ELSEVIER

International Journal of Cardiology 126 (2008) 400–406

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Fall in readmission rate for heart failure after implementation of B-type natriuretic peptide testing for discharge decision: A retrospective study

Roberto Valle [a,*], Nadia Aspromonte [b], Emanuele Carbonieri [c], Alessandra D'Eri [a], Mauro Feola [d], Prospero Giovinazzo [a], Federica Noventa [a], Carolina Prevaldi [e], Sabrina Barro [a], Loredano Milani [a]

[a] *Heart Failure Unit, Department of Cardiology, Ospedale Civile, San Donà di Piave, Italy*
[b] *Heart Failure Unit, Department of Cardiology, Ospedale Santo Spirito, Roma, Italy*
[c] *Heart Failure Unit, Department of Cardiology, Ospedale Civile, San Bonifacio, Italy*
[d] *Heart Failure Unit, Department of Cardiology, Ospedale Civile, Cuneo, Italy*
[e] *Emergency Department, Ospedale Civile, San Donà di Piave, Italy*

Received 7 November 2004; received in revised form 18 December 2005; accepted 11 March 2006
Available online 4 September 2007

Abstract

Background: B-type natriuretic peptide is the most powerful predictor of long term prognosis in patients hospitalised with heart failure. On an outsetting basis, a decrease in B-type natriuretic peptide levels is associated to a decrease in event rate for outpatients managed using the neuro-hormone levels as the target in heart failure therapy. We have retrospectively checked whether the addition of pre-discharge B-type natriuretic peptide levels to a clinical–instrumental decisional score for discharge decision in patients admitted for heart failure reduced readmission rate for heart failure and related cost.
Methods: We studied two series of consecutive patients admitted to the Heart Failure Unit due to acute heart failure as a main diagnosis. One-hundred and forty-nine patients discharged on the basis of the sole clinical acumen were compared to one hundred and sixty-six subjects discharged adding B-type natriuretic peptide levels to the decisional score.
Results: During a six-month follow-up period, there were 52 readmissions (35%) among the clinical group ($n=149$) compared with 38 (23%) readmissions in the B-type natriuretic peptide group ($n=166$) ($\chi^2=5.5$; $P=0.02$). Survival did not differ between groups (87%). Changes in B-type natriuretic peptide values were correlated to clinical events: a B-type natriuretic peptide value on discharge of ≤ 250 pg/ml or a reduction of $\geq 30\%$ in B-type natriuretic peptide values predicted a 23% event rate (death, plus readmission for heart failure), whereas a far higher percentage (71%) were observed in the remaining patients ($\chi^2=32.7$; $P=0.001$). Likewise, the overall costs of care were lower (−7%) in the B-type natriuretic peptide group: 2.781 ± 923 *vs* 2.978 ± 1.057 euros per patient respectively.
Conclusions: our study suggest that the addition of pre-discharge B-type natriuretic peptide levels to a clinical–instrumental decisional score for discharge decision in patients admitted for heart failure may contribute to reduce the number of readmissions and related cost.

Keywords: B-type natriuretic peptide; Heart failure; Prognosis; Discharge criteria; Hospitalisation

1. Introduction

Heart failure is a major public health problem, because of its heavy economical burden, mainly due to frequent hospital admissions and relevant short-term post-discharge mortality [1–3]. In particular, readmission rates are very high (45% at six months) [4], being estimated to consume a relevant part of healthcare cost [5]. In an era of cost containment, cost concerns about hospital expenditures for heart failure prompt alternative management strategies.

It has been recently shown that B-type natriuretic peptide correlates well with the severity of heart failure and are the

* Corresponding author. Ospedale, San Donà di Piave, I-30027, Italy. Tel.: +39 421 227537; fax: +39 421 227521.
E-mail address: robertovalle@libero.it (R. Valle).

0167-5273/$ - see front matter © 2007 Published by Elsevier Ireland Ltd.
doi:10.1016/j.ijcard.2006.03.097

most powerful predictor of prognosis in patients with heart failure [6]. In particular, in patients admitted for acute heart failure, B-type natriuretic peptide levels are reported predicting prognosis in the following 3–6 months: patients with higher pre-discharge values have the worst prognosis, while those with lower or decreased levels with respect to admission have the best prognosis [6], so that B-type natriuretic peptide has been suggested as a discharge criterion [7,8]. Furthermore, on an outsetting basis, it has been shown that a decrease in B-type natriuretic peptide levels is associated to a decrease in event rate for patients managed using the neuro-hormone levels as the target in heart failure therapy [9,10].

