Predictive value for death and rehospitalization of 30-day postdischarge B-type natriuretic peptide (BNP) in elderly patients with heart failure. Sub-analysis of Italian RED Study

Salvatore Di Somma*, Rossella Marino, Giorgio Zampini, Laura Magrini, Enrico Ferri, Kevin Shah, Paul Clopton and Alan S. Maisel

Abstract

Background: Our aim was to determine if, in elderly heart failure (eHF) patients, serial B-type natriuretic peptide (BNP) assessments obtained during follow-up after hospital discharge could have prognostic utility for death and rehospitalizations. In eHF patients, BNP assessment at hospital discharge has been demonstrated to have a high prognostic value; however, its predictive role for future cardiovascular events in eHF patients, when assessed in the period after discharge, both for the correct timing and cut-off levels, has not been completely elucidated.

Methods: This study is a monocentric subanalysis of the Italian RED (Rapid Emergency Department) study. We studied 180 consecutive patients admitted for acute HF through serial BNP assessments: at hospital arrival; at discharge; and at 30, 90, and 180 days follow-up outpatient visit.

Results: Both a BNP >400 pg/mL at 30 days after discharge and the percentage variation of BNP from discharge to 30 days (Δ%BNP), compared with a BNP at discharge >400 pg/mL, showed a higher area under the curve (AUC) and odds ratio (OR) in predicting events [AUC=0.842, p<0.0001; OR 7.9 (3.3–19.0), p<0.0001 for 30 days BNP and AUC=0.851, p<0.0001; OR 9.5 (4.065–22.572), p<0.0001 for Δ%BNP compared with AUC=0.638, p<0.002; OR 2.4 (1.1–5.3), p=0.032 for BNP at discharge].

Conclusions: In patients at a high risk for future events, BNP levels assessed 30 days after hospital discharge in the absence of signs and symptoms could be predictive of subsequent hospitalization and death. These patients should be considered for closer monitoring and treatment adjustment.

Keywords: B-type natriuretic peptide (BNP); cardiac events; follow-up; heart failure.

Introduction

The overall worldwide prevalence of clinically identified heart failure (HF) is estimated to be 3–20 cases per 1000 population; however, this increases to >100 cases per 1000 population in persons older than 65 years. High mortality, morbidity, and hospitalization as a result of acute HF (AHF) represent an increasing public health dilemma [1–5].

The aging of the population and the prolongation of life expectancy of patients with cardiovascular diseases lead to an increasing prevalence of HF in old age. The high prevalence of comorbidities, the often associated complex “polypharmacy,” and cognitive dysfunction characterize elderly HF patients and may interfere with their prognosis and treatment. This may explain the very high rate of early readmissions or death in elderly patients with symptomatic HF [6].

Studies have shown that readmission after hospitalization for HF is common, with almost half of the patients readmitted within 6 months [7, 8]. The life expectancy of these patients is very poor after repeated episodes of AHF [9]. Multiple studies have demonstrated the diagnostic ability of natriuretic peptides (BNP, NT-pro BNP) in HF, as well as their role in predicting total mortality, cardiovascular deaths, and rehospitalizations [10–13]. BNP measured...
Materials and methods

This study is a monocentric subanalysis of the Italian RED (Rapid Emergency Department) study. In the first part of the study, we analyzed patients admitted to the emergency department (ED) for acute decompensated HF (ADHF) from eight Italian ED centers from January 2006 to November 2007 [13]. In this second part of the study, we considered 180 patients aged >70 years admitted only from the ED of Sant’Andrea Hospital in Rome for AHF, in the same chronicologic period. The patients’ characteristics at admission and the drugs taken after discharge are reported in Table 1. In our center, we additionally measured the BNP levels at each control visit during the follow-up until 180 days postdischarge, whereas in other sites only the clinical condition of the patients were recorded during follow-up visits. We included for statistical analysis only those patients who, at the first follow-up visit, were still asymptomatic and without any clinical sign of HF decompensation. However, the inclusion criteria for all patients studied reflect the criteria of the first part of the study and were based on the diagnosis of HF performed following the guidelines of the European Society of Cardiology [16], as well as age >18 years and the possibility of signing the informed consent form. The exclusion criteria for enrollment were as follows: acute coronary syndromes, myocardial infarction, body mass index of ≥30 kg/m², renal failure maintained on hemodialysis, or dyspnea due to trauma or other causes. The study conformed to the Helsinki Declaration, and the protocol was approved by the local ethical committees. Written informed consent for the study was obtained from each patient before entering the study.

