Little is still known about the types of plasma molecules in pathophysiological conditions[20,21]. With the

Table II. Main clinical conditions characterized by altered B-type natriuretic peptide/N-terminal pro-B-type natriuretic peptide plasma levels.

Disease	CNH level
Cardiovascular diseases	
Heart failure	Highly increased
ACS and acute myocardial infarction	Increased
Hypertension with LVH and fibrosis	Slightly increased
Supraventricular tachyarrhythmias	Increased
Respiratory diseases	
Acute dyspnea	Normal or slightly increased
Pulmonary embolism	Increased
Chronic respiratory disorders	Normal or slightly increased
Primary pulmonary hypertension	Increased
Endocrine-metabolic disorders	
Hyperthyroidism	Slightly increased
Hypothyroidism	Slightly decreased
Cushing's syndrome	Increased
Hyperaldosteronism	Increased
Diabetes	Normal or increased
Hepatic cirrhosis with ascites	Increased
Renal failure (acute or chronic)	Increased
Septic shock	Increased
Amyloidosis	Normal or increased
Subarachnoid hemorrhage	Normal or increased
Paraneoplastic syndromes	Normal or increased
Antineoplastic therapy	Normal or increased

ACS = acute coronary syndrome; CNH = cardiac natriuretic hormone; LVH = left ventricular hypertrophy.

exception of pre-proBNP, all the metabolically related molecules are likely to be present in the plasma which is the biological sample generally used for measurements[18-21]. The understanding of possible methodological discrepancies is even more difficult owing to the molecular heterogeneity of the pro-BNP-derived peptides, in either healthy or CHF subjects, the nature of which has not been thoroughly clarified yet. For instance, it has been reported that the amino-terminal sequence of the pro-BNP and its derived peptides, such as the NT-proBNP, has a leucine zipper-like pattern, which may induce an oligomerization process and thus the development of multiple molecular forms. As a consequence, some epitopes are likely to be more exposed, while it could be difficult to recognize other parts of the molecules by the antibodies used in different methods[53]. Finally, it should be noted that BNP degradation occurs, *in vivo* and *in vitro*, by the cleavage of two amino-terminal amino acids, serin77-prolin78, by plasma proteases[19].

Antibody specificity

Differences among various methods are mainly related to the specificity of antibodies used in the assays. According to the different combination of the antibodies employed in the sandwich, the methods are able to measure one or more plasma molecules. For instance, as for BNP assays, the combination of an antibody directed against the ring structure with an antibody against the N-terminal part of the molecule may be specific for the BNP; conversely, the use of an antibody against the C-terminal associated with an antibody against the ring structure can also measure the intact pro-BNP[18,19]. The first arrangement is, however, more prone to proteolytic processes, and this results in a significant instability of the sample. As regards NT-proBNP measurement, the recognized antibody epitopes are also crucial for immunoassay specificity; it is important to remember that the methods for NT-proBNP measurement are rarely evaluated for their cross-reactivity with proBNP, NT-proBNP and their degradation products.

Features of commercially available assays

Generally speaking, it would be correct to assert that there are currently two types of commercially available assays. The former group, which uses a sandwich with an antibody against the ring portion (90-97 amino acids) and a second antibody against the N-terminal part of the peptide (77-86 amino acids), is specific for the measurement of biologically active hormone, i.e. BNP. The latter, which is more heterogeneous, comprises methods that measure proBNP and all (or some) of its metabolic products, including BNP and NT-proBNP, with variable specificity. Nevertheless, when using these natriuretic peptides as biomarkers of cardiac dysfunction (and not for the evaluation of a biologically active hormone and its possible alterations) both analytical approaches can be acceptable, once their clinical usefulness has been proven.

Recently, non-competitive immunoassays have been proposed, using polyclonal or monoclonal antibodies, with isotopic, enzymatic or fluorogenic signal detection, and antigens for calibration of the analytical system of synthetic or recombinant origin[54,55]. Although these fully automated commercial assays make results available in a short time and with excellent analytical precision, the BNP/NT-proBNP values continue to significantly depend on the type of assay used, as a result of the specificity of the employed antibodies and of different analytical standardization deriving from the different calibration materials. Further, most of the clinical studies reported in the literature have been performed by home-made non-commercially available methods, the reported results being thus not comparable and transferable to other methods[56,57]. The above-mentioned discrepancies among the levels obtained with different methods directly influence reference and cut-off values, which often change according to the method used (Table III)[29,57,58].

Table III. Reference values and analytical imprecision of some commercially available assays for the B-type natriuretic peptide (BNP)/ N-terminal pro-B-type natriuretic peptide (NT-proBNP) measurement.