Finally, Wu et al. [11] have recently demonstrated a reduced readmission rate for alternating diagnoses of heart failure and pulmonary disease after implementation of B-type natriuretic peptide testing, possibly due to a more correct identification of patients.

Given the above scenario, we have retrospectively checked whether the addition of pre-discharge B-type natriuretic peptide levels to a clinical–instrumental score for discharge decision in patients admitted for heart failure in our Heart Failure Unit reduced readmission rate for heart failure and related cost.

2. Patients and methods

2.1. Patients

We studied two series of consecutive patients admitted to our Heart Failure Unit due to an instabilisation of heart failure as main diagnosis. One-hundred and sixty-six patients discharged from July 1st 2002 (implementation of B-type natriuretic peptide testing for discharge decision) to June 30th 2003 (hereafter B-type natriuretic peptide group) were compared to one hundred and forty-nine subjects discharged from January 1st to December 31st 2001 (hereafter clinical group). Patients discharged from January 1st and June 30th 2002 were excluded, since during such period the utility of B-type natriuretic peptide assay was tested in our Heart Failure Unit.

2.2. Inclusion and exclusion criteria

The criteria to be admitted to our Heart Failure Unit (and then in the present study) are: 1) symptoms of decompensated heart failure [12], due to an exacerbation of symptoms in patients with at least 1 New York Heart Association class deterioration; 2) New York Heart Association functional class III, or IV; 3) evidence of systolic and/or diastolic dysfunction on echocardiographic examination on admission (see below). Patients with concomitant unstable angina or acute myocardial infarction were excluded [13].

2.3. Treatment and clinical criteria of stability

All patients were treated according to the international guidelines on heart failure [14,15]. Before implementation of B-type natriuretic peptide testing for discharge decision, we usually discharged patients when a clinical/instrumental finding of stability was achieved [16,17]. This finding was made if 6 criteria were simultaneously met: a) subjective improvement on the basis of NYHA class, or at least no orthopnoea, for refractory NYHA IV patients; b) $90 <$ systolic blood pressure < 120 mm Hg; c) heart rate < 100 bpm; d) pulse oxymetry in ambient air $> 90\%$; e) diuresis > 1000 ml/day; f) improvement in fluid overload (normal hydration or slight hyper- or de-hydration on electrical impedance analysis) [18].

2.4. B-type natriuretic peptide use as a further criterion

From July 1st 2002, B-type natriuretic peptide level has been added as a further criterion: blood samples were taken from all subjects for the B-type natriuretic peptide assay at the time of admission to the ward and on the day when the clinical/instrumental finding of stability was achieved. We used a B-type natriuretic peptide value of ≤ 250 pg/ml [19] or a reduction of $\geq 30\%$ [20] with respect to admission to identify patients who could be discharged, provided that the favourable modifications in the neuro-hormone corresponded to the above mentioned clinical/instrumental finding of stability [16,17]. Patients with a B-type natriuretic peptide value of >250 pg/ml, in the absence of a reduction of $\geq 30\%$, were given "aggressive" treatment, namely: a) increased diuretic treatment (up to 500 mg/day of furosemide), b) strict blood pressure and heart rate control: target values < 100 mm Hg (for systolic blood pressure) and < 80 bpm respectively), c) possible inclusion in the therapeutic regimen of i.v. vasodilators. They were reassessed every second day and discharged in the event of persisting clinical stability, after measurement of B-type natriuretic peptide levels, but independently from the plasma level of the latter. Blood samples were collected into tubes containing potassium ethylene diamine tetra-acetic acid and immediately analysed by the B-type natriuretic peptide Triage method (Biosite Diagnostics, La Jolla, CA, USA) [21]. Serum creatinine was checked on discharge.

