Herz 2019 · 44:450–454
https://doi.org/10.1007/s00059-018-4687-1
Received: 23 October 2017
Revised: 26 January 2018
Accepted: 26 January 2018
Published online: 7 March 2018

H. R. Omar[1] · M. Guglin[2]

[1] Internal Medicine Department, Mercy Medical Center, Clinton, USA
[2] Division of Cardiovascular Medicine, Linda and Jack Gill Heart Institute, University of Kentucky, Lexington, USA

Post-discharge rise in BNP and rehospitalization for heart failure

Heart failure (HF) is the leading cause of hospitalization among adults over 65 years of age in the United States. Despite advances in medical and device therapy, the rate of rehospitalization remain quite high up to ~50% at 6 months [1], and 70% of these rehospitalizations are related to worsening HF [2, 3]. A major portion of the financial burden in HF is represented by readmission rates. This has stimulated public and private payers to target readmission as a main focus of pay-for-performance initiatives [4] and to apply monetary penalties to hospitals with high readmission rates. This prompted research to study predictors that assist in risk-stratifying patients and identifying those at higher risk of complications. Among these predictors is the B-type natriuretic peptide (BNP), whose absolute value on admission, on discharge, and its percentage reduction throughout hospitalization is associated with postdischarge outcomes [5–7]. We have also previously advocated that the value of longitudinal BNP monitoring [8] is more important for diagnostic and prognostic purposes than utilizing a single BNP measurement [9]. We speculated that a rise in BNP in the early post-discharge period is a sign of increased congestion.

The aim of the current study was to examine whether the magnitude of the rise in BNP from discharge to the 1-month follow-up of patients hospitalized with decompensated HF is associated with an increased risk of rehospitalization.

Methods

Study population and the ESCAPE trial

The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial randomized 433 patients with acute HF to either clinical management guided by pulmonary artery catheterization (PAC) or to clinical management alone. The patients had a left ventricular ejection fraction <30%, 3 months of HF symptoms despite appropriate therapy, a systolic blood pressure <125 mm Hg, and at least one symptom and sign of congestion. Patients with creatinine levels >3.5 mg/dl, and those who required dobutamine or dopamine 3 g/kg/min or milrinone before randomization, were excluded. The study showed that PAC did not affect outcomes, which was the number of days alive outside the hospital at 6 months following randomization [10].

BNP measurement

Patients enrolled in the ESCAPE trial had BNP measured at multiple study time points including at admission, discharge, 1 month, 2 months, 3 months, and 6 months. BNP was measured using the Shionogi assay as previously described. NT-proBNP was not measured in the ESCAPE trial. We hypothesized that, in patients hospitalized with decompensated HF, the magnitude of the rise in BNP level from discharge to 1-month follow-up (BNP at 1 month—discharge BNP) would predict future rehospitalization. Patients who were rehospitalized within the first 4 weeks of discharge were thus excluded from the current analysis. The study endpoint was all-cause rehospitalization up to 6 months after randomization.

Statistical analysis

Primary analysis compared patients who were rehospitalized versus those who were not rehospitalized following the index hospitalization with decompensated HF. Owing to the small sample size and nonnormality of distribution of most variables, we compared continuous variables using the Mann–Whitney U test and presented the results as median and interquartile (IQR) range. Categorical variables were compared using the Chi-square test or Fisher's exact test as appropriate, and the data are presented as counts and percentages. The paired-sample t test was used to compare longitudinal BNP values at 1 month relative to discharge. The ability of the magnitude of BNP increase from discharge to the 1-month follow-up to predict all-cause rehospitalization was assessed using receiver operating characteristics (ROC) curves. Optimum BNP cut-off values were those that provided the highest combined sensitivity and specificity for predicting the study outcome. Statistical analysis was performed using IBM SPSS 21.0 statistical software (version 21.0. Armonk, NY, USA) and the MedCalc software (version 16.8, bbva, Ostend, Belgium). Statistical significance was assessed using two-sided p values and was set at $p \leq 0.05$.

