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ANMCO/ELAS/SIBioC Consensus Document: biomarkers in heart failure

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Biomarkers have dramatically impacted the way heart failure (HF) patients are evaluated and managed. A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological or pathogenic processes, or pharmacological responses to a therapeutic intervention. Natriuretic peptides [B-type natriuretic peptide (BNP) and N-terminal proBNP] are the gold standard biomarkers in determining the diagnosis and prognosis of HF, and a natriuretic peptide-guided HF management looks promising. In the last few years, an array of additional biomarkers has emerged, each reflecting different pathophysiological processes in the development and progression of HF: myocardial insult, inflammation, fibrosis, and remodelling, but their role in the clinical care of the patient is still partially defined and more studies are needed before to be well validated. Moreover, several new biomarkers have the potential to identify patients with early renal dysfunction and appear to have promise to help the management cardio-renal syndrome. With different biomarkers reflecting HF presence, the various pathways involved in its progression, as well as identifying unique treatment options for HF management, a closer cardiologist-laboratory link, with a multi-biomarker approach to the HF patient, is not far ahead, allowing the unique opportunity for specifically tailoring care to the individual pathological phenotype.

Heart failure (HF) is a complex syndrome involving neurohumoral and inflammatory changes of different cell types including cardiac myocytes, fibroblasts, endothelial, and vascular smooth muscle cells. A consequence of the complex pathophysiological substrate of HF is the ever increasing number of circulating molecules (i.e. biomarkers) found/discovered to be altered in patients with HF.
Many molecules have been labelled as circulating 'biomarkers' in HF. The present document aims at helping the clinician in (i) appropriately using available biomarkers, and (ii) approaching new biomarkers through the literature with a critical attitude. Of all biomarkers reported to provide original information in diagnosis, prognosis, or management of HF, only cardiac troponins I or T and natriuretic peptides are cardio-specific. This explains why the largest body of evidence supporting their clinical use has been collected on these two families of biomarkers.

Background

The consensus document for Italian clinical cardiologists has been published very recently, where the evidence on the use of troponins and natriuretic peptides in HF are reported in several sections.[1]

The present document does not aim at comprehensively reviewing all established and candidate laboratory biomarkers in HF. Other types of biomarkers, such as imaging or genetic biomarkers, will not be discussed in detail, but will be evaluated in comparison with laboratory biomarkers. Unless otherwise specified, 'biomarkers' will be used for 'circulating biomarkers' or 'laboratory biomarkers' throughout the present document.

Objectives

Aims of the present review are

(1) To summarize the evidence supporting the clinical use of cardiac specific biomarkers, the main issue being how to make a good use of these validated markers in specific clinical/ambulatory settings.
(2) To provide the interested clinician with concise, essential information on the so-called 'new biomarkers' in order to help them in a critical use of the literature.

Premises

Before dealing with individual biomarkers, grouped by 'reasonable' categories, a general agreement on the following two methodological issues should be reached:

(1) Assays of the biomarkers;
(2) Sample size of studies to assess clinical performance of biomarkers.

Analytical issues

The contribution of the laboratory to the clinical management of HF by the biomarkers, represents one of the most important breakthroughs of the last decades. Standardization and validation of diagnostic methods, combined with a close link between the laboratory and the clinic improves the confidence of the cardiologist in the use and in a correct interpretation of analytical results on circulating biomarkers.

Cardiovascular biomarkers are usually measured with non-competitive immunometric assays in clinical laboratory practice.[2] Analytical performance of biomarker laboratory tests has progressively improved in the last 20 years. In particular, the last generation of immunometric assays using automated platforms is able to measure circulating levels of biomarkers [such as B-type natriuretic peptide (BNP), N-terminal proBNP (NT-proBNP), cTnI, and cTnT] with a limit of detection (LoD) of few ng/L (from 1 ng/L to 5 ng/L), a limit of quantification (LoQ) $\leq$ 10 CV% in the range of 5–15 ng/L, and a turn round time (TAT) of less than 30 min.[2] These very good analytical performances allowed

the use of these biomarkers as favourite methods even in the emergency department. Despite this remarkable increase in analytical performances, these immunoassays still suffer significant systematic differences between the biomarkers values measured by commercially available laboratory tests, especially for BNP[2,3] and cTnI[4] methods. Accordingly, clinicians should take great care in comparing results obtained by laboratories using different methods.