2.5. Echocardiography

Echocardiography examinations were performed on admission to the ward, with a Vingmed System Five apparatus. All the echocardiograms were obtained blinded to the B-type natriuretic peptide value. Left ventricular systolic dysfunction was defined as an ejection fraction (EF) $< 50\%$. The left ventricular EF was measured using Simpson's biplane method. The classification of diastolic function was: 1) impaired relaxation (peak E/A velocity ratio (E/A) < 0.8 and deceleration time (DT) > 220 ms, pulmonary vein (PV) systolic to diastolic (S/D) ratio > 1, and atrial reversal (AR) < 35 cm/ms); 2) pseudonormal (E/A 1 to 2, DT 150 to 220 ms, PV S/D ratio < 1, and AR > 35 cm/ms); 3) restrictive (E/A ≥ 2, DT ≤ 150 ms, PV S/D ratio < 1, and AR > 35 cm/ms). The presence of one of these patterns, in the presence of a normal EF ($>50\%$), was defined as isolated diastolic dysfunction. In

patients suffering from atrial fibrillation at the time of the echocardiogram, the diastolic function was classified as: 1) restrictive pattern (DT ≤150 ms) or 2) indeterminate (DT >150 ms) [22].

2.6. Follow-up

All patients were discharged according to the usual procedures: those who belonged to the Basic Health District of the trial hospital were assigned to an out-patient cardiological/nursing follow-up protocol, and the remainder were referred to their General Practitioners. All patients were followed up for six months from the time they were discharged, either by clinic visits, computerized chart review, or telephone call, if no contact had occurred.

2.7. Statistics

Categorical data are presented as numbers (percent), and continuous data as means±standard deviation. We used the Mann–Whitney *U*-test for the comparison between samples, while the association between variables was verified with Fisher's exact test. B-type natriuretic peptide levels were evaluated both as a continuous variable and as a categorical variables (based on distribution tertiles and cut-off values). Cox proportional hazards regression models were used to examine the relation of B-type natriuretic peptide levels with the incidence of events, using a combined endpoint (deaths plus readmissions to hospital for heart failure, as principal diagnosis, DRG 127) during the six months after discharge. A value of $P<0.05$ was considered significant. Analyses

Table 1
Clinical/demographic characteristics of the 315 patients studied, globally and in relation to the discharge procedure

Parameter	All $n=315$	Clinical discharge $n=149$	P	Clinical acumen+BNP discharge $n=166$
Age (years)	77±9	77±9	n.s.*	77±9
Sex (M/F) (%)	47/53	46/54	n.s. #	48/52
Functional class on admission (NYHA)	3.6±0.5	3.6±0.5	n.s.*	3.6±0.5
Functional class on discharge (NYHA)	2.3±0.7	2.3±0.8	n.s.*	2.3±0.7
Echocardiographic parameters				
– LV ejection fraction (%)	48±16	47±15	n.s.*	48±16
– LV ejection fraction>45% (%)	50	49	n.s.#	50
– Diastolic "restrictive" pattern	23	22	n.s.#	24
Etiology (%)				
– Ischaemic heart disease	38	37	n.s.#	39
– Hypertensive heart disease	23	23	n.s. #	23
– Valvular	17	17	n.s. #	17
– Other or unknown	22	23	n.s.#	21
Laboratory parameters				
BNP on admission (pg/ml)	–	–	–	764±699
BNP on discharge (pg/ml)	–	–	–	456±612
– Blood creatinine on discharge (mg/dl)	1.5±0.9	1.4±0.8	n.s.*	1.5±1.1
Co–morbidity (%)				
– Atrial fibrillation	40	38	n.s. #	41
– Renal failure (creatinine>2 mg/dl)	16	17	n.s. #	16
– Left bundle branch block on ECG	16	17	n.s. #	16
Treatment being given on entry/discharge (%)				
– ACE-inhibitors	60/81	59/80	n.s./n.s. #	61/79
– Angiotensin receptor blockers	10/12	11/11	n.s./n.s.#	9/12
– Beta-blockers	59/78	57/77	n.s./n.s. #	60/78
– Spironolactone	27/48	26/49	n.s./n.s. #	28/48
	48	49	n.s.#	47
Assigned to cardiological/home based follow-up (%)				
Events during follow-up (%)				
– Readmissions for DRG 127	90 (29)	52 (35)	<0.05#	38 (23)
– Deaths	41 (13)	19 (13)	n.s. #	22 (13)

The values are expressed as mean±standard deviation unless otherwise specified. The comparisons relate to "clinical acumen discharge" *vs* "clinical acumen +BNP discharge". * Mann–Whitney *U*-test; #Fisher's exact test.

