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Article type : Review

Combining echo and natriuretic peptides to guide heart failure care in the outpatient setting: a position paper

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Running title: Combining echo and natriuretic peptides to treat heart failure.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/eci.12846

Abstract

Background: Chronic heart failure (HF) is a relevant and growing public health problem. Although the prognosis has recently improved, it remains a lethal disease, with a mortality that equals or exceeds that of many malignancies. Furthermore, chronic HF is costly, representing a large and growing drain on healthcare resources. **Methods:** This narrative review is based on the material searched for and obtained via PubMed up to May 2017. The search terms we used were: "heart failure, echocardiography, natriuretic peptides" in combination with "treatment, biomarkers, guidelines". **Results:** Particularly, hospitalization contributes to the greatest proportion of expenditure. Recent studies have supported the value of natriuretic peptides (NPs) and Doppler echocardiographic biomarkers of increased left ventricular (LV) filling pressures or pulmonary congestion as tools to scrutinize patients with impending clinically overt HF. Therefore, combination of pulsed-wave tissue and blood-flow Doppler with NPs appears valuable in guiding HF management in the outpatient setting. In as much as both the echo and the plasma levels of NPs may reflect the presence of fluid overload and elevations of LV filling pressures, integrating NP and echocardiographic biomarkers with clinical findings may help the cardiologist to identify high-risk patients, i.e. to recognize whether a patient is stable or the condition is likely to evolve into decompensated HF, to optimize treatment, to improve the prognosis and to reduce re-hospitalization. **Conclusion:** we discussed the rationale and the clinical significance of combining follow-up echo and NP assessment to guide management of ambulatory patients with chronic HF.

Key words: heart failure, treatment, natriuretic peptides, biomarker.

Chronic heart failure (HF) is the common clinical expression of many diseases of the heart and is a significant and growing public health problem in both general practice and hospital settings, with high prevalence associated with high morbidity and mortality [1].

HF is reaching epidemic proportions, with millions of affected patients both in Europe and in the United States [2-4]. The prevalence of chronic HF is difficult to ascertain with accuracy. The overall prevalence in industrialized countries has been estimated at approximately 1-2% of the adult population, and this increases with age, affecting as many as 10 of every 1000 individuals aged 65 years and over [5, 6]. Today, the number of patients with HF in Italy is estimated to be around 600,000 [7, 8]. It is has been foreseen that the impact of this disorder will double in the next decade. This epidemic growth of HF is mainly due to the aging of the population and improvements in outcome after myocardial infarction.

Four to seven percent of HF patients do not survive the acute episode, while 20% die within a year and 50% die within five years [9, 10]. As far as the outcome of stable ambulatory HF patients is concerned, the most recent European data (ESC-HF pilot study) revealed that the 12-month all-cause mortality rate was 7% and the 12-month hospitalization rate was 32% [11]. As might be expected, HF carries a heavy economic burden [3]. Most costs concern hospitalizations (70%), while outpatient visits, including echocardiographic exams, drug prescriptions and blood tests, make up a smaller proportion of the healthcare budget.

Against this background, attempts should be made to reduce hospitalization, and thus costs. In Italy, the healthcare system provides free hospital care for acutely ill patients. In addition, patients with chronic HF are exempt from charges for elective investigations following discharge. Nevertheless, the rate of hospital admission is still high and new strategies for reducing hospitalizations and improving the prognosis need to be implemented [12, 13].

The prevention of precipitating factors, the management of co-morbidities and the early identification of predisposing factors constitute a real challenge for the cardiologist. More than 90% of cases of worsening HF result from fluid overload and elevations of left ventricular (LV) filling pressures [14], which are very often accompanied by the increased synthesis and secretion of natriuretic peptides (NPs) [15].

Neither the physical signs nor the symptoms are specific to the state of HF [16]. However, greater access to echocardiography and NP testing has yielded not only improved diagnostic assessment but also objective serial evaluation of the progression of HF, which may be crucial to guiding patient management.

