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Echo and natriuretic peptide guided therapy improves outcome and reduces worsening renal function in systolic heart failure: An observational study of 1137 outpatients

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ABSTRACT

Background: B-type natriuretic peptide (BNP) and echocardiography are potentially useful adjunct to guide management of patients with chronic heart failure (HF).Thus, the aim of this retrospective, multicenter study was to compare outcomes and renal function in outpatients with chronic HF with reduced ejection fraction (HFrEF) who underwent an echo and BNP guided or a clinically driven protocol for follow-up.

Methods and results: In 1137 consecutive outpatients, management was guided according to echo-Doppler signs of elevated left ventricular filling pressure and BNP levels conforming to the protocol of the Network Labs Ultrasound (NEBULA) in HF Study Group in 570 (mean EF = 30%), while management was clinically driven based on the institutional protocol of the HF Unit of the Cardiovascular and Thoracic Department in 567 (mean EF = 33%). Propensity score, matching several confounding baseline variables, was used to match pairs based on treatment strategy. The median follow-up was 37.4 months. After propensity matching, a lower incidence of death (HR 0.45, 95%CI: 0.30–0.67, $p < 0.0001$), and death or worsening renal function (HR 0.49, 95%CI 0.36–0.67, $p < 0.0001$) was apparent in echo-BNP-guided group compared to clinically-guided group. Worsening of renal function (≥0.3 mg/dl increase in serum creatinine) was observed in 9.8% of echo-BNP-guided group and in 21.4% of clinical assessed group ($p < 0.0001$). The daily dose of loop diuretics did not change in echo-BNP-guided group, while it increased in 65% of patients in clinically-guided group ($p < 0.0001$).

Conclusions: Echo and BNP guided management may improve the outcome and reduce worsening of renal function in outpatients with chronic HFrEF.

1. Introduction

Optimising therapy in patients with heart failure (HF) is proven but challenging, and thus, it is appealing to use natriuretic peptides (NPs) and echocardiography to guide therapy in these patients. The serum concentration of B-type natriuretic peptide (BNP) reflects the degree of ventricular overload: correlations with increased left ventricular (LV) filling pressures and wall stress have been observed, and this is supported by the close association with increased pulmonary capillary wedge pressure (PCWP) and restrictive mitral flow [1]. Moreover, NPs appear particularly valuable in targeting therapies against persistent neurohormonal activation that have formed the cornerstone in the management of HF over recent decades [2–4].

Doppler echocardiography is safe, widely available and relatively inexpensive and the imaging method of choice in patients with HF since it provides useful information for patient management, and provides an assessment of LV size and function and LV filling pressures as well as right ventricular function [5]. Particularly, by estimating surrogate measures of PCWP [6], echocardiography may be useful to titrate the dose of cardiovascular drugs, especially diuretics [7]. The value of repeated echocardiograms during follow-up visits has been supported by the

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recent ESC Guidelines on HF [8] in which echocardiographic assessment was recommended not only to evaluate cardiac structure and function, but also for planning and monitoring treatment and to obtain prognostic information.

With these considerations in mind, we postulated that BNP and Doppler echocardiography, when utilized serially in an integrative and "personalized" manner, can be useful in managing ambulatory patients that are high risk for exacerbation of symptoms, and thus contribute significantly to improved clinical outcome. The combination of these diagnostic techniques may overcome their intrinsic limitations, with potentially crucial benefits for the patient. The purpose of this study was to investigate the role of Doppler echocardiography and BNP assessment during follow-up visits in ambulatory patients with chronic HF with reduced ejection fraction (HFrEF).

2. Materials and methods

2.1. Study patients

This was a retrospective multicenter, observational study that involved 1137 consecutive outpatients enrolled between January 2004 and December 2013, from tertiary ambulatory referral HF centers (220 at the Cardiovascular Unit and 570 at the HF Unit of the Cardiovascular and Thoracic Department, Pisa, Italy, 213 at the Divisions of Cardiology of the University Hospital of Perugia, Italy, and 137 from the Cardiovascular and Thoracic Department, Policlinico San Matteo, Pavia, Italy). All patients fulfilled the criteria for definition of HF in the presence of structural abnormalities [8]; were in stable clinical conditions; and had a LV ejection fraction (EF) <50%.