More difficulties are to be expected from point-of-care testing (POCT), whose reliability is, at the present time, not always adequately optimized and evaluated.[5] As far as the POCT methods for cardiac troponins are concerned, it is important to consider that the commercial methods so far available, do not satisfy the analytical quality specifications recommended by the international guidelines.[6-8] The POCT methods usually measure the recommended upper limit of normal with an error $>$ 20% CV and so they should be used for *rule-in* and *rule-out* of myocardial infarction only where (or when) the more sensitive immunoassay methods using automated platforms are not available.[8] As far as the POCT methods for the measurement of natriuretic peptides are concerned, these assays are often used in both emergency departments and primary care, although their analytical sensitivity and reproducibility is lower than that of immunoassay methods using automated platforms.[9-11]

Sample size

It is common belief that sample size calculations, in order to minimize the risk of false-negative results, are the matter of clinical trials testing drugs. This is definitely wrong, since the same risk is inherent in studies assessing predictive value or associations of risk factors, such as biomarkers. Without an adequate power, say above 60%, the risk of a false negative result is too high to reject the null hypothesis. The same is true for positive results obtained in small samples, too susceptible of bias and play of chance to be translated into clinical practice.

An authoritative example of power calculation is provided by an analysis of Framingham on renin. Given the lack of a significant association of renin with cardiovascular risk, the statistical power to detect modest effects was assessed. At an alpha of 0.05, the power was at least 80% for each outcome (hard cardiovascular disease and all-cause mortality), in the full sample and in the hypertensive sub-sample, for the true HR of 1.25 per SD of log-renin.[12]

The data reported in *Table 1*, considering different combinations of hazard ratios and power, provide an idea on the number of patients needed for a reliable assessment of association between biomarkers and risk.

Table 1 Number of patients to be enrolled in studies testing prognostic value of biomarkers. Different calculations are presented according to power (type II error) and impact on outcomes expressed as hazard ratio (HR) of above vs below the median level of the biomarker

HR	Sample size	Power
1.2	4240	80%
1.4	1192	80%
1.6	580	80%
1.2	3334	70%
1.4	937	70%
1.6	457	70%

HR, hazard ratio.

Table 2 Accuracy of history and physical findings in diagnosing acute congestive heart failure (modified from references 13 and 14)

Variable	Sensitivity	Specificity	Accuracy
History of HF	62	94	80
Dyspnea	56	53	54
Orthopnoea	47	88	72
Rales	56	80	70
Third heart sound	20	90	66
Jugular vein distension	39	94	72
Oedema	67	68	68

HR, heart failure.

Myocardial stress and function laboratory biomarkers

Pathophysiological and clinical interpretation

HF is considered the fatal finishing line of all cardiovascular disorders. HF is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intra-cardiac pressures at rest or during stress.[13] Positive history and some physical signs (such as orthopnoea, rales, third heart sound, or jugular vein distension) share a good diagnostic specificity, but also a poor sensitivity in diagnosing acute congestive HF (*Table 2*).[13,14] Therefore, the diagnosis of both acute and chronic HF is based on the clinical judgment including a combination of history, physical examination, and appropriate investigations, as recommended by all international guidelines.[15-19]

The pathophysiological interpretation of plasma BNP/NT-proBNP variations may be difficult in some clinical settings. The cardiac endocrine function has a pivotal role in the regulation of body fluids, electrolytes, and haemodynamics.[20] The cardiac peptide hormones, ANP and BNP, share diuretic, natriuretic, vasodilating, and anti-hypertrophic activities.[20] A continuous and intense information exchange flows from the endocrine heart system to nervous and immunological systems and to other organs, including kidney, endocrine glands, liver, adipose tissue, immune-competent cells, and *vice versa*. This close link between cardiac natriuretic peptide system and counter-regulatory systems with sodium-retentive, vasoconstrictive and hypertrophic activities (including renin-angiotensin-aldosterone system, endothelins, catecholamines, arginine-vasopressine system, and pro-inflammatory cytokines) may explain the increase in circulating levels of