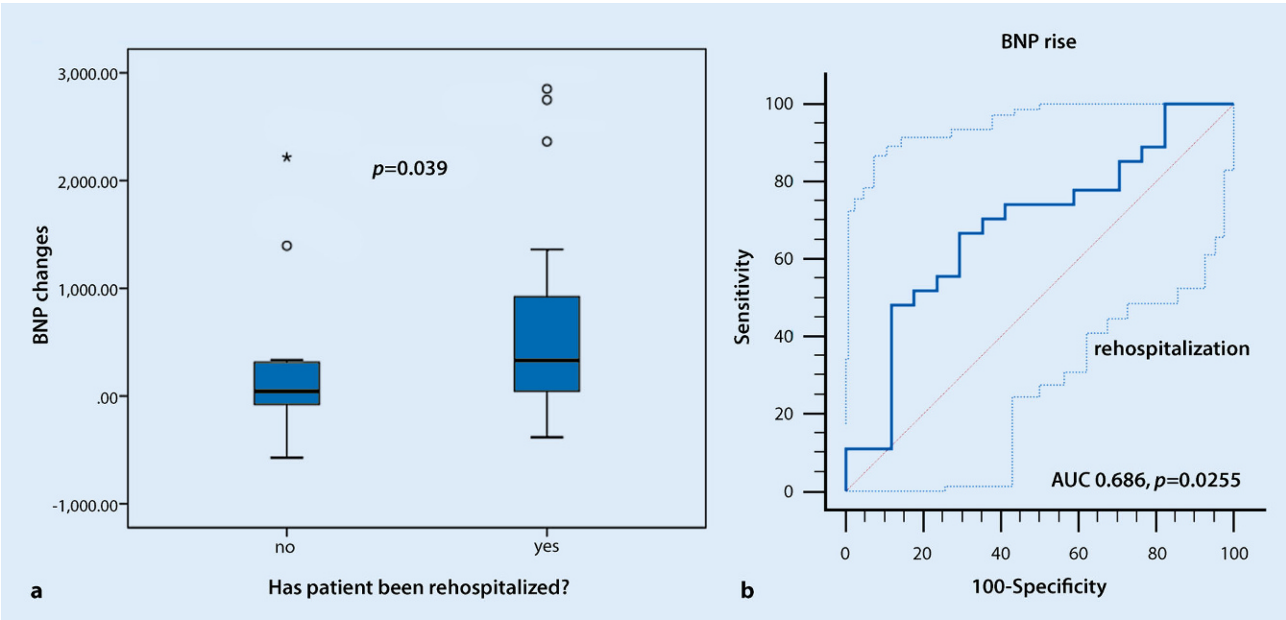

Fig. 1 ▲ **a** Box and whisker plot illustrating the relationship between the magnitude of BNP change from discharge to 1-month follow-up and all-cause rehospitalization among ESCAPE trial patients. The *five horizontal lines* represent the 10th, 25th, 50th, 75th, and 90th percentiles of each variable, *from bottom to top*, excluding outliers shown as *circles* and extreme outliers shown as an *asterisk*. **b** Receiver operator characteristics curve showing the ability of BNP rise from discharge to 1-month follow-up to predict all-cause rehospitalization. *BNP* B-type natriuretic peptide

Results

Among the 433 patients enrolled in the ESCAPE trial, 51 (12%) had BNP levels recorded both at hospital discharge and at the 1-month follow-up. Seven of 51 patients were excluded from the current analysis since they were rehospitalized within the first 4 weeks of discharge. The remaining 44 patients had a mean age of 56 years, 71% were men, 66% were Caucasian, and 91% were classified as New York Heart Association (NYHA) class IV at baseline. At 6 months following randomization, 61% (27/44) of those patients were rehospitalized, and the 6-month mortality rate was 13.6% (6/44). The average BNP value on discharge for these 44 patients was 467 pg/ml (median: 330 pg/ml; IQR: 142–599 pg/ml), which increased to 919 pg/ml (median: 565 pg/ml; IQR: 176–1,392 pg/ml) at the 1-month follow-up ($p = 0.001$). There were no significant differences in rehospitalized and non-rehospitalized patients with regards to markers of congestion on hospital discharge such as the frequency of NYHA class IV ($p = 1.000$), the presence of rales ($p = 0.634$), a positive hepatojugular reflux ($p = 0.749$), at least 1+ lower extremity edema ($p = 1.000$), jugular venous distension >8 cm ($p = 0.724$), or BNP level ($p = 0.294$). Patients who were rehospitalized after 1 month of hospital discharge had a significantly higher magnitude of rise in BNP from discharge to the 1-month follow-up compared with those who were not rehospitalized (median [IQR]: 329 [11, 956] vs. 44 [−90, 316] pg/ml, $p = 0.039$, in both groups, respectively). ROC showed that the absolute rise in BNP from discharge to the 1-month follow-up had an area under the curve (AUC) of 0.686 (95% confidence interval [CI]: 0.529–0.8181, $p = 0.0255$) in predicting rehospitalization, and an absolute value of BNP rise >191 pg/ml had the highest combined sensitivity (67%) and specificity (71%) for predicting rehospitalization (**Fig. 1**). Among the 27 patients who were rehospitalized, the average time to rehospitalization was 79 days (median [IQR]: 75 [45–101] days). **Table 1** shows the results of the comparison of the baseline characteristics of ESCAPE trial patients according to whether or not they were rehospitalized after the index hospitalization.