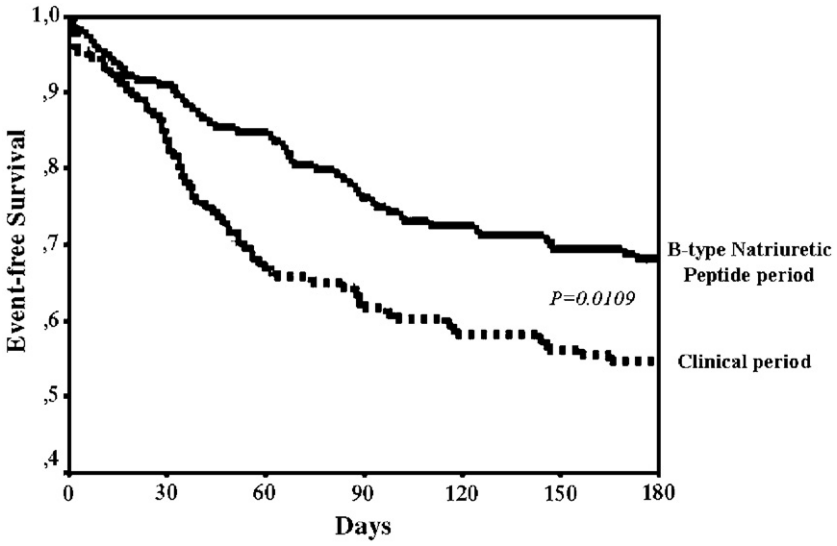

Fig. 1. Kaplan–Meier curves showing the cumulative incidence of death and readmission according to B-type Natriuretic Peptide levels/changes in the study population. Tarone–Ware's test for all the comparisons.

were performed using SPSS software per Windows, release 11.0 (SPSS Inc., Chicago, USA).

2.8. Cost analysis

Hospitalisation cost was estimated on the basis of the DRG 127 tariff (2206 euros) in the "clinical group", while in the "B-type natriuretic peptide group" it valued adding to the cost of DRG 127 tariff, the expenditure resulting from B-type natriuretic peptide testing, which was valued 24 euros (22 euros due to the crude single assay cost, plus 2 euros due to other cost).

3. Results

3.1. Baseline characteristics, B-type natriuretic peptide and events

The characteristics of the populations studied were summarised in Table 1. They were elderly patients (77±9 years), equally distributed for gender (males=47%), who suffered from numerous cardiovascular comorbidities, especially atrial fibrillation (40%) and renal failure (16%). The ratio of isolated diastolic dysfunction to the total cases was 50%, and the 23% of subjects presented a restrictive mitral pattern. The B-type

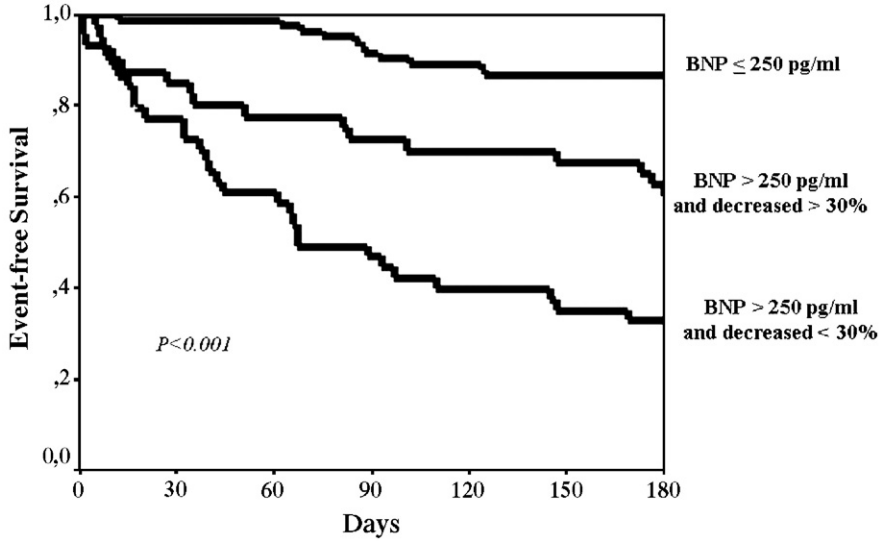

Fig. 2. Kaplan–Meier curves showing the cumulative incidence of death and readmission according to the use of B-type Natriuretic Peptide as a discharge criterion in the study population. Tarone–Ware's test for all the comparisons.