BNP/NT-proBNP in patients with some extra-cardiac diseases.[20]

A deficiency in biological action of circulating cardiac natriuretic peptide hormones may contribute to explain the altered electrolyte and fluid balance occurring in chronic HF: a phenomenon, defined as the 'endocrine paradox' of HF.[20] Patients with congestive HF show signs of fluid retention and vasoconstriction, despite the extremely high circulating BNP levels, measured by immunoassay methods at present time commercially available.[1,20] Indeed, a blunted natriuretic response after pharmacological doses of ANP and BNP has been observed in experimental models and in patients with chronic HF, suggesting a resistance to the biological effects of natriuretic peptides.[20] An explanation of the paradox of high circulating levels of the hormone, but low plasma natriuretic activity may be the large cross-reactivity of proBNP on the immunoassay methods considered specific for BNP.[1,21] This cross-reaction produces a great overestimation of the measured levels of BNP, because proBNP is the predominant peptide form present in plasma of patients with severe HF.[1,20] Another cause of resistance to biological action of natriuretic peptides is that proBNP is able to bind to the natriuretic peptide receptors, but it stimulates the receptor with lower potency than the active hormones, ANP and BNP, and so it produces a decrease in natriuretic activity by displacing the more biologically active peptide hormones from the receptors.[22]

Another important clinical issue in the interpretation of measurements of natriuretic peptides in HF is that circulating BNP and NT-proBNP levels mirror the effectiveness of the treatment of acute or chronic HF, with lowering of levels over time associated with better clinical outcomes.[23-26]

Use of BNP/NT-proBNP in clinical diagnosis of acute and chronic heart failure

All the most recent national and international guidelines[13,16-20] recommend the natriuretic peptides, and in particular the peptides related to the B-type cardiac peptide hormone (such as BNP and NT-proBNP), as the first line biomarkers for the diagnosis of both acute and chronic HF. In particular, the 2013 ACCF/AHA guidelines recommend the BNP and NT-proBNP measurement for the diagnosis or exclusion of HF in patients with chronic or acute decompensated HF (with the maximum degree of class of recommendation I and level of evidence A).[16] The clinical contribution to the diagnosis of BNP/NT-proBNP assay is particularly significant when the etiology of dyspnoea is unclear. Moreover, the 2013 ACCF/AHA guidelines recommend the measurement of natriuretic peptides with the maximum degree of evidence (class I and level A) also for the prognosis of HF patient.[16]