Discussion

We have shown by univariate comparison that the magnitude of the rise in BNP level from hospital discharge to the 1-month follow-up was significantly higher in patients who were rehospitalized later on compared with those who were not rehospitalized. An absolute increase in BNP of ~200 pg/ml from discharge to the 1-month follow-up predicted rehospitalization; this highlights its value for outpatient evaluation of patients recently discharged after HF decompensation, even in those whose symptoms do not suggest overt HF. These findings were observed despite similar degree of clinical congestion and comparable BNP values on hospital discharge of those who will be rehospitalized or not. It is known that rehospitalizations for HF are preceded by a gradual rise in ventricular filling pressure that begins more than 2 weeks before any detectable changes in weight or clinical symptoms [11]. Data from trials of implantable hemodynamic monitors show that the risk for HF events is related to the degree of filling pressure elevation, with progressively higher risk once the median 24-h pulmonary

Abstract · Zusammenfassung

Herz 2019 · 44:450–454 https://doi.org/10.1007/s00059-018-4687-1

H. R. Omar · M. Guglin

Post-discharge rise in BNP and rehospitalization for heart failure

Abstract

Background. The B-type natriuretic peptide (BNP) level on discharge of patients hospitalized with decompensated heart failure (HF) is widely considered as the "baseline" value, and treatment should be targeted to maintain this level. The prognostic value of an increase in BNP level from discharge to the 1-month follow-up in predicting rehospitalization has not been previously explored.
Methods. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial data were utilized to determine whether an increase in BNP level from discharge to the 1-month follow-up is associated with a higher risk of rehospitalization. The study endpoints were all-cause rehospitalization up to 6 months following randomization.
Results. Among 44 patients (mean age, 56 years, 71% men) who had their BNP levels checked on discharge and at the 1-month follow-up, the average BNP level on discharge of the whole cohort was 467 pg/ml, which increased to 919 pg/ml at 1 month ($p = 0.001$). The median and interquartile range of the magnitude of rise in BNP level from discharge to 1-month follow-up was higher in rehospitalized compared with non-rehospitalized patients (329 [11, 956] vs. 44 [–90, 316] pg/ml, $p = 0.039$, in both groups, respectively). Receiver operator characteristic curves showed that the magnitude of the rise in BNP from discharge to the 1-month follow-up had an area under the curve of 0.686 ($p = 0.0255$) in predicting all-cause rehospitalization. Rehospitalized and non-rehospitalized patients had similar degree of clinical congestion and comparable BNP level on hospital discharge.
Conclusion. The magnitude of the rise in BNP level from discharge to the 1-month follow-up is a useful prognostic factor that predicts rehospitalization in patients with HF.

Keywords

Heart failure · Hospitalization · Brain natriuretic peptide · Prognostic factors · Health costs

Anstieg des BNP-Werts nach Entlassung und stationäre Wiederaufnahme wegen Herzinsuffizienz