Table 2
Hospital expenditures (euros) per 100 patients, in relation to the discharge procedure

	Unit cost	Clinical acumen		BNP plus clinical acumen		Cost saving
		No.	Total cost	No.	Total cost	
Basic hospitalisations	2206	100	220,600	100	220,600	
B-type natriuretic peptide assay	24			281	6744	
Readmissions	2206	35	77,210	23	50,738	
Hospital costs			297,810		278,082	19,728

natriuretic peptide — guided patients did not differ from those discharged on the basis of the sole clinical acumen in terms of any of the characteristics both on admission and discharge (Table 1).

On admission, B-type natriuretic peptide plasma value was ≥100 pg/ml in all patients (mean±SD=764±699 pg/ml), while on discharge it was 456±612 pg/ml. During the B-type natriuretic peptide period, one-hundred and twenty-one patients (73%) presented a pre-discharge B-type natriuretic peptide ≤250 pg/ml or a reduction of ≥30% in B-type natriuretic peptide values. In 29 patients (17%) from the B-type natriuretic peptide group we had to extend the hospital stay to obtain a reduction in B-type natriuretic peptide values under 250 pg/ml. In these patients, a longer i. v. diuretic (frusemide) treatment was performed: +28 h with respect to the remaining subjects.

During the six-month follow-up period, there were 52 readmissions (35%) among the clinical group (n=149) compared with 38 (23%) in the B-type natriuretic peptide group (n=166) (χ^2=5.5; P=0.02). Survival did not differ between groups: 87% for patients discharged on the basis of the sole clinical acumen and 87% with the addition of B-type natriuretic peptide levels (χ^2=0.895; P=1.0) (Table 1). In univariate Cox analysis, left ventricular ejection fraction (hazard ratio, HR=0.9808; 95% confidence interval, CI=0.9661–0.9957; P<0.05), age (HR=1.0457; CI=1.0179–1.0744; P<0.005), NYHA class on discharge (HR=1.8913; CI=1.3730–2.6053; P<0.0001), restrictive mitral pattern on echocardiography (HR=0.3644; CI=0.2276–0.5834; P<0.0001), creatinine on discharge (HR=1.4895; CI=1.2369–1.7936; P<0.0001), and B-type natriuretic peptide (analysed as a cutoff level of 250 pg/ml) (HR=0.2058; CI=0.1128–0.3755; P<0.0001) were associated with death and/or readmission. Multivariate Cox regression identifies only three parameters as predictors of events: creatinine (HR=1.3875; CI=1.0858–1.7729; P<0.01), left ventricular ejection fraction (HR=9.335; CI=0.9606–0.9917; P<0.005), and B-type natriuretic peptide cutoff level (250 pg/ml) (HR=0.2717; CI=0.1412–05227; P<0.0001), the latter being the strongest one. Changes in B-type natriuretic peptide values were correlated to clinical events: a B-type natriuretic peptide value on discharge of ≤250 pg/ml or a reduction of ≥30% in B-type natriuretic peptide values predicted a 23% event rate within six months (respectively 11 deaths and 17 readmissions, for overall 28 out of 121 patients), whereas a far higher percentage (71%) of unfavourable events were observed in the remaining patients (respectively 11 deaths and 21 readmissions, for overall 32 out of 45 patients) (χ^2=32.7; P=0.001). Furthermore, event rate increased from the lowest for patients with B-type natriuretic peptide plasma levels on discharge ≤250 pg/ml (16%, n=81), through those with plasma levels >250 pg/ml and a decrease ≥30% (42%, n=40), to the highest for those with plasma levels >250 pg/ml and a decrease <30% (71%, n=45) (χ^2=137; P<0.001) (Fig. 1). The ability of the B-type natriuretic peptide changes to discriminate between patients with events and event-free is demonstrated by the ROC analysis: the AUC value was 0.76 (confidence interval 0.68–0.84) for patients with a plasma value ≤250 pg/ml or reduction of 30%. Finally, Kaplan–Meier curves showed a lower cumulative incidence of death and readmission in relation to the use of B-type Natriuretic Peptide as a discharge criterion in comparison to the sole clinical acumen (Fig. 2).