Method	Mean ± SD	Median	Range	97.5° percentile	15% CV
IRMA BNP	10.7 ± 9.9	7.1	0.4-66.1	40	20
MEIA BNP	22.2 ± 29.7	13.4	< 5-220.7	105	100
ADVIA BNP	13.5 ± 11.9	9.4	< 3-65.9	45	20
POCT BNP	10.4 ± 7.2	7.6	< 8-62.5	40	15
ECLIA NT-proBNP	49.4 ± 35.4	40.9	6.7-219.8	155	< 15

Values are expressed as ng/l. ADVIA BNP = method for Centaur analyzer (Bayer Diagnostics); ECLIA NT-propBNP = electrochemoluminescence method (ECLIA) for Elecsys analyzer (Roche Diagnostics); IRMA BNP = manual immunoradiometric assay (IRMA) (Shionogi); MEIA BNP = microparticle enzyme immunoassay method for AxSYM analyzer (Abbott Diagnostics); POCT BNP = point-of-care testing Triage (Biosite Diagnostics). From Clerico et al.[58], modified.

Therefore, there is a need for standardization that, through the selection of appropriate reference materials and an adequate reference measurement procedure useful for their certification, and especially through the definition of the analyte to be measured, allows to obtain the same results even when the measurements are performed with different methods[58,59]. In the meantime, in order to correctly employ the measurement of these markers in clinical practice, it is mandatory to use method-dependent reference and cut-off values without extrapolations from one method to another.

Interferences

For the commercially available methods, no problems have been reported with the most important endogenous interferents (hemolysis, hyperbilirubinemia, hypertriglyceridemia). There are, instead, important issues related to the type of sample to be used and the *in vitro* stability. For BNP measurement, the use of an EDTA plasma sample with the possible addition of plasma protease inhibitors to prevent molecule degradation *in vitro* has been recommended[17-19,58]. Conversely, when measuring the NT-proBNP by the ECLIA method, it is recommended to collect serum or heparinized plasma samples[60]. Indeed, a significant difference has been reported between values obtained using serum or plasma heparin and EDTA plasma samples[60].

Blood samples should not be collected in glass tubes when using an immunoassay employing a combination of antibodies against amino acid 90-97/amino acid 103-107 epitopes for BNP measurement. It has been demonstrated that the above antibody combination is highly susceptible to the effect of kallikrein, a plasma protease activated by the contact with the wall of glass tube, that degrades the C-terminal portion of BNP (and proBNP), making impossible the identification of the molecule by the immunoassay using the above reported sandwich[17,61]. The stability of the blood sample can therefore be obtained by the use of plastic tubes.

The *in vitro* stability is not a problem for NT-proBNP[60,62,63], while BNP is more unstable as proteolytic phenomena deprive it of the two N-terminal amino acids. This should be taken into account when the method employed for BNP measurement uses an antibody against this epitope[18,63].

Biological variability

In order to correctly interpret the results of these biochemical markers, it is necessary to carefully evaluate the physiological variation in the studied subject. It has recently been demonstrated that the majority of the variability of BNP and NT-proBNP results is due to the biological variation, while the contribution of the analytic variability, i.e. imprecision, is little[64,65]. The coefficient of variation that reflects the average biological variability in the subject (intraindividual coefficient of variation) is on average > 30%. As a result, this high biological variability of natriuretic peptides makes it very difficult to use reference limits obtained from population studies[66,67].

Biological variability can determine a number of important quality features for the considered analytes. For instance, it is widely accepted that analytical imprecision of the assay does not significantly influence its clinical use – as long as 50% of the biological intraindividual coefficient of variation value is not overcome[68]. Due to the high biological variability, the goal for analytical imprecision of the assays measuring natriuretic peptides could be less stringent, an imprecision (as coefficient of variation) < 15% being acceptable.

Conclusions

The reference and cut-off values employed in the different clinical studies are method-dependent and cannot interchangeably be applied to other methods. When assessing the clinical value of the tests, it is necessary to take into consideration the method employed to obtain the results, as no other method is able to provide equivalent results.

Until the analytical specificity of the assay becomes clear and consequently standardization is established, it is advisable to use ng/l and not pmol/l as measurement units.

Recommendation 1

Recommendation 1. Before clinical use all new tests for CNH assay should be evaluated for the following analytical and pre-analytical characteristics:
• type of antigen used as calibrator;
• antibody specificity and identification of epitopes;
• cross-reactivity with all similar moieties within the plasma, including proBNP (amino acids 1-108);
• interferences related to:
- endogenous interfering agents,
- type of biological sample (serum, plasma with different anticoagulant agents),
- type of tube,
- sample stability at different storing temperatures.
Category of evidence: class I.
Level of evidence: type C.