Thus, the measurement of circulating levels of NPs, i.e., B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP), in combination with the acquisition of hemodynamic information by means of echo can be a valuable aid to identifying signs of impending decompensation. This task may be successfully carried out, especially if the cardiologist has a specific competence in HF diagnosis and management and has an echocardiographic background.

This narrative review was based on the material searched for and obtained via PubMed up to May 2017. The searched terms in the database were: “heart failure, echocardiography, natriuretic peptides” in combination with “treatment, biomarkers, guidelines”.

Basics of the biomarker-guided approach

Biomarkers are defined as characteristics that are objectively measured and evaluated as indicators of normal or abnormal biological function or a pharmacological response to therapy. In many disease states, drug selection and dosage are strictly dependent on biomarkers. Classic experience with diabetes has taught physicians to monitor blood glucose and to adjust the dosage of hypoglycemic agents to blood levels. The idea of transferring a similar approach to HF seems attractive.

The use of NP levels to guide HF therapy has been studied extensively in the last decade. The rationale for the biomarker-guided management of patients with chronic HF is to prevent disease progression, optimize treatments and improve quality of life and prognosis. Elevated BNP (above approximately 125 pg/mL) or NT-proBNP (above approximately 1000 pg/mL) values are prognostically meaningful in chronic HF, and a rising pattern is predictive of impending adverse outcome, irrespective of other subjective and objective prognostic metrics [17, 18]. The results of several studies support the use of serial NP testing to monitor the response to therapy and improve outcome in patients with chronic HF and reduced EF [18, 19]. However, not all studies in which therapy has been guided by NPs have shown superiority over the standard strategy [20-22]. In fact, NP, which is commonly helpful for risk stratification, risks to be less useful to monitor treatment. Probably, clinical examination to verify cardiac status (i.e. decompensation) is critical and has to be combined with NP for a better risk stratification.

An important limitation of all these prospective trials was that fixed cut-points for NPs were established *a priori*, independently from patients' characteristics (e.g., age, LV EF, LV filling pressures, renal function etc.) and concomitant diseases affecting the right ventricular strain (i.e. pulmonary hypertension or chronic thromboembolism). Since the clinical stability of individual patients may be expressed by different NP values, attempting to lower NP levels below a fixed threshold may be impracticable or even counterproductive. It is, therefore, important to individualize NP targets by means of so-called "dry" NP levels [23], which can be defined as the NP value that corresponds to clinical stability with no signs of fluid overload. Reaching a low BNP, bringing the patient as close as possible to his "dry" level, can reduce the rate of both events and re-hospitalizations. Relative changes of 40% in BNP values and of 25% in NT-proBNP values have been suggested as meaningful thresholds for detecting whether a significant variation has occurred [24].

While the term biomarker is commonly used in association with measurements of circulating substances, hemodynamic parameters may also be referred to as biomarkers. It has become apparent that symptoms and prognosis in HF patients are closely related to LV filling pressures and their changes after optimized tailored therapy. Specifically, it has been recognized that pulmonary capillary wedge pressure (PCWP) is the ideal candidate to reflect the hemodynamic goal [25]. The prognostic importance of reducing PCWP in response to therapy was first demonstrated in 1990 by Stevenson et al. [26]. Moreover, NPs play a key compensatory role in chronic HF, counterbalancing overstimulation of the renin-angiotensin system and sympathetic nervous system, which contributes to the progression of the disease. These are the reasons why NP circulating levels and echo assessment of PCWP are considered worthwhile targets of therapy in HF.

The potential role of echocardiographic biomarkers in heart failure

Doppler echocardiography is the imaging method of choice; it is able to provide useful information for patient management, as it is capable of assessing LV size and function and filling pressures as well as right ventricular function. Although the role of Doppler echocardiography in cardiac diagnoses, risk stratification and clinical decision-making has long been established [27], most cardiologists have been sceptical as to the use of echocardiography to noninvasively monitor hemodynamic parameters and structural ventricular abnormalities of patients with HF during follow-up. This point of view is evident in the ACC/AHA Guidelines for Clinical Application of Echocardiography, which do not support the use of follow-up echo-Doppler to guide therapy in patients with HF unless clinical status changes [28].