3.2. Cost analysis

The overall costs of care were lower (−7%) for B-type natriuretic peptide — discharged patients in comparison with those of the clinical group: 2.781±923 *vs* 2.978±1.057 euros per patient respectively, making a difference of 197 euros (Mann–Whitney U-test, Z=−5.8; P<0.01). This difference is due to the lower expenditure resulting from the lower readmission rate for DRG 127 among the B-type natriuretic peptide group, which amply compensates for the additional expenditure generated by B-type natriuretic peptide assay implementation (Table 2).

4. Discussion

4.1. B-type natriuretic peptide and discharge decision

The main finding of our study was that the addition of pre-discharge B-type natriuretic peptide levels to a clinical–instrumental decisional score for discharge decision in patients admitted for heart failure contributed to reduce the number of readmissions, and related costs.

Recently, natriuretic peptides (B-type natriuretic peptide) became available as a new tool for prognostic stratification of patients with heart failure in different clinical spheres (see [6] for a review). In particular, it has been reported that pre-discharge B-type natriuretic peptide is strictly associated to unfavourable events in the six months after discharge, being a strong, independent marker of death or readmission [6]. On the other hand, a decline in plasma concentrations of B-type natriuretic peptide in comparison with the high values of the unstable phase after treatment with drugs of proven efficacy in heart failure [23–25], reflects an improvement in filling pressures [26,27]. B-type natriuretic peptide plasma levels reflect left ventricular haemodynamic dysfunction and fluid

overload [28,29], so that a larger fall in B-type natriuretic peptide plasma levels may reflect a more complete normalisation of congestion and wall stress.

According with these reports, in our study patients with low or markedly decreased B-type natriuretic peptide level at discharge showed a lower event rate during a six-month follow-up with respect to the remaining patients (Table 1), independently from the absence of clinical improvement (as represented by NYHA class) on discharge, in B-type natriuretic peptide population (Table 1). On the other hand, Maisel et al. [30] clearly demonstrated the "disconnect" between the perceived severity (as represented by NYHA class) and B-type natriuretic peptide levels, and the association of the sole latter with the clinical events. However, in all the above quoted studies on the prognostic role of B-type natriuretic peptide [6], physicians were kept blind to B-type natriuretic peptide levels, so that these reflected the stabilisation obtained by the use of the sole clinical acumen. According to Cleland and Goode [31], studies using natriuretic peptides have suggested that physicians do not treat heart failure aggressively enough, and pre-discharge B-type natriuretic peptide levels may be a useful reminder that more treatment is required. Finally, it has been reported that titration of treatment to reduce plasma natriuretic peptide concentrations causes a profound inhibition of the renin–angiotensin–aldosterone system [32] and decreases total cardiovascular events [9,10].

So, it is conceivable that in our study addition of pre-discharge B-type natriuretic peptide levels to a clinical–instrumental decisional score for discharge decision caused a more aggressive treatment which produced a more complete correction of fluid overload and left ventricular wall stress, thereby possibly translating in the observed decrease of early readmission with respect to patients discharge on the basis of the sole clinical acumen.

4.2. Cost analysis

Balancing effectiveness and costs of care for acute heart failure patients is a major task for physicians and Health Care Systems. Early readmission is a critical problem in the management of heart failure [4], due to its dramatic costs [1–3]. In the U.K. for example, it has been recently calculated that if a 50% of second admissions within a calendar year had been avoided in 2000, savings equivalent to £56.4 million would have resulted [5]. Unfortunately, at present, it is difficult to identify patients at risk of events after hospitalisation *a priori*, and discharge of a patient admitted to hospital with acute heart failure is still largely based on a clinical opinion, although it is supported by instrumental indexes [16]. In hospital, the search for tools that more clearly define the risk profile of each patient is combined with the organisational need to identify patients liable to suffer future events at the time of discharge. This is a health planning problem that can partly be solved by differentiating the intensity of post-discharge follow-up programmes, which can be graduated on the basis of the forecast morbidity.