Use of B-type natriuretic peptide/N-terminal pro-B-type natriuretic peptide in heart failure

Introduction

To date there is no universally accepted definition of heart failure that can totally satisfy every clinical condition[4-6,69]. Heart failure is a complex syndrome that can ensue from any alteration of the cardiac structure or function, which compromises the cardiac capacity of supplying an adequate flow in response to the metabolic demands of peripheral tissues[4-6,69]. This syndrome is clinically characterized by non-specific symptoms, such as dyspnea and fatigue, and by signs such as fluid retention with edema[4-6,69].

CHF is an issue of wide concern because of its high healthcare costs: 0.4-3% of the European population is affected and only 50% of all patients survive up to 4 years after diagnosis[4-6,69]. Heart failure represents the main cause for hospitalization among elderly subjects in industrialized countries and its prevalence is increasing due to the overall aging of the population and higher chances of survival of myocardial infarction patients[6].

Conservative evaluations suggest that in North America and Europe heart failure has an ischemic origin in over 50% of cases, whereas hypertension contributes up to 75% of cases and idiopathic dilated cardiomiopathy seems to be the cause only in 10-20% of patients[5,6,69].

There is no diagnostic test on which the diagnosis of heart failure can be based on: therefore, the physician should rely on all the available data derived from clinical history, clinical examination and from appropriate diagnostic and screening exams[4-6]. Recent studies evidenced that accuracy of clinical diagnosis is often inadequate, especially in women, in elderly and obese individuals[4-6]. Other studies have shown that of all CHF diagnoses made by general practitioners, less than 40% are actually confirmed by a specialist[3-6,69,70].

Hence it is important to provide physicians with an accurate and reliable laboratory screening method – a tool that allows to make a differential diagnosis for CHF in a quick and cost-effective manner.

Several studies indicate that BNP or NT-proBNP could be the solution, becoming a relevant step toward the monitoring and treatment of patients with CHF[6,14,29,70-79].

The different indications for the use of CNH in CHF will be herein presented on the basis of the importance of the scientific evidence available in the literature.

In the reported studies in this section we will not refer to the nature of the measured peptide (we indifferently refer to BNP or NT-proBNP) and the analytic method used, since these aspects have already been treated extensively in the previous sections.

Prognosis in symptomatic heart failure

High CNH levels are predictive of a negative outcome in terms of survival in outpatients with CHF and are the most important index of cardiovascular risk and of death in these patients, if compared with other biohumoral markers[29,70,73,80-86]. In the context of a great international clinical study, in a relatively selected population of about 4300 patients with CHF, BNP showed to have a significant prognostic value in terms of mortality and morbidity when added to a model that included clinical, demographic and echocardiographic variables[85]. This prognostic value has recently been confirmed in a randomized clinical study[86]. However, there are still not sufficient data to state that repeated BNP measurements in a single patient have a greater prognostic value than a single measurement[87,88].

Diagnosis in chronic heart failure

The guidelines of the European Society of Cardiology report that CNH can be used for diagnosing CHF in symptomatic patients, in particular as the first step of a rule-out diagnosis[5] as recently confirmed in a meta-analysis[89]. The use of the BNP and NT-proBNP assays was approved as laboratory tests for CHF in November 2000 and November 2002 respectively by the Food and Drug Administration in the United States.

Yet, there is not general agreement on the definition of which cut-off value may immediately identify subjects with CHF[29]. In addition to the differences in the definition of the levels of discrimination between

"pathologic" and "normal", which depend both on the type of the measured peptide and on the selected analytic method, CNH plasma levels in subjects without cardiovascular diseases tend to increase with age and to be higher in women than in men[29,52,90-92], reason for which variable cut-off values based on age and gender are being taken into consideration[78].

Other factors may further influence the BNP/NT-proBNP plasma levels, in particular obesity, genetic factors, the presence of renal, hepatic or pulmonary dysfunction, and the medical treatment, as previously discussed[93-95] (Table II). The whole of these factors contributes to increasing the scattering of CNH levels in CHF patients, with the result of a significant overlapping of the BNP levels measured in healthy subjects and in patients with symptomatic heart failure[96].

In addition to the great scattering of BNP levels in patients with heart failure, the contribution that the BNP gives to the diagnosis of CHF is obscured by its high intraindividual biological variability in the plasma[64,65,67].

On the basis of the Bayesian approach, in order to maximize the negative predictive value of the exam (ruling out of CHF in symptomatic patients), it seems appropriate to use cut-off values equivalent to the upper limit of reference obtained in a healthy population with the analytic method used.