The exclusion criteria were: myocardial infarction or unstable angina in the previous three months, coronary artery bypass graft or percutaneous coronary angioplasty in the previous three months, more than mild aortic or organic mitral valve disease, hypertrophic cardiomyopathy, secondary forms of cardiomyopathy, such as restrictive cardiomyopathy or infiltrative cardiomyopathy, congenital heart diseases and any life-threatening conditions with adverse prognosis other than cardiovascular disease. The study was approved by local institutional review boards. All patients gave written informed consent. The study was conducted in accordance with institutional policies, national legal requirements, and the revised Helsinki declaration.

2.2. Study protocol

The study comprised consecutive ambulatory patients whose follow-up management was directed according to the presence of Doppler signs of elevated LV filling pressure and BNP serum levels: echo-BNP-guided group ($n = 570$ from Cardiovascular Unit of the Cardiovascular and Thoracic Department of Pisa, Divisions of Cardiology of the University Hospital of Perugia, and the Cardiovascular and Thoracic Department, Policlinico San Matteo of Pavia) and consecutive outpatients ($n = 567$) in which management was based on the standard of care according to the institutional protocol of the HF Unit of the Cardiovascular and Thoracic Department: clinically-guided group. All patients underwent baseline evaluation by an experienced cardiologist that included a complete clinical evaluation, blood pressure measurement, complete M-mode, two-dimensional and Doppler echocardiogram, and the assessment of comorbidities. The functional status of patients was determined according to the classification of the New York Heart Association (NYHA). In the clinically-guided group, patients underwent to standard follow-ups based on clinical conditions (signs and symptoms, NYHA class, repetitive hospitalizations, and comorbidities) and baseline LV EF. Echocardiography was repeated only in the case of changes in clinical status.

In echo-BNP-guided group, the follow-up protocol, including serial BNP and echo (when needed), was the same in the centers that followed this strategy. First, patients were clinically evaluated (history, clinical examination, up-titration of therapy, measure of renal function and BNP). If patients fulfilled the Framingham criteria for symptomatic HF or exhibited BNP levels at or above 125 pg/ml [9], echocardiography was performed as an adjunct to the physical examination, focused on the evaluation of echocardiographic signs of elevated LV filling pressures [6]. Therapeutic decisions, including clinical interventions to lower BNP and/or elevated LV filling pressures, were made, thereafter, based on physical, biochemical and echocardiographic findings. A closer follow-up (2-to-4 weeks) was planned in symptomatic and asymptomatic patients exhibiting echo-Doppler signs of elevated LV filling pressures and/or a clinically relevant rise in BNP concentration, while the frequencies of visits were extended out to 4 to 6 months in patients who were doing well.

2.3. Echo-Doppler

Transthoracic two-dimensional and Doppler echocardiographic examination was carried out with commercial equipments with 2nd-harmonic imaging (iE33 X-matrix Ultrasound System, Philips, Andover, Massachusetts, Vivid 7, General Electrics VingMed Sound, Horten, Norway). LV volumes and LV EF were calculated from apical two- and four-chamber views using the modified Simpson's rule. Pulsed wave Doppler mitral velocity curves were obtained from the apical four-chamber view by positioning a 1–2 mm sample volume between the tips of the mitral valve leaflets in diastole. E wave deceleration time (EDT) was measured from transmitral velocity tracings. A cut-off of 140 ms in EDT was selected as a surrogate marker of increased PCWP [10] to discriminate patients with high PCWP (EDT </= 140 ms; restrictive) vs patients with normal PCWP (EDT > 140 ms; non-restrictive). In patients with atrial fibrillation, deceleration time of mitral flow velocity curve <120 ms identified restrictive filling. Right ventricular function was assessed using tricuspid annular plane systolic excursion (TAPSE). All measurements were performed according to the recommendations of the European Association of Echocardiography/American Society of Echocardiography [5].