Documentation of personal medical history was collected, and each patient underwent physical examination, electrocardiogram, chest X-ray, arterial blood gas analysis, and echocardiographic examination with at least an evaluation of ejection fraction. Blood tests for hemochromocytometry, creatinine, urea, electrolytes, and cardiac enzymes were performed. The test results and therapy were reported by the ED on a case report form, and the ED physicians were asked to rate the severity of HF according to the New York Heart Association classification. Each patient was treated with a standard dose of nitrates, β-blockers, angiotensin-converting enzyme inhibitors, and diuretics according to guidelines for ADHF and as assessed by physical examination at admission [16]. During hospitalization, the treatment regimen was recorded and modified accordingly, with the aim of obtaining clinical improvement following current guidelines [16].

Table 1  Patients’ characteristics.

<table>
<thead>
<tr>
<th>Demography</th>
<th>All patients (n=170)</th>
<th>No events group (n=134)</th>
<th>Events group (n=36)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Mean age, years (mean±SD)</td>
<td>74.5±13.2</td>
<td>74.25±13.14</td>
<td>75.42±14.06</td>
<td>n.s.</td>
</tr>
<tr>
<td>Systolic pressure (mean±SD)</td>
<td>155±41 mmHg</td>
<td>157±44 mmHg</td>
<td>150±49 mmHg</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diastolic pressure (mean±SD)</td>
<td>93±16 mmHg</td>
<td>94±18 mmHg</td>
<td>88±18 mmHg</td>
<td>n.s.</td>
</tr>
<tr>
<td>Pulse rate (mean±SD)</td>
<td>105±16 bpm</td>
<td>108±12 bpm</td>
<td>93±23 bpm</td>
<td>n.s.</td>
</tr>
<tr>
<td>EF &lt;40%</td>
<td>75 (44)</td>
<td>56 (42)</td>
<td>19 (52)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>119 (70)</td>
<td>90 (67)</td>
<td>29 (80)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>96 (56)</td>
<td>75 (56)</td>
<td>21 (58)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>80 (47)</td>
<td>65 (48)</td>
<td>15 (41)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diabetes</td>
<td>48 (28)</td>
<td>20 (15)</td>
<td>28 (77)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>COPD</td>
<td>26 (15)</td>
<td>6 (4)</td>
<td>20 (55)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Troponin I &gt;0.03 ng/mL</td>
<td>41 (24)</td>
<td>36 (27)</td>
<td>5 (14)</td>
<td>n.s.</td>
</tr>
<tr>
<td>O₂ saturation &lt;90%</td>
<td>37 (22)</td>
<td>30 (22)</td>
<td>7 (20)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Creatinine &gt;1.5 mg/dL</td>
<td>56 (33)</td>
<td>44 (33)</td>
<td>12 (33)</td>
<td>n.s.</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>55 (32)</td>
<td>45 (33)</td>
<td>10 (27)</td>
<td>n.s.</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>66 (39)</td>
<td>58 (43)</td>
<td>8 (22)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diuretics</td>
<td>170 (100)</td>
<td>134 (100)</td>
<td>36 (100)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

EF, ejection fraction; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme.
From each enrolled patient, venous blood sample was collected into an EDTA tube to measure BNP levels at admission in the ED, and this was repeated at the time of discharge. BNP measurement was tested using the Triage-BNP test device (Biosite-Inverness Medical, San Diego, CA, USA), a single-use, ready-to-use fluoroexcence immunoassay, following the manufacturer’s recommendations for point-of-care testing [17]. Troponin I (Tnl) was measured with a sandwich immunoassay through a chemiluminescent method by using a luminomter. The range, according to the manufacturer, is 0.03–80 ng/mL (Access AccuTnI3; Beckman Coulter, Galway, Ireland) [18]. The following concomitant clinical and laboratory parameters were considered for the discharge criteria: reduction of dyspnea, respiratory rate <30 breaths/min, oxygen saturation >90%, complete clearance of rales at chest examination, and significant reduction of lower limb edema [16].