Usually there are no differences in the diagnostic use of BNP and NT-proBNP immunoassays.[1] However, two recent studies from the PARADIGM-HF (prospective comparison of angiotensin II receptor blocker neprilysin inhibitor (ARNI) with angiotensin-converting-enzyme inhibitor (ACEI) to determine impact on global mortality and morbidity in heart failure (HF)] trial[27,28] reported conflicting results between BNP and NT-proBNP levels. PARADIGM-HF study evaluated the clinical effects of a new drug (denominated LCZ696 or ENTRESTO), including a combination of sacubitril, a neprilysin (NEP) inhibitor, and valsartan, an angiotensin II receptor blocker. The mechanism of of action of this drug is complex, combining the effect of the angiotensin II receptor blocker and that of the neprilysin inhibitor. The enzyme neprilysin causes degradation not only of natriuretic peptides but also of a variety of components affecting the mechanisms of action for several other circulating hormones, including adrenomedullin, bradykinins, angiotensin I, endothelin-1, and substance P.[29] The rationale for the use of a drug containing a neprilysin inhibitor in HF patients is that this proteolytic enzyme can degrade the biologically active natriuretic peptides (ANP, BNP, and CNP).[29] For this reason, a drug, containing a substance inhibiting natriuretic peptide degradation (such as LCZ696), may increase the circulating levels of the biologically active natriuretic hormones and, by doing so, may improve the clinical conditions of HF patients by increasing diuresis and natriuresis and reducing cardiac stress.[29] PARADIGM-HF study found that plasma BNP levels were higher during treatment with LCZ696 than with enalapril, but, on the contrary, circulating levels of NT-proBNP and cardiac troponin T (cTnT) were lower during treatment with LCZ696 than with enalapril in the first week of treatment.[27] Authors explained these conflicting results obtained in the PARADIGM-HF study by considering the combined action of LCZ696 drug. Indeed, BNP (but not NT-proBNP) is a substrate for neprilysin[29,30]; as a result, the increase in BNP levels should reflect the inhibiting action of the drug on the enzyme neprilysin. On the contrary, the decrease in NT-proBNP levels may reflect the beneficial effects of the drug on myocardial function and vascular haemodynamics, especially by inhibiting the renin-angiotensin-aldosterone system activity.[29,30] Indeed, the reduction of cardiac stress during LCZ696 treatment should reduce the production and secretion of natriuretic peptides from cardiomyocytes (and so a fall of the circulating levels of NT-proBNP, too).[1] In conclusion, clinicians should accurately consider the clinical setting in order to correctly interpret the variations of natriuretic peptides measured by commercially available laboratory methods. In particular, clinicians should distinguish the increase in BNP levels, due to the inhibiting effect of LCZ696 from those due to deterioration of clinical conditions.

Several studies, including also several meta-analyses,[31-37] demonstrated the clinical relevance of BNP/NT-proBNP assay in patients with both acute and chronic HF in different clinical settings (including emergency department and primary care). The measurement of BNP and NT-proBNP is useful in supporting clinical judgment for the diagnosis or exclusion of HF in the setting of chronic ambulatory HF or acute decompensated HF (with the maximum degree of class of recommendation I and level of evidence A).[16] Indeed, all international guidelines, starting from the first years of this century, state that lower values of BNP or NT-proBNP actually exclude the presence of HF, while higher values have reasonably high positive predictive value to diagnose HF.[13,16-19,38-41] Therefore, BNP/NT-proBNP assay is recommended for ruling-out HF, but not to establish the diagnosis.[13] Although some international guidelines[13,17-19]

suggest some cut-off values of BNP assay for the ruling-out or ruling-in HF, these values are only indicative, because there are large systematic between BNP immunoassay methods.[2,3] On the contrary, the cut-off values reported by international guidelines for NT-proBNP assay are more reliable, because only one manufacturer distributes the standard and materials for all immunoassay methods, commercially available in Europe for NT-proBNP measurement.[2,3]

BNP/NT-proBNP assay can be also useful for detection of early phases of HF (phase A or B),[16,40] when patients are still asymptomatic or pauci symptomatic (functional NYHA classes I and II).[42] BNP/NT-proBNP assay cannot differentiate the type of cardiac dysfunction (systolic vs. diastolic); however, the BNP/NT-proBNP levels found in HF patients with preserved left ventricular ejection fraction usually are lower than those of HF patients with reduced left ventricular ejection fraction.[13,36] As recommended by national and international guidelines,[13,16-19,38-41] the clinical information obtained from electrocardiographic and echocardiographic examination and from the BNP/NTproBNP assay are not equivalent, but they contribute independently to the HF diagnosis and to the definition of the patient's clinical status.

At present time, with the exception of cardiac natriuretic peptides, no other cardiovascular biomarkers are recommended by international guidelines for the diagnosis of both acute and chronic HF with the maximum degree of class of recommendation and level of evidence.[13,16-19]

Synthesis of evidences

(1) The measurement of cardiac natriuretic peptides is recommended for the diagnosis of HF in patients with dyspnoea by national and international guidelines since year 2005.
(2) Due to the high degree of clinical sensitivity and negative predictive value, the measurement of cardiac natriuretic peptides is useful for excluding the diagnosis of HF, especially using method-specific reference limits and taking into account sex and age of the patient as well as the presence of obesity and kidney failure.
(3) The measurement of cardiac natriuretic peptides cannot differentiate the type of cardiac dysfunction (systolic vs. diastolic).
(4) The clinical information obtained from echocardiographic examination and from BNP/NT-proBNP assay is not equivalent, but they contribute independently to the HF diagnosis and to the definition of the patient's clinical status.