2.4. Measurement of biological variables

Venous blood was collected at the time of the visits. BNP concentrations were processed by Alere Triage BNP Test for Beckman Coulter Immunoassay Systems (Alere San Diego Inc., San Diego, CA, USA), a two-site immunoenzymatic (sandwich) quantitative assay. For BNP, the lower assay detection limit was 1 pg/ml. The estimated glomerular filtration rate (eGFR) was calculated from the simplified formula derived from the Modification of Diet in Renal Disease study [11].

2.5. Follow-up data

Survival data were obtained through follow-up visits of patients and, in the case of a missed visit, verified through telephone contacts (patients, relatives and family physicians). If no information was available via telephone, we obtained information by local authority registry and hospital records. The main end-point of the study was all-cause mortality at follow-up. Worsening renal function (WRF) (≥0.3 mg/dl increase in serum creatinine from baseline to follow-up) and the combined end-point of death plus WRF were other considered end-points.

2.6. Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median ± interquartile (IQR) ranges, when appropriate. Categorical variables are shown as frequency (percentage) unless otherwise noted. We compared the baseline demographic, clinical, and echocardiographic characteristics of the total study cohort, stratified by the adopted treatment strategy during follow-up (echo-NP-guided versus clinically-guided). Continuous variables were analyzed using either a *t*-test or Wilcoxon rank-sum test, and categorical variables were compared using χ^2 or Fisher exact test where appropriate. A p value < 0.05 was considered statistically significant. A BNP of 460 pg/ml was used to define individuals as having a high level (>460 pg/ml) or low level (≤460 pg/ml). This threshold was selected as the concentration of BNP at baseline which gave the greatest prognostic accuracy for all-cause mortality at receiver operating characteristic curve.

To reduce the effect of confounding caused by differences in baseline demographic, clinical, and echocardiographic characteristics between echo-NP versus clinical-guided patients, we used propensity score (PS) matching in combination with Cox regression modeling [12]. This method, now widely used in cardiovascular research to reduce bias in observational studies, may allow for more accurate assessment of outcomes associated with treatment strategy. PS was obtained by logistic regression, where the dependent variable was treatment strategy (BNP-guided group vs clinical group), and the independent variables were all variables with potential outcome or treatment association. Variables considered for PS construction were age, gender, NYHA class, baseline creatinine values, diabetes mellitus, ischemic heart disease, systolic and diastolic blood pressure, heart rate, LV volumes and ejection fraction, TAPSE, EDT, beta-blockers therapy, daily dose of furosemide at study entry, and time-to-event (Fig. 1). No variable selection procedure was used, as this model was not the focus of the study, and there was no need to obtain a parsimonious model.

To create paired samples of patients with similar PS, stratified by therapy (i.e., echo-BNP-guided vs clinically-guided follow-up), a propensity-based greedy-matching method (5-to-1 digit matching) was used in which unmatched observations, possibly leading to non-representative samples of the original database, were discarded. Even if this process leads to a reduction in the original patient numbers, such analysis is likely to provide a more valid estimate of the treatment effect because analyzed patients were matched on many confounders simultaneously. The procedure yielded 295 well-matched pairs. The success of the PS matching was assessed by checking standardized differences between groups before and after matching [12]. Balancing was considered successful if the standardized differences were <10% (Fig. 1).

Once a propensity-score matched sample was obtained, the absolute risk reduction was estimated as the difference between the proportion of echo-BNP-guided subjects experiencing the outcome and the proportion of clinically-guided subjects experiencing the outcome in the matched sample. Then, the statistical significance of the risk difference was tested using McNemar's test for correlated binomial proportions. In the full dataset a propensity-score adjusted Cox regression analysis was used to calculate the hazard ratio of event, with stratified Kaplan–Meier curve. In the matched sample, a Cox model was used to regress survival on treatment status, with a robust variance estimator used to account for the clustering within matched sets. All analyses were performed using STATA 13 (StataCorp LP, College Station, TX) and SAS 9.4 statistical software (SAS Institute, Cary, North Carolina).