In recent years, the idea that a change in clinical status was the only prerequisite to performing echocardiography during follow-up has been challenged. It has become apparent that most symptoms and signs of HF have little sensitivity with regard to the detection of elevated PCWP, despite good specificity [29]. The ADHERE registry data highlighted the limited reliability of clinician

interpretation, as evidenced by incomplete symptom relief, in many patients with HF after hospital discharge [14].

Patients with HF are at high risk of death, but perhaps equally burdensome is the high rate of readmission. With the introduction of more portable devices and focused cardiac ultrasound, a new window of opportunity has emerged for the more widespread use of echocardiography for serial evaluations of patients [30]. The value of repeated echocardiograms during follow-up visits has been supported by the ESC Guidelines on HF [31]. Echocardiographic assessment was recommended not only to assess cardiac structure and function, including LV diastolic function, but also to plan and monitor treatment and to obtain prognostic information.

The term hemodynamic congestion has been used to indicate elevation of the filling pressures in HF patients without overt clinical congestion [32]. Often, hemodynamic congestion precedes clinical congestion by days or even weeks [33]; clinical congestion may therefore be seen as the “tip of the iceberg” of the hemodynamic derangements that precede the appearance of symptoms. Thus, the recognition and quantification of hemodynamic congestion are crucial steps in a thorough evaluation of HF patients in any clinical setting: failure to recognize subclinical elevation of PCWP puts outpatients with HF at high risk of decompensation and adverse outcome [34].

Echocardiography offers a unique opportunity to identify the presence of increased LV filling pressures (Table 1) [35], thus providing sensitive markers of hemodynamic congestion. In the absence of directly measured hemodynamic parameters, the echo-Doppler assessment of LV filling may be utilized to indirectly estimate the degree of LV filling pressures. Since the backward transmission of elevated mean left atrial and LV end-diastolic pressures is a prerequisite to cardiogenic pulmonary congestion, echo-derived assessment of filling pressures may be considered a surrogate marker of impending decompensation [36].

A number of indices have been used to achieve accurate assessment of filling pressures including: LV pulsed-wave filling velocities (E/A ratio, E wave deceleration time), pulmonary venous flow (ratio of systolic wave velocity and diastolic wave velocity and the difference in duration between pulmonary venous flow and mitral flow at atrial contraction), tissue Doppler imaging and left atrial volume index (Table 1) [37, 38]. Particularly, an E wave deceleration time <150 ms has been found to be highly predictive of a PCWP >15 mmHg [39]. The restrictive transmitral flow pattern (reduced E wave deceleration time below 150 ms) has been shown to be an important predictor of cardiac morbidity and mortality in patients with systolic HF. Patients with HF and depressed EF who had a restrictive flow and who did not reverse this alteration after unloading therapy had the worse prognosis [39].

Pulmonary venous flow patterns have provided an additional contribution to the risk stratification of patients with HF [40]. More recently, Doppler tissue imaging - particularly the ratio of mitral to myocardial early velocities (E/e') - has entered the clinical scenario, thus providing additional prognostic information. Studies that have evaluated E/e' in order to monitor PCWP in an outpatient setting have demonstrated that a ratio of E/averaged myocardial early velocity (averaged E/e') ≥13 reliably reflects increased LV filling pressures [41]. Left atrial longitudinal strain derived from speckle tracking echocardiography is also sensitive in estimating intracavitary pressures. It is angle-independent, thus overcomes Doppler limitations and provides highly reproducible measures of left atrial deformation [42].