Clinical use of cardiac natriuretic peptides as prognostic biomarkers in heart failure patients

More than 1000 published studies, including several meta-analyses,[43-56] evaluated the prognostic accuracy of natriuretic peptides (in particular BNP and NT-proBNP) in patients with acute or chronic HF. Plasma BNP and NT-proBNP levels usually decrease during treatment of chronic HF, correlating with improved clinical outcomes, including mortality, hospital stay and/or readmission rate.[15,24,25,41,43-47,48,51-54,56-60] According to these experimental and clinical evidences, measurement of natriuretic peptides is recommended with the maximum score (class I and level A) for prognosis in both ambulatory and acute HF patient by the 2013 AACF/AHA guidelines for the management of HF.[16]

Synthesis of evidences

(1) Cardiac natriuretic peptides measurement is recommended for risk stratification in all patients with acute and chronic HF.
(2) The short- and long-term risk of death and of cardiovascular events increases gradually with the increase of biomarker values, even for BNP and NT-proBNP levels within the normal range.
(3) The prognostic information provided by the cardiac natriuretic peptides is independent of that provided by other known cardiovascular risk factors and is associated additively with that of cardiac troponins and cardiac fibrosis markers, such as galectin-3 and sST2 protein.

Use of cardiac natriuretic peptides in clinical management of HF patients

There is an increasing consensus about the use of natriuretic peptide-guided HF management.[26] Several clinical trials and meta-analyses[23-25,43-56,58-60] demonstrated that either baseline level of BNP and NT-proBNP or its decrease after treatment hold a powerful prognostic value in HF patients. In particular, the decrease in peptide natriuretic levels during treatment is associated with clinical improvement, whereas unchanged or increased levels are associated with disease progression and worse prognosis.[23-26] The rationale for the use of BNP-guided treatment is that the variation in plasma peptide concentrations before and after a period of standard therapy is able to distinguish 'responders' with a better prognosis (i.e. a decrease $>$ 30% in peptide levels after therapy), from 'non-responders' patients with a more severe prognosis (i.e. not decrease or even increase in peptide levels after therapy), who probably need both a re-evaluation of clinical status and a re-assessment of treatment.[16,26,45] Moreover, it is important to note that the rationale for the use of natriuretic peptide-guided HF management is based also on the assumption that laboratory tests are able to accurately assess the true status of the cardiac endocrine function.[2,20]

Despite this large number of experimental and clinical evidences found in the literature,[23-25,43-56,58-60] the international guidelines still report an interlocutory judgement about the natriuretic peptide-guided HF management. It should be recognized that evidence is not based on a single, well designed, adequately sized phase III trial. The ESC 2016 guidelines[13] provide only some general recommendations about the usefulness of the natriuretic peptides as a guide-to therapy. In particular, it is recommended to begin treatment with valsartan-sacubitril only in patients with high levels of natriuretic peptides. The 2013 ACCF/AHA guidelines[16] recommended that the dosage of BNP or NT-proBNP to optimize the therapy should be limited to euvolaemic patients and in the context of a well-structured program of management of chronic HF (class of evidence: IIa, level of evidence: B). As for acute HF, the effectiveness of therapy guided by natriuretic peptides has low levels of recommendation and evidence (class of evidence: class IIb, level of evidence: C

type).[16] The NICE guidelines[19] summarize the evidence in the literature and concluded that the use of natriuretic peptides to guide treatment in chronic HF may lead to potential reduction in mortality in some subgroups, although the overall usefulness in all HF patients remains uncertain.