For the follow-up, all patients visited the HF outpatient clinic at 30, 90, and 180 days after hospital discharge. In the outpatient clinic at 30, 90, and 180 days, a complete clinical evaluation was performed aimed at detecting any relapse of HF, including the presence of dyspnea, respiratory rate >30 breaths/min, oxygen saturation <90%, presence of rales at chest examination, and lower limb edema [16]. BNP assessment was repeated during each visit (at 30, 90, and 180 days). We selected only those patients who, at the clinical examination performed during the 30 days follow-up, were in a stable condition of HF, asymptomatic, and without signs of AHF.

Events were defined as death and hospital readmissions for cardiac dyspnea or rapid congestion as a sign of ADHF. During the period from discharge to 180 days, patients were asked to refer to the outpatient clinics if any new onset of symptoms of HF deterioration occurred. Patients with events discontinued the subsequent follow-up visits. At 180 days after discharge, patients were divided in two groups on the basis of adverse events that occurred during this follow-up period.

Statistics

Statistical analysis was performed using MedCalc software version 12.1.4 (MedCalc Software, Mariakerke, Belgium) and SPSS software version 14 (SPSS, Chicago, IL, USA). Continuous data were presented as median and interquartile range (IQR), whereas categorical data were presented as percentages. The Mann-Whitney U-test was used to compare the differences between subjects with events and those without events. Friedman ANOVA was applied to compare differences between the BNP levels measured at different times. Fisher’s exact test was used to test differences between categorical data. Multivariate binary logistic analysis, applying the backward-stepwise method, was performed to evaluate the predictive value of BNP for the occurrence of events at discharge and at 30 and 90 days postdischarge, and of the clinical and laboratory variables significantly associated with the presence of events in the univariate analysis. Receiver operating characteristic curves (ROCs) were plotted, and the area under the curve (AUC) was estimated to establish the appropriate sensitivity and specificity. The cut-off used to calculate the ability of BNP to predict events was 400 pg/mL, as reported in the most relevant literature as a sign of cardiac wall stress [12]. The coefficients obtained from the logistic regression were expressed in terms of odds ratio (OR) with 95% confidence intervals. All tests were two-sided, and statistical significance was set at p<0.05.

Results

The entire population studied comprised 180 patients discharged with a diagnosis of AHF. At 30 days, 170 patients were still asymptomatic and they were considered for serial measurements of BNP. However, 10 patients who experienced rehospitalization and death were excluded from the other study phases. In the subsequent period up to 180 days, 36 (21.2%) patients had events: 14 deaths (8.2%) and 22 rehospitalizations (19.9%).

Table 1 shows the characteristics of the whole patient population, and distinguished between the group with events and those without events at the time of hospital admission. The mean age of patients was 74.5 years. Comparison of demographic data (Table 1) through univariate analysis between subjects with events and those without events during the follow-up showed that there were no significant differences between these two populations except for the presence of chronic obstructive pulmonary disease in 4% of patients without events vs. 5% of patients with events (p<0.05), and for the presence of diabetes in 15% of patients without events vs. 77% of patients with events (p<0.05).

BNP data

In the whole studied population, the BNP median (IQR) value at admission was 849 (437–1390) pg/mL; at discharge, 494 (220–804) pg/mL; at 30 days, 359 (197–802) pg/mL; and at 90 days, 265 (147–646) pg/mL. The median value of Δ%BNP from discharge to 30 days for the whole studied population was −11.8% (−34.2 to 19.2). BNP values measured at discharge and at 30, 90, and 180 days of follow-up were statistically lower than the BNP values at admission (p<0.001). In all cohort of patients, the discharge BNP levels were higher than the BNP at 90 days (p<0.001), but not at 30 days.

Table 2 shows the BNP median levels and IQR in patients with and without events. The statistical significance between the two groups at discharge and at 30 and 90 days is also reported. Comparing the BNP levels at 30 and 90 days with the discharge values in both groups of patients, we found a significant difference at each considered time (p<0.001).

ROC analysis was used to compare the ability of BNP in predicting the risk of death and rehospitalization. A BNP cut-off of 400 pg/mL was established. The sensitivity and specificity for BNP in predicting events were 71.7% and 52.7% at discharge (AUC=0.638; p<0.002) and 82.6% and 69.3% at 30 days, respectively (AUC=0.842; p<0.0001) (Figure 1). In the group with events, the median value of
percentage variation of BNP from discharge to 30 days (Δ%BNP) was +52.2% (6.55–163.4) (p < 0.001). In the group without events, the median value of Δ%BNP was –19.3% (–45.4 to –2.92) (p < 0.001). The ROC calculated for Δ%BNP had an AUC of 0.851 (p < 0.0001); a percentage increase of >4% was the cut-off identified, with a sensitivity of 77.8% and a specificity of 81.9% (Figure 1).