Ultrasonography of the lungs is another promising technique in patients with HF, since it is potentially useful in assessing pulmonary congestion, i.e., increased pulmonary tissue water. It has been clearly demonstrated that B-lines (previously known as lung comets) evaluated by pulmonary ultrasound are significantly correlated with E/e' and NT-proBNP levels, suggesting that assessing lung ultrasound at the bedside can be feasible and accurate in detecting decompensation [43]. Even though a number of studies have shown that lung ultrasound evaluation of pulmonary congestion is useful in the risk stratification of patients with chronic HF, the prognostic value of extravascular lung water in HF outpatients is less certain [44] . In addition, lung comets tend to appear late during the

course of the disease, and have low specificity in distinguishing between patients with pulmonary congestion and those with fibrosis [45]. Hence, since the appearance of B-lines is a late manifestation of signs and symptoms, it is more reasonable to rely on echocardiographic modalities to assess elevated LV filling pressures, which are a prerequisite to LV decompensation, rather than to depend on markers of increased pulmonary tissue water, which are obviously later findings [46].

Combining echo and natriuretic peptides during follow-up

Over the years, it has become apparent that ambulatory patients who receive a regular follow-up have fewer exacerbations and readmissions and that a personalized and tailored management is a fundamental step to achieve a better quality of care and to improve the outcome [47]. Therefore, a number of strategies have recently been implemented to reach these targets [48].

Nowadays, new evidences have supported the concept that better management and optimization of evidence-based drug and device therapies can be achieved by combining echo and NPs in the follow-up evaluation of HF patients [49]. This strategy may be proficiently combined with the standard components of the patient follow-up visit (Table 2). Indeed, NPs and Doppler echocardiography, when utilized serially in an integrative and personalized manner, can be valuable in monitoring patients who are high risk of clinical exacerbation, with a significant benefit for the outcome (Figure 1) [50]. The complimentary use of these methodologies can balance their intrinsic limitations, with crucial benefits for the patient. The limitations of the NP-based approach (including biological variability, slow time-course, poor specificity and lack of conclusive scientific evidence) may be overcome by this strategy. By contrast, assessment of NP concentrations seems especially useful in patients in whom Doppler echocardiographic parameters are inconclusive in the determination of LV filling pressures.

Unfortunately, the assessment of HF patients by echo and NPs is not frequent, especially during the follow-up. Recent results from an Italian Registry show that in-patients with acute HF often undergo echo (91%), but measurement of NPs is not very common (30%) [9]. After hospital discharge, patients with HF are usually managed by general practitioners, and only a minority are followed up by a cardiologist. Nonetheless, quite a few patients with chronic HF undergo echo and NP peptide assessment after hospital discharge [9]. To offset these limitations, potentially effective strategy to prevent HF readmissions should be implemented by integrating NPs and echo.

The value of integrated NPs and echo-guided management of outpatients with chronic HF can be established when this strategy will be prospectively compared with the standard of care [51]. In a recent retrospective study, we observed a greater survival benefit in patients in the echo- and BNP-guided group than in a clinically-guided group [52] (Figure 2). This finding was associated with a better management of renal function (Table 3). Patients whose follow-up was based on standard of care had a significantly higher prevalence of worsening renal function, which was likely related to higher diuretic dosages (Table 3). The outcome was better in terms of the combined endpoint of death or worsening renal function. A plausible reason behind these observations is that the early recognition of the euvolemic state, i.e., normal tissue water content, by means of the echo- and BNP-guided strategy, helps to prevent excessive dosing of loop diuretics, which may predispose patients to renal dysfunction [53]. We can, therefore, assume that clinical findings are of limited value in assessing diuretic requirements during follow-up, whereas the echo- and BNP-driven approach is important in order to overcome this limitation and to optimize HF treatment, including the loop diuretic regimen. Since renal dysfunction is known to be one of the most predictive markers of adverse outcomes in chronic HF, guiding HF care by means of echo and NPs, such as BNP, seems valuable in order to reduce the patient's risk [54, 55]. Moreover, differently from patients whose management was based on echo and BNP, prescriptions of ACE inhibitors significantly decreased in the clinically-guided group and these patients were less likely to be treated with cardiac resynchronization therapy (Table 4) [52]. The latter findings likely indicate that the combination of

echo with NPs may effectively contribute to the ooptimization of guideline adherence for both pharmacological and device therapies [55].