Initial evaluation of patients with acute heart failure

The diagnostic role of the BNP/NT-proBNP plasma levels in patients with signs and symptoms of heart failure in the acute phase or during exacerbation has been evaluated by a number of studies. Almost all of these were performed in emergency departments or in the emergency ward by using at first a point-of-care method (POCT) for the BNP assay, and, more recently, totally automated methods[97-111].

In the multicenter study Breathing Not Properly, the use of a BNP cut-off value of 100 ng/l (POCT Biosite method) gave the test a 90% sensitivity, a 76% specificity, and an 81% accuracy for the diagnosis of the cardiac origin of the acute dyspnea – higher values than those obtained at clinical evaluation[103]. A lower cut-off value (50 ng/l) gave the test a 97% sensitivity, a 62% specificity, a 71% positive predictive value, and a 96% negative predictive value: this confirms the usefulness of the test in the ruling out of these patients. Furthermore, a critical analysis of the results of this multicenter study evidenced a "gray zone" within the values of the test (in the specific case between 50 and 500 ng/l) in which the differential diagnosis between heart failure and other causes of dyspnea cannot be based on the use of BNP alone[98]. Accordingly, the use of different cut-off values for age, gender, and ethnic origin does not improve the diagnostic accuracy, in ruling out patients with suspicion of CHF[110].

In a more recent prospective and randomized study, the BNP assay improved the efficacy of diagnosis and treatment of patients with acute dyspnea, significantly reducing the period of hospitalization and the total cost of treatment[111]. Other studies confirmed that the NT-proBNP assay could be especially useful for ruling out the diagnosis of heart failure in patients who arrive to the emergency ward with acute dyspnea[108,109].

It is evident that, at the moment, plasma CNH assay should be performed only to exclude a cardiac origin of acute dyspnea in patients presenting with ambiguous signs and symptoms that may be confused with other pathologies (e.g. chronic obstructive pulmonary disease).

Evaluation of left ventricular dysfunction

Several studies tried to correlate BNP plasma levels with left ventricular function in patients with the indication for echocardiography[29]. In general, the diagnostic power of the test was related to a decreased ventricular function and its prevalence in the study population. In a recent study in which the prevalence of left ventricular dysfunction (ejection fraction < 45%) turned out to be 11%, the BNP measurement allowed to identify patients without dysfunction with a 96% predictive value[112]. In another study, a different definition of left ventricular dysfunction (ejection fraction < 50% or diastolic dysfunction) obviously increased the prevalence (47%). In this context, both specificity (98%) and sensitivity (86%) of the method were satisfying[99].

Asymptomatic ventricular dysfunction screening

Recent studies evidenced that more than one half of subjects with ventricular systolic or diastolic dysfunction are asymptomatic[113-120]. A simple and relatively economic test, like the BNP assay, could be extremely useful in identifying subjects who require more sophisticated exams (e.g. echocardiography).

In an investigation conducted on more than 3000 volunteers in Framingham, the BNP measurement did not result useful in the population screening[114]. These data have been also confirmed by other studies[118]. Better results have been obtained in a prospective study performed on a group of high-risk patients selected on the basis of clinical criteria (high blood pressure and/or not normal electrocardiogram)[119]. In this group, the number of echocardiographic exams necessary for identifying one ventricular dysfunction was reduced from 17 to 12, thanks to the data obtained on BNP levels. These prospective findings should however be confirmed in prospective studies.

When the definition of the investigated dysfunction becomes wider (and consequently when the prevalence of the researched pathology increases) and any cause of

cardiac dysfunction is included, the BNP diagnostic value seems to increase, even if it always holds a ruling out value[120,121]. Although this procedure significantly reduced the costs of screening by selecting and dividing the study population into subgroups, a prospective study is essential before it can be recommended for the systematic screening of populations.

Guide to therapy

The reported relation between BNP/NT-proBNP plasma levels and the cardiac ventricular function kindled the hope that BNP monitoring may help and guide the cardiologist in evaluating the efficacy and in optimizing therapy for heart failure. However, only few preliminary studies (enrolling till now a limited number of patients) evaluated this interesting hypothesis[29,76,122-126].

In one study, 20 patients with mild-to-moderate heart failure were randomized to receive ACE-inhibitors on the basis of repeated BNP measurements or of a traditional clinical approach[122]. In the group of patients where the therapy was guided by BNP, a significant reduction in BNP levels was noticed along with a more marked and lasting inhibition of the renin-angiotensin system, whereas heart rate had slightly decreased.