In multivariate binary logistic analysis including clinical variables, the BNP level at each considered time, and its percentage variation (applying the backward-stepwise method), only the BNP at discharge, at 30 days posts discharge, and its increase of 4% were independently associated with the development of events [OR 2.4 (1.1–5.3), p=0.032; OR 79 (3.3–19.0), p<0.001; and OR 9.5 (4.0–22.5), p<0.0001, respectively] (Table 3).

Moreover, patients with events were subdivided in two subgroups considering deaths (n=14) and rehospitalizations (n=22) for HF during the follow-up. The BNP level in patients who died was 661 (400–928) pg/mL at discharge, 1119 (695–1585) pg/mL at 30 days, and 1099 (817–1380) pg/mL at 90 days. The BNP level in patients with

### Table 2

<table>
<thead>
<tr>
<th>Total population</th>
<th>No events group</th>
<th>Events group</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admission</td>
<td>849 pg/mL (170 patients), IQR (437–1390 pg/mL)</td>
<td>807 pg/mL (134 patients), IQR (591–1245 pg/mL)</td>
<td>930 pg/mL (36 patients), IQR (646–1630 pg/mL)</td>
</tr>
<tr>
<td>Discharge</td>
<td>494 pg/mL (170 patients), IQR (220–804 pg/mL)</td>
<td>380 pg/mL (134 patients), IQR (220–804 pg/mL)</td>
<td>646 pg/mL (36 patients), IQR (199–743 pg/mL)</td>
</tr>
<tr>
<td>30 Days</td>
<td>359 pg/mL (170 patients), IQR (197–802 pg/mL)</td>
<td>237 pg/mL (134 patients), IQR (148–520 pg/mL)</td>
<td>870 pg/mL (36 patients), IQR (364–915 pg/mL)</td>
</tr>
<tr>
<td>90 Days</td>
<td>265 pg/mL (162 patients), IQR (147–646 pg/mL)</td>
<td>217 pg/mL (134 patients), IQR (127–445 pg/mL)</td>
<td>876 pg/mL (28 patients), IQR (661–1200 pg/mL)</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>OD 95% Confidence interval</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge BNP &gt;400 pg/mL</td>
<td>2.4 1.1–5.3</td>
</tr>
<tr>
<td>30 Days BNP &gt;400 pg/mL</td>
<td>7.9 3.3–19</td>
</tr>
<tr>
<td>Δ%BNP &gt;4%</td>
<td>9.5 4.0–22.5</td>
</tr>
</tbody>
</table>

Figure 1 ROC curve analysis of the ability of discharge BNP, 30 days BNP, and Δ%BNP from discharge to 30 days of follow-up in predicting events.
rehospitalization was 617 (246–915) pg/mL at discharge, 775 (500–980) pg/mL at 30 days, and 776 (579–1177) pg/mL at 90 days. Comparing the BNP values between patients with deaths and rehospitalizations at discharge and at 30 and 90 days, we did not find any statistically significant difference.

**Discussion**

Our study demonstrates that in elderly patients with stable clinical HF condition, the assessment of BNP at 30 days after hospital discharge represents an important and valid tool for recognizing those patients who will develop a new episode of ADHF in the next months. We also found that the BNP at 30 days postdischarge, compared with the level obtained at the time of discharge, is better in predicting future cardiac events such as rehospitalization or death.

Both the AUC of BNP at 30 days after discharge and the AUC of percentage variation from discharge to 30 days, compared with the AUC of BNP at discharge, have a better cumulative discriminating power for the prediction of events (AUC at 30 days: 0.842, sensitivity: 82.6%, specificity: 69.3%; AUC Δ%BNP >4%: 0.851, sensitivity: 77.8%, specificity: 81.9%; AUC at discharge: 0.638, sensitivity: 71.6%, specificity: 52.7%) (Figure 1). Moreover, the logistic regression analysis showed that both a value of BNP >400 pg/mL obtained at 30 days after discharge and a Δ%BNP of >4% are independent factors of events with a high OR value (7.9 and 9.5). This result indicates that the role of BNP evaluation at this time of follow-up seems to be greater than the evaluation at the time of discharge with a BNP level >400 pg/mL (OR 2.4) (Table 3).