Zusammenfassung

Hintergrund. Der Wert des natriuretischen Peptids vom B-Typ („B-type natriuretic peptide", BNP) bei Entlassung von Patienten, die wegen dekompensierter Herzinsuffizienz stationär aufgenommen worden waren, wird weithin als „Ausgangswert" betrachtet, und die Behandlung sollte sich auf den Erhalt dieses Werts ausrichten. In Hinblick auf die Vorhersage einer stationären Wiederaufnahme ist der prognostische Nutzen eines BNP-Wert-Anstiegs von der Entlassung bis zur Nachuntersuchung nach einem Monat bisher nicht untersucht worden.
Methoden. Die Daten der Studie Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) wurden verwendet, um zu untersuchen, ob ein Anstieg des BNP-Werts von der Entlassung bis zur Nachuntersuchung nach einem Monat mit einem höheren Risiko für eine erneute stationäre Aufnahme verbunden ist. Studienendpunkt war die stationäre Wiederaufnahme aus sämtlichen Gründen bis zu 6 Monate nach Randomisierung.
Ergebnisse. Für 44 Patienten (Durchschnittsalter: 56 Jahre, 71% m.), bei denen der BNP-Wert zur Entlassung und anlässlich der Nachuntersuchung nach einem Monat bestimmt wurde, betrug der Durchschnitts-BNP-Wert der ganzen Kohorte bei Entlassung 467 pg/ml und stieg auf 919 pg/ml nach einem Monat ($p = 0,001$). Der Mittelwert und Interquartilsabstand des BNP-Anstiegs von der Entlassung bis zur Nachuntersuchung nach einem Monat war bei den stationär Wiederaufgenommenen höher als bei denen, die nicht erneut stationär aufgenommen worden waren (329 [11, 956] vs. 44 [–90, 316] pg/ml; $p = 0,039$, in beiden Gruppen). Die Receiver-Operator-Characteristic-Kurven zeigten, dass die Größe des Anstiegs beim BNP-Wert von der Entlassung bis zur Nachuntersuchung nach einem Monat eine Fläche unter der Kurve (AUC) von 0,686 ($p = 0,0255$) bei der Vorhersage der stationären Wiederaufnahme aus sämtlichen Gründen aufwies. Stationär wiederaufgenommene und nicht wiederaufgenommene Patienten hatten einen ähnlichen Grad klinischer Kongestion und vergleichbare BNP-Spiegel bei der Entlassung aus dem Krankenhaus.
Schlussfolgerung. Die Größe des Anstiegs des BNP-Werts von der Entlassung bis zur Nachuntersuchung nach einem Monat ist ein nützlicher prognostischer Parameter zur Vorhersage der stationären Wiederaufnahme bei Patienten mit Herzinsuffizienz.

Schlüsselwörter

Herzinsuffizienz · Hospitalisierung · „Brain natriuretic peptide" · Prognostische Faktoren · Gesundheitsausgaben

artery diastolic pressure rises >18 mm Hg [12]. In the ESCAPE trial, among the 244 patients who were rehospitalized, 163 (67%) were rehospitalized more than 30 days after discharge, and therefore there is potential for prevention of a portion of these hospitalizations by utilizing the findings in the current study. The magnitude of the rise in BNP level from discharge to the 1-month follow-up, therefore, can identify those at risk for readmission who may require medication adjustments, more frequent follow-up visits, or outpatient-focused strategies known to minimize hospital readmissions.

We have not come across any study that examined (a) the ability of the rise in BNP from discharge to the 1-month follow-up to predict rehospitalization and (b) the magnitude of BNP elevation that is clinically relevant. These results also further confirm our previous findings that longitudinal follow-up of BNP levels between two points in time is more valuable for its diagnostic and prognostic implications compared to the utility of single BNP measurement.

BNP is a known marker of volume overload. It is widely used in various cardiovascular conditions, primarily in HF, thanks to its diagnostic and prognostic value [13–15]. A rise in BNP

Table 1 Demographic, clinical, laboratory, echocardiographic, and central hemodynamic characteristics of ESCAPE trial patients according to whether or not they were rehospitalized