In another study, 69 patients with compromised systolic function and symptomatic heart failure were treated following a sequential protocol consisting of one ACE-inhibitor plus other drugs and were assigned to clinical management with or without the knowledge of NT-proBNP levels[123]. In the group of patients monitored with NT-proBNP, cardiovascular events decreased by 65% during a period of 9.5 months.

Several clinical and epidemiological studies showed a correlation of CNH levels with a reduced cardiac function, in particular a reduced left ventricular systolic function[4,5] as well as diastolic or right ventricular function, and with age and renal function: all these results explain the important correlation between BNP levels, symptoms and prognosis in patients with heart failure[127]. These promising data are now waiting to be confirmed by clinical randomized studies. Even though the evidence published so far is encouraging, some aspects have to be clarified, like a certain unpredictability of the beta-blocker effect (a therapy of undisputed efficacy) on CNH levels in patients with heart failure. The contrasting effects of beta-blockers on CNH (decrease, neutrality or even increase) are likely to be due to the duration of treatment (early increase at the moment of the introduction followed by progressive decrease) but also to the pharmacological selectivity of the different compounds[29,124,128-130]. Moreover, whereas mean CNH levels may reflect the therapeutic answer in a partially homogeneous population of patients and thus may be used as a surrogate endpoint in clinical studies, this approach may not always be adopted in single patients due to BNP high biological variability[97]. In other words, when monitoring single patients with heart failure, differences in BNP levels over time may be considered relevant if they exceed the high critical difference characteristic of these markers[64,65,67].

Conclusions

There are two main fields of application of the BNP/NT-proBNP assay that are likely to be adopted in clinical practice:

• rule-out diagnosis of new cases of heart failure in subjects evaluated by the general practitioner (aim: to decrease the number of "useless" cardiologic examinations);

• differential diagnosis of acute heart failure in the emergency ward (aim: to decrease the time in starting a specific and effective treatment).

The possibility that CNH measurement can help the periodic evaluation of the clinical stability of outpatients with heart failure or at home seems to be more remote, in the same way as the glycemia control of diabetic patients (aim: to decrease the number of the specialist's examinations of outpatients).

Recommendations 2-8

Recommendation 2. It is advisable to perform a BNP/NT-proBNP assay in order to rule out the diagnosis of CHF in patients with a suspicious diagnosis, but with ambiguous signs and symptoms or manifestations that can be confused with other pathologies (like chronic obstructive pulmonary disease).
Category of evidence: class I.
Level of evidence: type B.

Recommendation 3. It is advisable to perform a BNP/NT-proBNP assay in order to confirm the diagnosis of heart failure in patients with a suspicious diagnosis, but with ambiguous signs and symptoms or manifestations that can be confused with other pathologies (like chronic obstructive pulmonary disease).
Category of evidence: class IIa.
Level of evidence: type B.

Recommendation 4. The BNP or NT-proBNP assay is complementary to, but does not replace, the clinical and instrumental evaluation of patients with heart failure.
Category of evidence: class I.
Level of evidence: type C.

Recommendation 5. Routinary BNP or NT-proBNP assay for patients with a certain clinical diagnosis of heart failure is not necessary.
Category of evidence: class I.
Level of evidence: type C.

Recommendation 6. Routinary BNP or NT-proBNP assay is not appropriate for the screening of left ventricular dysfunction in asymptomatic populations.
Category of evidence: class I.
Level of evidence: type C.

Recommendation 7. BNP and NT-proBNP plasma levels may provide valuable information in the clinical assessment of patients with CHF in selected situations, when risk stratification for death is required.
Category of evidence: class I.
Level of evidence: type B.

Recommendation 8. Routinary BNP or NT-proBNP assay is not indicated in order to choose the proper therapy in patients with acute heart failure or CHF.
Category of evidence: class IIb.
Level of evidence: type B.

B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide in acute coronary syndrome

The results of several studies carried out on more than 12 000 patients, pointed out that increased CNH levels are predictive of death or severe heart failure in the whole spectrum of patients with ACS[26,131-144]. Therefore these studies suggested the clinical use of the CNH assay in this patient subset.

Concepts of risk stratification in acute coronary syndrome

The early risk stratification in patients with ACS is fundamental in order to concentrate the diagnostic and therapeutic resources on higher-risk patients, who need an early aggressive antithrombotic treatment and a rapid revascularization.

The predictive instruments of risk (death, recurrent ischemic events or heart failure), based on the survey of clinical, electrocardiographic and biohumoral variables (markers of cardiac damage, mainly troponins), are relatively inaccurate. For this reason new indicators should be made available as to enable the identification of those subjects who are missed at the traditional instrumental evaluation.