Analyzing the levels of BNP in patients who developed events during the follow-up, we found a significant statistical increase of BNP level at 30 days compared with the discharge level. However, in the group of patients free from events, there was a significant decrease of BNP level measured at 30 days follow-up compared with the BNP assessment at the time of discharge (Table 2).

Particularly from our data, it seems that patients with a BNP value increase of 4% at 30 days after discharge could have a higher risk of developing events in the next 5 months. On the contrary, a percentage decrease of BNP value at 30 days compared with the discharge BNP is associated with a significantly lower possibility of developing a new episode of rehospitalization and/or death.

In the past, many studies were focused on monitoring BNP decrease during hospitalization in an attempt to confirm the clinical improvements resulting from adequate treatment [13, 17]. Many data from the literature also showed that the value of BNP at the time of hospital discharge must be taken into account as a prognostic indicator of future events [19]. Also, our group demonstrated in the previous Italian RED study that a significant decrease of BNP level from admission to discharge is associated with better outcome at follow-up, both in terms of major cardiovascular events and rehospitalization rate [15].

Logeart et al. [20] showed that discharge BNP is a strong predictor of subsequent events, more relevant than clinical and echocardiography parameters. Naffaa et al. [21] recently compared in HF patients the prognostic power of BNP, interleukin-6, and procalcitonin, showing that only discharge BNP is an independent prognostic marker of all-cause of mortality. Our study confirmed the prognostic power of discharge BNP in HF patients, and furthermore demonstrated that BNP at 30 days has a higher ability of identifying patients who have an increased risk of rehospitalization.

This is one of the few studies addressing the importance of early serial BNP evaluations after discharge in monitoring elderly patients at risk of new rehospitalization even in absence of clinically significant symptoms (such as shortness of breath and all clinical signs of congestion). In consideration of the negative influence of comorbidities on prognosis, typical of elderly HF patients, we could state that 30 days BNP is a valid tool for identifying, as soon as possible and before their appearance, the clinical signs and symptoms of ADHF in the elderly. The value of follow-up BNP could be useful in preventing worse consequences in this already frail and debilitated group of patients.

Our results on serial BNP assessment show that a gradual and continuous decrease of BNP after hospital discharge is associated with a minor tendency to develop events. This could result from a continuous favorable effect of the medication prescribed at the time of discharge to optimize HF treatment.

From discharge, BNP levels in high-risk patients could slowly increase during the first month. Assuming that the BNP increase immediately after discharge is an effect of inadequate treatment, we can speculate that the subsequent 30 days are crucial in mirroring the true efficacy of the treatment given to these patients during hospitalization. The Stars-BNP study [22] demonstrated that the BNP value can be reduced by the use of β-blockers; thus, treatment in the after-discharge period should be monitored to lower the BNP during follow-up.

Future studies should address how to use BNP values after discharge to effectively change clinical management and to reduce the high risk of morbidity and mortality in
patients with HF. Using biomarkers such as natriuretic peptides aids in therapeutic adjustment, and will help to control the course of chronic HF management.

Conclusions

BNP assessment in elderly patients with HF at 1 month after discharge from the hospital has a relevant prognostic value, even greater than that of the assessment at the time of hospital discharge. Patients with BNP levels >400 pg/mL at 30 days after discharge, or with an increase of >4% (Δ%BNP), should be considered as having a high risk for rehospitalization and death, and be considered for optimization of therapeutic and preventive strategies. This high-risk group of patients should be considered for closer monitoring and treatment adjustment to prevent future events. Future studies incorporating BNP monitoring to help clinical decisions after discharge should be explored.

Limitations

The study results are limited by the small number of patients enrolled and by the small number of events.

Author contributions: Salvatore Di Somma managed the day-to-day activities of the study and wrote the majority of the manuscript. Rossella Marino, Giorgio Zampini, Laura Magrini, Enrico Ferri, Kevin Shah, Paul Clopton, and Alan Maisel assisted with patient recruitment, analysis, and writing/approving the manuscript.

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Employment or leadership: Drs. Salvatore Di Somma and Alan Maisel are consultants for Alere.

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References

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