Future perspectives

In recent years, it has become apparent that a single parameter is, for prognosis, weaker than the effect of different parameters combined. Indeed, several combination of variables and several HF score have been proposed [57]. Particularly, a number of echocardiographic parameters may be utilized to built up an echocardiographic risk score that can be used to risk stratify HF patients and to guide management in an outpatient setting. In a large series of patients with stable systolic HF, we recently identified five independent predictors of mortality (LV end-systolic volume index, left atrial volume index, E wave deceleration time, pulmonary artery systolic pressure, and tricuspid plane systolic excursion) among 14 initial candidate echocardiographic variables. These independent echocardiographic predictors were used to derive the Echo Heart Failure Score (EHFS) [58]. In the subsequent follow-up, mortality rate (per 100 patients/year) significantly increased with EHFS (ranging from 0 to 5), with an almost four-fold increased risk of mortality in those patients with EHFS of at least three [58]. These findings suggest that EHFS may offer promising applications for clinical use, since it is based on variables that can easily be measured at the outpatient clinic or echo lab and may be useful for serial follow-up evaluations and to monitor the effect of unloading therapy on each single parameter constituting the score, with obvious implications for prognosis.

Another prospective development is to integrate measures of NPs and echo markers of increased LV filling pressures with parameters that indicate low cardiac output or depressed stroke volume. Nowadays, Doppler echocardiography can provide reliable and repeatable measures of cardiac output and stroke volume, which can be estimated across any cardiac orifice, such as the LV outflow tract,

where cross-sectional area and the velocity time integral of blood flow can be measured [59]. Integration of estimates of LV filling pressures and the determination of NP circulating levels through measures of LV pumping capacity can be used to design a diagnostic diagram that can be proficiently employed to distinguish between stable patients and those who are decompensated or at high risk of decompensation (Figure 3). Like the Forrester hemodynamic categorization [60], this method can provide information that reflects the patient's fluid status and tissue perfusion by dividing patient into four subsets: A) well-perfused without congestion, B) low-perfused without congestion, C) well-perfused and congested, D) hypoperfused and congested. Differently from similar noninvasive algorithms that are applicable only in the acute setting, this strategy can also be used in ambulatory patients since it does not necessitate the presence of symptoms of decompensation [61]. The significance of this approach is that it facilitates the early recognition of high-risk patients (B, C and D), on the basis of changes in NP levels from "dry" to "wet" and modifications of echo-Doppler variables, which reflect the evolution toward congestion or low perfusion, in order to modulate treatment to prevent exacerbations and further hospitalizations. The inclusion of patients in subsets A, B, C, or D may be used not only to better interpret the patient's status but also for prognostic stratification. Our preliminary results show that when high-risk patients do not revert to a lower risk profile on therapy, the event-rate tends to increase substantially.

Conclusions

Despite the great number of candidate biomarkers currently proposed for HF management, only NPs are recommended by the international Guidelines for the diagnosis and risk stratification of patients with HF. Compared with other imaging techniques (nuclear perfusion imaging, cardiac computed tomography, or cardiac magnetic resonance imaging), echocardiography is less expensive, requires less space, and needs no costly radioisotopes. Moreover, it is widely available and efficient, as it requires no image processing and results are immediately available. The combination of NPs and echo-Doppler seems to bear many of the features of an "ideal biomarker", as they are easily available

and economical and may provide additional information that may modify clinical practice beneficially and cost-effectively. The combined assessment of NPs and echocardiographic parameters may help the cardiologist to identify high-risk patients, i.e. to identity whether a patient is stable or the condition is likely to evolve into decompensated HF. Therefore, the integration of clinical evaluation, NP testing, and echocardiography may optimize treatment of the individual patient, thus reducing the burden of new hospitalizations, preventing renal failure, and improving quality of life and prognosis.

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Figure legends

Figure 1. Flowchart for therapeutic decision making in patients with chronic heart failure.

Figure 2. 12-month all-cause mortality and 12-month survival of all-cause mortality plus worsening renal function of patients of the BNP and echo guided group vs patients of the clinically guided group.