Natriuretic peptides have recently attracted interest of the investigators and established them as one of most important factors in heart failure diagnosis and management. The prognostic value of natriuretic peptides is an interesting and promising topic due to grim prognosis of heart failure. Our paper points out the potential role of a "B-type Natriuretic Peptide guided" decision of discharge as triggering a decrease in readmissions, over a short-lasting period, suggesting for a benefit even in cost-effectiveness of this approach. Indeed, the health cost analysis shows that it is not only safe, but also financially advantageous to discharge those patients who show a pattern of clinical stabilisation associated with a reduction in B-type natriuretic peptide values to ≤ 250 pg/ml at discharge. The significant decrease in readmission rate might also be interpreted, as an index of better quality of life induced by means of the enhanced medical effort suggested by B-type natriuretic peptide evaluation. Anyway, cost savings obtained by this approach would allow intensive follow-up protocols for patients with high B-type natriuretic peptide level at discharge who should be considered at very high risk.

5. Limitations and merits of the study

Our study has a number of limitations: it is a retrospective study, making use of a historic control. So, though there were no changes in the clinical practice patterns, drug prescription, the group of attending physicians, or the comorbidities between patients in the B-type natriuretic peptide and clinical group (Table 1), confirmation of a causal connection between B-type natriuretic peptide — guided management and a low rate of readmissions must await the results of an *ad hoc* study, that is already under way. A further limit is the assumption that cost evaluation was performed only on the basis of estimated DRG 127 cost, which is actually independent of length of hospitalisation, number and type of diagnostic procedures and treatments.

The greatest merit of the study is that it has identified a practical cut-off value allowing an immediate decision at the time of discharge. A further advantage is the type of the sample, which represents the normal "unselected" population of consecutive patients, admitted to the Heart Failure Unit of medium-sized hospitals, during a 12-month period.

6. Conclusion

Our study suggest that the addition of pre-discharge B-type natriuretic peptide levels to a clinical–instrumental decisional score for discharge decision in patients admitted for heart failure contributed to reduce the number of readmissions, and related costs. Reducing heart failure readmissions helps justify the costs for implementing B-type natriuretic peptide testing in the Heart Failure Unit. Further research is needed to confirm that changes in B-type natriuretic peptide levels can in the future be a guide to optimise care of patients admitted for heart failure.

Acknowledgements

We wish to thank Maura Chinellato (Basic Health Services Department, San Donà di Piave). Four anonymous referees improved an earlier version of the manuscript.