Synthesis of evidences

(1) Patients who respond to treatment with a significant decrease in circulating levels of BNP or NT-proBNP have a better prognosis, particularly with regard to the decrease of mortality and/or major cardiovascular events.
(2) BNP/NT-proBNP guided therapy significantly reduces mortality in patients younger than 75 years while hospitalization is reduced for all ages and for all causes of hospitalization.
(3) In light of the current scientific evidence, it is appropriate to measure the BNP/NT-proBNP levels in patients hospitalized for acute HF at least at the admission and before the discharge to assess the patient's response to therapy. A reduction in levels greater than 30% should be considered significant.
(4) There is no evidence in the literature regarding the serial evaluation of BNP/NT-proBNP during hospitalization (except for the admission and discharge)

Laboratory biomarkers of myocardial injury

Pathophysiological and clinical interpretation of myocardial release of troponin in heart failure patients

Cardiac troponin I (cTnI) and cTnT are the most widely used biomarkers of myocardial injury in clinical research and in patients with acute coronary syndromes.[1,2] More recently, the availability of highly sensitive assays has markedly increased the analytical sensitivity, thus allowing to monitor also the majority of patients with stable chronic HF, whose concentrations of troponins were often below the LoD of earlier generation assays.[61-64] cTnI and cTnT are essentially equivalent as markers of cardiac injury in HF patients. In virtually all HF patients, highly sensitive methods can measure circulating cTnI and cTnT levels above their respective limits of detection. In particular, patients with HF, aged 70 years or more, often have circulating concentrations of cTnI and cTnT assayed with high sensitivity methods above the decision limit (99th percentile in a reference population of apparently healthy individuals).[61-64]

From an analytical point of view, some important issues should be discussed in detail, regarding the analytical sensitivity and specificity of laboratory tests at present employed for cTnI and cTnT measurement. First, it is important to accurately define the analytical specifications characterizing the highly sensitive methods.[66,67] One should define methods with high sensitivity only the immunoassays that measure the 99th percentile of the distribution of proteins cTnI and cTnT in the reference population (99th ULN) with an error (expressed as coefficient of variation, CV) equal to or lower than 10%,[66,67] as required by all the most international guidelines, including the Third Universal Definition of Myocardial Infarction.[6] The methods showing an intermediate imprecision (10–20%) should be considered clinically usable (but not highly sensitive methods).[6-8,66,67] The reference population on which the 99th URL value is calculated should consist of at least 300 apparently healthy subjects of both genders with a broad age distribution (usually from 18 to 70 years).[7,66,67] It is important to note that highly sensitive immunoassay methods should also measure the levels of cTnI and cTnT in the majority (i.e. >50%) of apparently healthy adults, who compose the reference population. In particular, the most sensitive, commercially available in Europe, cTnI method is able to measure troponin levels above the detection limit in the great majority (>95%) of healthy subjects,[66,67] also including neonates, children, and adolescents.[68,69] Second, as far as the cardiospecificity of cardiac troponin immunoassay methods is concerned, recent studies suggested that the cTnT may be re-expressed in skeletal myocytes of patients with a wide spectrum of neuromuscular diseases in the absence of clinical and cTnI evidence of myocardial injury.[70-75] Although cTnT and cTnI are both absent in healthy adult skeletal muscle, cTnT (but not cTnI) is present in foetal skeletal muscle. The injured skeletal muscle repairs itself by regeneration; this process recapitulates embryonic myogenesis, and so patients with chronic neuro-muscular diseases can present increased circulating levels of cTnT, but not of cTnI.[70-72] From a clinical point of view, it is important to note that cTnT circulating levels may be increased above the 99th URL value in patients with neuromuscular diseases.[74,75] Furthermore, heart involvement can be excluded by normal values of ECG, echocardiogram, and BNP/NT-proBNP levels. However, to exclude myocardial injury in this group of patients it may be preferable to measure also the cTnI concentration using a high-sensitive method.[74]