Figure 3. Assessment of hemodynamic stability by B-type natriuretic peptide and echo: **A**) well-perfused without congestion, **B**) low-perfused without congestion, **C**) well-perfused and congested, **D**) hypoperfused and congested.

Table 1 – Echocardiographic and Doppler criteria to assess elevated left ventricular filling pressures.		
Major criteria of elevated left ventricular filling pressures		
Measurement	Modality	Variable
Mitral velocities	Pulsed-wave blood flow Doppler	E wave deceleration time <150 ms
Mitral and annular velocities	Pulsed-wave tissue and blood flow Doppler	Ratio of mitral to myocardial early velocities (E/e'): medial >15, lateral ≥13, average ≥13
Pulmonary vein flow	Pulsed-wave blood flow Doppler	Difference in duration between pulmonary venous flow and mitral flow at atrial contraction ≥30 ms
Pulmonary vein flow	Pulsed-wave blood flow Doppler	Ratio of systolic wave velocity and diastolic wave velocity ≤40%
Minor criteria of elevated left ventricular filling pressures		
Measurement	Modality	Variable
Left atrial size	2D echocardiography	Left atrial volume index ≥40 ml/m^2
End-diastolic pulmonary regurgitant velocity	Continuous-wave blood flow Doppler	Estimated pulmonary artery diastolic pressure >13 mmHg
Systolic tricuspid regurgitant velocity	Continuous-wave blood flow Doppler	Estimated pulmonary artery systolic pressure ≥40 mmHg

Table 2 – Major components to evaluate during outpatient visit.

- Clinical, echographic and biochemical signs of fluid overload
- Clinical and echocardiographic signs of low cardiac output or low perfusion
- Comorbid conditions, including arrhythmias, hypertension, diabetes, chronic obstructive lung disease, anemia, and estimated glomerular filtration rate
- Medication and diet compliance
- Rehabilitation and exercise regimen
- Patient's education
- Family and social support

Table 3 – Changes in diuretic dose (furosemide) between baseline and follow-up and the effects on renal function.

	Echo and BNP guided	Clinically-guided	P value
Number of patients	570	567	
Follow-up duration (days)	1165 (IQR: 513-2076)	1274 (IQR: 637-2319)	NS
Furosemide dose at baseline (mg/day)	25 (IQR:25-50)	21 (IQR:11-50)	NS
Furosemide dose at follow-up (mg/day)	25 (IQR:13-75)	32 (IQR:11-82)	NS
Dose increased	26% (145)	53% (299)	P<0.0001
Dose unchanged	53% (303)	28% (159)	P<0.0001
Dose decreased	21% (122)	19% (109)	NS
≥ 0.3 mg/dL in serum creatinine	12% (70)	22% (127)	P<0.0001
Newly diagnosed renal dysfunction (eGFR <60 ml/1.73 m^2)	12% (70)	14% (82)	NS

Legend: BNP: B-type natriuretic peptide, eGFR: estimated glomerular filtration rate, IQR: interquartile range, NS: non-significant.

Table 4 – Changes in treatment during follow-up in the study groups.						
	Echo and BNP-guided (n=567)			**Clinically-guided (n=570)**		
	Baseline	**Follow-up**	**P-value**	**Baseline**	**Follow-up**	**P-value**
Loop diuretics (%)	85 (481)	85 (481)	NS	87 (496)	90 (512)	NS
Beta-blockers (%)	66 (375)	78 (443)	<0.0001	82 (468)	84 (479)	NS
ACE inhibitors (%)	89 (502)	84 (479)	NS	90 (511)	81 (461)	<0.0001
Aldosterone receptor-Antagonists (%)	319 (56)	313 (55)	NS	62 (184)	64 (188)	0.615
Cardiac resynchronization therapy (%)	6 (33)	25 (142)	<0.0001	6 (35)	17 (95)*	<0.0001
Implantable cardioverter defibrillator (%)	10 (56)	28 (159)	<0.0001	8 (46)	19 (110)	<0.0001

Abbreviations as in Table 3

* P<0.05 versus Echo-NPs-guided group;