In order to achieve diagnostic power, several characteristics have to be verified before considering a new biochemical marker for clinical use (prognostic independent value, prognostic incremental value as regards to the prognostic variables commonly used, easiness and accuracy of measurement, positive effect of specific therapies administered when a marker increase is found). These characteristics should be assessed by resorting to an optimal use of the basic prognostic variables and by comparing the new biochemical marker to them[145].

Cardiac natriuretic hormones in acute myocardial ischemia

Increased CNH levels may be detected in patients with ACS even if there is no evidence of myocardial necrosis at the evaluation of biochemical markers such as troponins[26,144,146,147]. It has been demonstrated that BNP levels increase after coronary angioplasty, also with normal intracardiac pressure levels, and during exercise-induced myocardial ischemia[26,146,147]. This suggests that myocardial ischemia may rapidly induce BNP synthesis and release according to the severity of ischemia.

The mechanism of CNH production during ischemia is still unknown, even if it is believed that the regional increase in myofibril stretching and the local decrease of myocardial contractility are implicated[148,149]. However, some studies suggested that myocardial ischemia as well as hypoxia are able to directly stimulate the ventricular production of BNP[26-28,150,151]. It is known that BNP plasma levels closely correlate with aerobic capacity in patients with heart failure[152-154]. These results could explain the increased BNP levels in some patients with ACS without significant ventricular dilation[26,150,151]. According to this hypothesis, elevated BNP values (or NT-proBNP) could be due, at least partially, to the activation of the neurohormonal system as a consequence of myocardial ischemia or hypoxia[147].

Prognostic value of cardiac natriuretic hormones

The results of clinical studies indicate that elevated BNP and NT-proBNP levels:
a) are predictive of mortality;
b) are predictive of severe heart failure (pulmonary edema and shock);
c) are not predictive of recurrent ischemic events (mostly non-fatal myocardial infarction).

The prognostic value of elevated CNH levels is independent and incremental compared to clinical (age, diabetes, previous heart failure or heart failure at admission, blood pressure, heart rate), electrocardiographic (in patients with non-ST-elevation ACS) and biochemical variables (troponins).

Cardiac natriuretic hormone levels in acute coronary syndrome

The interpretation of elevated CNH levels turns out to be difficult since the increase is related to the severity of the ischemic event and to the period elapsing between the beginning of the ischemic event and the measurement of CNH levels that progressively increase during the first 24 hours from the acute ischemic event[148,150]. It has been demonstrated that patients with ST-elevation myocardial infarction show higher CNH

plasma levels than patients with non-ST-elevation myocardial infarction and that the latter shows higher CNH levels than patients with unstable angina[131-133,136,151,155]. CNH levels have been demonstrated to correlate with the extension of heart disease[156,157].

Following these considerations, it is intuitively difficult to identify a single cut-off value able to express all the potential risk deriving from increased CNH levels. A recent meta-analysis reported the median values of CNH levels, including the results published in major clinical studies assessing the prognostic value of CNH in patients with ACS, with special reference to the results obtained in the patient subsets where the marker was evaluated[148]. Of course this type of analysis is not useful for identifying cut-off values to adopt in clinical practice and therefore each laboratory and clinical team should evaluate the cut-off values to be applied in their context, by following the scientific literature or, better, by referring to clinical studies specifically carried out in similar contexts.

Prognostic value in short- and long-term mortality

The results of the above-mentioned meta-analysis show that the BNP and NT-proBNP prognostic value is similar both in the short (< 1 month: odds ratio-OR 3.38, 95% confidence interval-CI 2.44-4.68) and long term (< 10 months: OR 4.311, 95% CI 3.77-4.94)[148]. This information entails practical implications since the demonstration of a prognostic value also in the short term (the long-term prognostic impact was already showed in the first studies on patients with acute myocardial infarction in which CNH levels were measured in the subacute phase) justifies the research efforts directed to identify specific therapeutic interventions to be applied to patients with an early increase in BNP and NT-proBNP levels.

Prognostic value related to timing of measurement

The results of the meta-analysis show that the prognostic impact of CNH measurement is equivalent either when CNH levels are measured at admission (OR 4.42, 95% CI 3.83-5.51) or when are measured in the following days (OR 3.51, 95% CI 2.64-4.67)[148]. The confirmation of the prognostic value of an early measurement points to the need for identifying those treatments that, when administered to patients with increased CNH levels in the acute phase, can favorably influence the prognosis.