Prognostic relevance of cardiac troponins

Several studies demonstrated that increased circulating levels of cTnI and cTnT, especially when these biomarkers are measured with highly sensitive methods, are found in patients with HF, who often do not present obvious myocardial ischemia or underlying coronary artery disease.[61-64] These findings[61-64] suggest that increased cTnI and cTnT in these patients could be caused by cardiomyocyte injury or necrosis. In chronic or acute decompensated HF, elevated cardiac troponin levels are associated with worse clinical outcomes and/or mortality.[61-64,76-83] Indeed, HF patients, showing a significant and lasting decrease in troponin levels after appropriate pharmacological treatment have a better prognosis compared with those who did not show any or only a transient decrease.[61,76-83] Based on these results, 2013 AACF/AHA guidelines for the management of HF recommend that troponin I or T be routinely measured, in addition to natriuretic peptides, in both acute and ambulatory HF patients for improving risk stratification, with the maximum degree of evidence (class I and level A).[16] According to the guidelines by the Heart Failure Section of the Third Universal Definition of Myocardial Infarction Global Task Force, clinicians should be aware of the high frequency of troponin elevation in patients with HF, and for this reason they should keep in mind the possible causes of this phenomenon, and, independent of AMI diagnosis.[84]

Synthesis of evidences

(1) Increasing circulating levels of plasma cardiac troponin, even within a normal range, are associated with a worse prognosis in HF.
(2) The prognostic value of cardiac troponins is independent and incremental compared with other risk factors and cardiovascular biomarkers

Laboratory biomarkers of cardiac remodelling and fibrosis

Cardiac ventricular remodelling occurs progressively in untreated patients after large myocardial infarction and in those with cardiomyopathy. Myocardial remodelling in ischaemic and non-ischaemic cardiomyopathies involves not only the cardiomyocytes, but also non-myocyte cells and the extracellular matrix, which includes fluid, collagen, and glycoproteins.[85,86] Detection of fibrosis and of an ongoing remodelling process holds clinical value and should guide therapeutic strategy in HF patients. For this reason, there is an increasing interest in the development of new biomarkers and a great number of laboratory tests have been recently proposed, whose clinical usefulness, however, is not fully established yet.[86] Fibrosis is an ubiquitous mechanism of tissue repair. An increase in cardiac fibrosis is associated not only to normal ageing but also to arterial hypertension and other less common diseases. An excessive collagen synthesis and deposition and/or a decrease in its degradation cause an increase in collagen content of myocardium and blood vessel wall which can lead to cardiac dysfunction and ultimately cardiac failure. Part of the beneficial effect of recommended therapies for HF may be explained by their anti-fibrotic action. At present, there are no reliable markers with sufficient sensitivity and cardiac-specificity to be used clinically in HF patients.

However, many studies, even including some recent meta-analyses,[86-89] have been published on biomarkers of cardiac remodelling and fibrosis, especially concerning galectin-3 and sST2, in patients with acute and chronic HF. However, the evidence available is not sufficient to support their use in the clinical routine to improve prognostic stratification and diagnosis of individual patients.[16,86] In particular, more studies are needed to document the independent prognostic value of circulating markers of fibrosis, on top of the other established markers, cardiac troponins and natriuretic peptides.[13,16,86] Being non-cardiac-specific biomarkers, the value of galectin-3 and sST2 in HF patients should be established in front of other frequent comorbidities, such as diabetes, systemic chronic inflammatory disorders, renal and liver diseases.[13,86]

The 2016 ESC guidelines[13] mention the increasing interest in 'new' biomarkers of HF, but underscore that the evidence currently available is not sufficient to recommend their use in clinical practice. On the contrary, the 2013 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines[16] contain recommendations on biomarkers of inflammation and fibrosis, suggesting that the most promising biomarkers of this class are galectin-3 and soluble ST2. Even with the low level of recommendation, the 2013 ACCF/AHA guidelines suggest that the dosage of biomarkers of inflammation and fibrosis, along with the dosage of other biomarkers, may improve the prognostic stratification both in patients with chronic (class of evidence: IIb, level of evidence: B) and acute HF (class of evidence: IIb, level of evidence: A).[16]