References

[1] McMurray JJ, Stewart S. Epidemiology, aetiology, and prognosis of heart failure. Heart 2000;83:596–602.
[2] Berry C, Murdoch DR, McMurray JJ. Economics of chronic heart failure. Eur J Heart Fail 2001;3:283–91.
[3] Thom TJ, Kannel WB. Congestive heart failure: epidemiology and cost of illness. Dis Manage Health Outcomes 1997;1:75–83.
[4] Di Lenarda A, Scherillo M, Maggioni AP, et al. Current presentation and management of heart failure in cardiology and internal medicine hospital units: a tale of two worlds. The TEMISTOCLE study. Am Heart J 2003;146:E12.
[5] Stewart S, Jenkins A, Buchan S, et al. The current cost of heart failure to the National Health Service in the U.K. Eur J Heart Fail 2002;4:361–71.
[6] Doust JA, Pietrzak E, Dobson AJ, Glasziou PP. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: a systematic review. Br Med J 2005;330:625–34.
[7] Caldwell MA, Howie JN, Dracup K. BNP as discharge criteria for heart failure. J Card Fail 2003;9:416–22.
[8] Morimoto T, Hayashino Y, Shimbo T, Izumi T, Fukui T. Is B-type natriuretic peptide-guided heart failure management cost-effective? Int J Cardiol 2004;96:177–81.
[9] Troughton RW, Frampton CM, Yandle TG, et al. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Lancet 2000;355:1126–30.
[10] Jourdain P, Gueffet P, Le Helloco, et al. Benefit of BNP for optimising therapy in patients with heart failure due to systolic dysfunction: The Systolic heart failure treatment supported by BNP trial (STARS-BNP) multicenter randomised study. Eur J Heart Fail Suppl 2005;4:120.
[11] Wu AHB, Harrison A, Maisel AS. Reduced readmission for alternating diagnoses of heart failure and pulmonary disease after implementation of B-type natriuretic peptide testing. Eur J Heart Fail 2004;6:309–12.
[12] McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of CHF. The Framingham study. N Engl J Med 1971;285:1442–6.
[13] Luepker RV, Apple FS, Christenson RH, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies. Circulation 2003;108:2543–9.
[14] Task force for the diagnosis and treatment of chronic heart failure of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001;22:1527–60.
[15] Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2001;104:2996.
[16] Peacock WF. Rapid optimization: strategies for optimal care of decompensated congestive heart failure patients in the emergency department. Rev Cardiovasc Med 2002;3(suppl 4):41–8.
[17] Valle R, Prevaldi C, D'Eri A, et al. B-Type Natriuretic Peptide Predicts Post-Discharge Prognosis in Elderly Patients Admitted due to Cardiogenic Pulmonary Edema. Am J Geriatr Cardiol 2006;15:202–7.
[18] Paterna S, Di Pasquale P, Parrinello G, et al. Changes in brain natriuretic peptide levels and bioelectrical impedance measurements after treatment with high-dose furosemide and hypertonic saline solution versus high-dose furosemide alone in refractory congestive heart failure. J Am Coll Cardiol 2005;45:1997–2003.
[19] Aspromonte N, Canali C, Carbonieri E, et al. BNP-guided treatment of patients hospitalised with acute heart failure enables the timing of the patient's discharge to be optimised and can predict the medium-term risk. Acute cardiac care, Rome. European Society of Cardiology; 2004. Abstract Book: 94.
[20] Bettencourt P, Ferreira S, Azevedo A, Ferreira A. Preliminary data on the potential usefulness of B-type natriuretic peptide levels in predicting outcome after hospital discharge in patients with heart failure. Am J Med 2002;113:215–9.
[21] Biosite. TriageBNP package insert. San Diego, CA: Biosite Inc.; 2002.
[22] Valle R, Bagolin E, Canali C, et al. The BNP assay does not identify mild left ventricular diastolic dysfunction in asymptomatic diabetic patients. Eur J Echocard 2006;7:40–4.
[23] Yoshimura M, Mizuno Y, Nakayama M, et al. B-type natriuretic peptide as a marker of the effects of enalapril in patients with heart failure. Am J Med 2002;112:716–20.
[24] Feola M, Menardi E, Ribichini F, et al. Effects of the addition of a low dose of spironolactone on brain natriuretic peptide plasma level and cardiopulmonary function in patients with moderate congestive heart failure. Med Sci Monit 2003;9:341–5.
[25] Fung JW, Yu CM, Yip G, et al. Effect of beta blockade (carvedilol or metoprolol) on activation of the renin–angiotensin–aldosterone system and natriuretic peptides in heart failure. Am J Cardiol 2003;92:406–10.
[26] Richards AM, Crozier IG, Yandle TG, et al. Brain natriuretic factor: regional plasma concentrations and correlation with haemodynamic state in cardiac disease. Br Heart J 1993;69:414–7.
[27] Kazanegra R, Chen V, Garcia A, et al. A rapid test for B-type natriuretic peptide (BNP) correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study. J Card Fail 2001;7:21–9.
[28] Kinnunen P, Vuolteenaho O, Ruskoaho H. Mechanisms of atrial and brain natriuretic peptide release from rat ventricular myocardium: effect of stretching. Endocrinology 1993;132:1961–70.
[29] Magga J, Vuolteenaho O, Tokola H, Marttila M, Ruskoaho H. B-type natriuretic peptide: a myocyte-specific marker for characterizing load induced alterations in cardiac gene expression. Ann Med 1998;30 (suppl 1):39–45.
[30] Maisel A, Hollander JE, Guss D, et al. Primary results of the rapid emergency department heart failure outpatient trial (REDHOT). J Am Coll Cardiol 2004;44:1328–33.
[31] Cleland JCF, Goode K. Natriuretic peptide for heart failure. Fashionable? Useful? Necessary? Eur J Heart Fail 2004;6:253–5.
[32] Murdoch DR, McDonagh TA, Byrne J, et al. Titration of vasodilator therapy in chronic heart failure according to plasma brain natriuretic peptide concentration: randomized comparison of haemodynamic and neuroendocrine effects of tailored versus empirical therapy. Am Heart J 1999;138:1126–32.