Therapeutic strategies based on cardiac natriuretic hormone levels

Two studies so far have assessed the effect of an early invasive strategy in patients with non-ST-elevation ACS and with elevated CNH levels[141,158]. However, the obtained results are apparently contradictory.

Morrow et al.[141] retrospectively analyzed the patients of the TACTICS-TIMI 18 and they observed that those with increased BNP levels show the same 6-month mortality rate if either assigned to the early invasive strategy or to the conservative approach.

Jernberg et al.[158] retrospectively studied the patients of the FRICS-II and they observed that those showing higher NT-proBNP plasma levels associated with signs of systemic inflammation (defined on the basis of interleukin-6 elevation) may benefit most from the invasive strategy. The 2-year mortality rate of patients with such a "biohumoral pattern" was reduced by 50% (relative risk 0.46, 95% CI 0.21-1.00) with the more aggressive procedure.

The reasons for such differences are to be elucidated yet and they may be various; we suggest to refer to other publications for a more detailed analysis[148,159]. At present there is not enough evidence to indicate which strategy (therapeutic, pharmacological or interventional) may be particularly beneficial in patients with ACS presenting with increased CNH levels.

Recommendations 9-10

Recommendation 9. The BNP/NT-proBNP measurement is useful to establish the death risk profile in the short and long term in patients with ACS, especially in those who do not show overt or previous signs of heart failure or with negative troponin levels.
Category of evidence: class I.
Level of evidence: type A.

Recommendation 10. The BNP or NT-proBNP measurement should be performed at admission in all patients with documented ACS at clinical evaluation or electrocardiography.
Category of evidence: class IIa.
Level of evidence: type B.

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Appendix I

Nomenclature and abbreviations

• *B-type natriuretic pre-propeptide (pre-proBNP)*: it is the genetically coded product consisting of 134 amino acids.
• *B-type natriuretic propeptide (proBNP)*: it is produced by cleavage of the signal peptide of 26 amino acids from the pre-proBNP, turning to the proBNP (amino acids 1-108). It is present both in the myocardium and plasma.

• *B-type natriuretic peptide (BNP)*: it is a biologically active molecule (hormone) consisting of the pro-BNP COOH-terminal fragment (amino acids 77-108).
• *NH_2-terminal fragment of the B-type natriuretic propeptide (NT-proBNP)*: it consists of the proBNP NH_2-terminal fragment (amino acids 1-76) and it does not seem to have hormonal activity. It is detectable both in the bloodstream and in the myocardium. Sometimes further products of degradation/splitting of this molecule are identified with the same abbreviation [e.g. NT-proBNP (amino acids 1-121)], but scanty information is available on their metabolism and pathophysiology.
• Peptides of the A-type natriuretic peptide (ANP) family are similarly defined: pre-proANP, proANP, NT-proANP.

Appendix II

Cut-off values

Introduction. The Experts Committee held not to have to officially recommend any specific cut-off values for the following reasons:
a) the available BNP and NT-proBNP assaying methods show different immunological specificity and cut-off values (Table III)[29,55-58,159-164];
b) the optimal cut-off values frequently obtained at ROC curve analysis (corresponding to the maximum value of the addition specificity + sensitivity) not only depend on the type of the measured peptide (ANP, NT-proANP, BNP or NT-proBNP) and on the assaying method used, but also:
- on the gold standard used to classify the assay results (positive/negative, true/false);
- on the clinical condition in which the diagnostic accuracy is tested;
- on the disease prevalence in the examined context;
- on the disease severity of the study population;
- on the type of interpretation of the statistical analysis used.

For these reasons it is not possible to recommend a single cut-off value to be adopted in every clinical condition. However, the Committee deems that some merely indicative values should be suggested, reporting only the results obtained by using the assaying methods more validated in the literature and underlying the possible clinical limitations.

Rule-out diagnosis of heart failure. As reported in Recommendation 2, it is mostly suggested to perform a CNH assay in order to rule out the diagnosis of heart failure in patients with such a clinical suspicion. To this aim, a CNH level has to be established under which it is very unlike that a heart failure is responsible for the patient's symptoms. The selected value should have clinical degrees of sensitivity and of negative predictive value > 95%[165].

B-type natriuretic peptide utilization. The assaying methods mostly used in the diagnosis of symptomatic heart failure are the IRMA method (Shionogi), employed from the beginning of the '90s[29], and the POCT triage method (Biosite Diagnostics), whose usefulness is primarily based on the studies carried out by the Breathing Not Properly Multinational Study Investigators that examined several times the same group of patients, by dividing the study population into different subgroups[99,103,104,106,107,110]. At present there are not sufficient observations for the BNP assaying methods more recently available (Abbot AxSYM, Bayer ADVIA and Beckman Access).