Synthesis of evidences

(1) There are still some doubts on efficiency, prognostic role, and cost-effectiveness of biomarkers of cardiac remodelling and myocardial fibrosis, even if many studies have been published recently.
(2) In particular, more studies are needed to confirm their independent and additional prognostic contribution in comparison with other biomarkers, such as natriuretic peptides and cardiac troponins.
(3) Moreover, they are non-cardio-specific biomarkers and their usefulness has to be fully established in the presence of co-morbidities such as diabetes, chronic systemic inflammatory diseases, renal and liver diseases.
(4) Considering the wide range of biomarkers of cardiac remodelling and myocardial fibrosis, the clinician should direct his decision remembering the analytical characteristics of the assay, the efficiency and prognostic effectiveness of the biomarker also in relation to patients' setting, possible confounding variables, co-morbidities and costs.

Novel biomarkers and multi-markers models

In recent decades, several multi-marker models (probably more than 100) have been suggested and evaluated for different populations of HF patients.[13,14,90-92] Criteria to evaluate and compare the prognostic efficacy and efficiency of new cardiovascular risk biomarkers were recently reported and discussed in details.[91,92] Novel risk biomarkers should be evaluated in several phases, including initial proof of concept, prospective validation in independent populations, documentation of incremental information, when added to standard risk markers, assessment of effects on patient management and outcomes, and ultimately, cost-effectiveness.[91,92] Biomarkers that do not change the management of a disease unlikely will significantly affect patient outcome and therefore will not be cost-effective (judged in terms of quality-adjusted life-years gained).[14,91,92] The search is still open for novel biomarkers useful for prognosis and guide therapy in HF patients.[14,26,93] Promising candidate biomarker may be: growth differential factor-15 (GDF-15),[94-96] carbohydrate antigen-125 (CA-125),[97-99] C-terminal pro-vasopressin (copectin),[100-103] mid-regional pro-adrenomedullin (MR-proADM),[100,101,104] NEP,[30,105] and orexin.[93,106] Some of these molecules have been utilized for many years as tumour-markers (CA-125), neuro-hormones (copeptin, MR-proADM) or inflammatory markers (GDF-15) in clinical practice. Therefore, several studies are available on their biological activity and variation, pathophysiological and clinical relevance, reference range values and analytical characteristic of assay methods.[93] Conversely, there are scarce data on neprilysin[30] and orexin,[106-108] which should be considered as biomarkers in the early discovery phase and still under evaluation. A detailed discussion of that

clinical relevance of these promising HF biomarkers is out of the aim of this executive summary and interested readers can consult the references for more information.

The relatively modest performance allowed by individual biomarkers prompted several investigators to evaluate the hypothesis whether multiple biomarkers could be combined to improve prognostic performance.[14,90-92] The 'multimarker approach' has been tested in several studies, primarily with the use of circulating biomarkers.[14,90-92] There are fewer data incorporating imaging into multimarker algorithms and also few data on the use of circulating, genetic, and/or imaging biomarkers in combination.[14,90-92] Multivariable statistical models may be used to calculate some multivariable risk scores.[109] Multivariable risk scores may help predicting death in patients with HF, but they remain less useful for the prediction of subsequent HF hospitalizations.[13] A systematic review examining 64 prognostic models along with a meta-analysis and meta-regression study of 117 prognostic models reported only a moderate accuracy of models predicting mortality, whereas models designed to predict the combined endpoint of death or hospitalization, or only hospitalization, showed a poorer prognostic power.[110]

Synthesis of evidences

(1) There are several novel biomarkers for prognosis and to guide therapy in HF patients, which are in the early discovery phase and still under evaluation.
(2) More studies are needed to evaluate the clinical relevance and especially to confirm the independent and additional prognostic contribution of novel biomarkers in comparison with natriuretic peptides and cardiac troponins.
(3) Multivariable risk scores may help predicting death in patients with HF, but at present time they remain less useful for the prediction of subsequent HF hospitalizations or to guide therapy in the individual patient.

Consensus Document Approval Faculty

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