In order to apply correctly the rule of exclusion (*SnNout*), it would seem more appropriate to use a value approaching (or only just lower) the 97.5° percentile in healthy subjects. In accordance with the data reported in table III, values < 50 ng/l could be utilized for the IRMA, POCT Triage and ADVIA Centaur methods, whereas higher values should be used for the MEIA AxSYM system. It is important to notice that the Breathing Not Properly study showed an average sensitivity of 97% and a negative predictive value of 96% for a value corresponding to 50 ng/l[103].

N-terminal pro-B-type natriuretic peptide utilization. As for the NT-proBNP assay, the only commercially available method is the ECLIA method (Roche). In fact, the method for the Dimension system (Dade-Behring), which makes use of the same antibodies and calibration of the ECLIA method, has been introduced too recently to have any data available. It is necessary to remember that the majority of the studies published in the literature used manual methods for NT-proBNP-related peptide assay not easily applicable in routine clinical practice[21,105,123,124,127,135,138].

Similarly to the BNP assay, a value approaching the 97.5° percentile in healthy subjects may be used as cut-off value for the NT-proBNP in order to rule out the diagnosis of heart failure. This value may be indicated in 150 ng/l, by using both data available in the literature and those reported in table III.

Prognostic value in patients with acute coronary syndrome. It is very difficult to suggest a single cut-off value for the risk evaluation in ACS patients since the risk increases progressively (even if there is not always a linear correlation) with the increase in CNH levels[166].

Authors usually divide patients into groups according to the CNH levels (e.g. by using quartiles) and analyze separately the risk for each group. Clearly, patients belonging to the groups with higher BNP levels also show a higher mortality risk and a higher risk of other cardiac events.

Just as an indication, it can be noticed that data reported in the literature suggest that BNP or NT-proBNP levels higher than 2-fold the upper limit of reference usually seem to have an independent predictive value and to indicate a significant mortality risk.

Summary of recommendations

Recommendation 1. Before clinical use all new tests for CNH assay should be evaluated for the following analytical and preanalytical characteristics:
• type of antigen used as calibrator;
• antibody specificity and identification of epitopes;
• cross-reactivity with all similar moieties within the plasma, including proBNP (amino acids 1-108);
• interferences related to:
- endogenous interfering agents,
- type of biological sample (serum, plasma with different anticoagulant agents),
- type of tube,
- sample stability at different storing temperatures.
Category of evidence: class I.
Level of evidence: type C.

Recommendation 2. It is advisable to perform a BNP/NT-proBNP assay in order to rule out the diagnosis of CHF in patients with a suspicious diagnosis, but with ambiguous signs and symptoms or manifestations that can be confused with other pathologies (like chronic obstructive pulmonary disease).
Category of evidence: class I.
Level of evidence: type B.

Recommendation 3. It is advisable to perform a BNP/NT-proBNP assay in order to confirm the diagnosis of heart failure in

patients with a suspicious diagnosis, but with ambiguous signs and symptoms or manifestations that can be confused with other pathologies (like chronic obstructive pulmonary disease).
Category of evidence: class IIa.
Level of evidence: type B.

Recommendation 4. The BNP or NT-proBNP assay is complementary to, but does not replace, the clinical and instrumental evaluation of patients with heart failure.
Category of evidence: class I.
Level of evidence: type C.

Recommendation 5. Routinary BNP or NT-proBNP assay for patients with a certain clinical diagnosis of heart failure is not necessary.
Category of evidence: class I.
Level of evidence: type C.

Recommendation 6. Routinary BNP or NT-proBNP assay is not appropriate for the screening of left ventricular dysfunction in asymptomatic populations.
Category of evidence: class I.
Level of evidence: type C.

Recommendation 7. BNP and NT-proBNP plasma levels may provide valuable information in the clinical assessment of patients with CHF in selected situations, when risk stratification for death is required.
Category of evidence: class I.
Level of evidence: type B.

Recommendation 8. Routinary BNP or NT-proBNP assay is not indicated in order to choose the proper therapy in patients with acute heart failure or CHF.
Category of evidence: class IIb.
Level of evidence: type B.

Recommendation 9. The BNP/NT-proBNP measurement is useful to establish the death risk profile in the short and long term in patients with ACS, especially in those who do not show overt or previous signs of heart failure or with negative troponin levels.
Category of evidence: class I.
Level of evidence: type A.

Recommendation 10. The BNP or NT-proBNP measurement should be performed at admission in all patients with documented ACS at clinical evaluation or electrocardiography.
Category of evidence: class IIa.
Level of evidence: type B.

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