	Rehospitalized ($n = 27$)	Not rehospitalized ($n = 17$)	p
Demographics			
Age, years (median, IQR)	59 (51, 69)	51 (45, 62)	0.054
Male sex (n)	77.8% (21/27)	58.8% (10/17)	0.180
BMI, kg/m^2 (median, IQR)	29 (24, 33)	29 (24, 31)	0.656
Black race, n (%)	14.8% (4/27)	29.4% (5/17)	0.242
White race, n (%)	74.1% (20/27)	52.9% (9/17)	0.150
Comorbidities			
Ischemic etiology of HF (n)	59.3% (16/27)	41.2% (7/17)	0.242
CABG (n)	40.7% (11/27)	29.4% (5/17)	0.447
COPD (n)	7.4% (2/27)	11.8% (2/17)	0.624
IDDM (n)	33.3% (9/27)	35.3% (6/17)	0.894
Atrial fibrillation (n)	40.7% (11/27)	5.9% (1/17)	0.011
ICD (n)	48.1% (13/27)	23.5% (4/17)	0.102
Malignancy (n)	11.1% (3/27)	11.8% (2/17)	1.000
Admission physical examination			
Elevated JVP >12 cm (n)	63% (17/27)	76.5% (13/17)	0.349
S3 gallop (n)	63% (17/27)	58.8% (10/17)	0.784
Positive HJR (n)	74.1% (20/27)	93.8% (15/16)	0.109
At least 2+ edema (n)	37% (10/27)	29.4% (5/17)	0.603
Admission laboratory values			
Na, meq/l (median, IQR)	136 (133, 138)	137 (136, 140)	0.189
BUN, mg/dl (median, IQR)	37 (24, 56)	27.5 (17.8, 52.3)	0.327
Creatinine, mg/dl (median, IQR)	1.5 (1.2, 2.1)	1.3 (0.9, 1.7)	0.134
BNP, pg/dl (median, IQR)	394 (147, 1199)	528 (158, 1004)	0.969
Admission echocardiography			
EF, % (median, IQR)	19 (15, 28)	15 (9, 32)	0.446
LVEDD, cm (median, IQR)	6.8 (5.9, 7.8)	6.2 (5.9, 6.8)	0.274
LVESD, cm (median, IQR)	5.7 (5.1, 7.1)	5.5 (4.8, 6.6)	0.502
IVC inspiration, cm (median, IQR)	1.5 (1, 1.8)	1.3 (0.9, 2.1)	0.774
IVC expiration, cm (median, IQR)	2.2 (1.8, 2.5)	2.2 (1.5, 2.5)	0.390
IVC collapsibility index, % (median, IQR)	34 (23, 44)	25 (10, 45)	0.445
Admission PAC variables			
PCWP, mm Hg (median, IQR)	22 (18, 37)	24 (17, 27)	0.539
RAP, mm Hg (median, IQR)	11 (6, 16)	9 (5, 16)	0.743

BMI body mass index, *CABG* coronary artery bypass graft, *COPD* chronic obstructive pulmonary disease, *IDDM* insulin-dependent diabetes mellitus, *ICD* implantable cardiac defibrillator, *JVP* jugular venous pressure, *HJR* hepatojugular reflux, *BNP* B-type natriuretic peptide, *EF* ejection fraction, *LVEDD* left ventricular end diastolic dimension, *LVESD* left ventricular end systolic dimension, *IVC* inferior vena cava, *PCWP* pulmonary capillary wedge pressure, *RAP* right atrial pressure, *PAC* pulmonary artery catheter

levels results from an elevation in end-diastolic wall stress, stiffness, and pressure load [15, 16]. When utilized in conjunction with clinical findings, BNP may guide the initial diagnostic workup and treatment of patients with suspected HF [14, 17, 18]. Moreover, a BNP-guided strategy reduced the risk of HF-related death or hospital stay for HF in the Systolic Heart Failure Treatment Supported by BNP (STARS-BNP) study [19]. In the ProBNP Outpatient Tailored Chronic HF Therapy (PROTECT) study, the substantial reduction in NT-proBNP was accompanied by a significant reduction in a composite outcome, including worsening HF, hospitalization for HF, and cardiovascular death [20]. Similarly, in patients with HF due to left ventricular systolic dysfunction, NT-proBNP-guided therapy was superior to clinical management, with lower event rates, better quality of life, and cardiac remodeling.

It is therefore logical to expect that an increase in BNP levels after discharge can predict rehospitalization. Studies have shown that BNP values measured after treatment were more predictive of post-discharge outcomes than were values on presentation. Many actually consider discharge BNP or BNP checked shortly after discharge as "baseline," and treatment should be targeted to maintain the BNP level close to this value.

BNP is influenced by multiple other factors—independent of the severity of HF—such as age [21], body mass index [22], sex, chronic kidney disease [23], and congenital factors [24]. Also, BNP levels correlate poorly with filling pressures [25], therefore, utilizing single BNP measurements to predict rehospitalization can be challenging [9]. The interpatient and intrapatient variability in BNP levels has minimized the value of single measurements, and added more weight to the diagnostic and prognostic ability of individualized longitudinal BNP measurements, which acknowledges the inherent between-patient variability in BNP levels.

Study limitations

There are several limitations to the current study. The main limitation is the small number of cases, which allowed only for univariate comparison. Adjustment for covariates known to affect BNP level—other than severity of HF—was not possible because of the small study population. The ESCAPE study included patients with severe systolic HF and advanced symptoms that do not represent the general HF population, and therefore our findings should not be extrapolated to the general HF population. Whether therapeutic interventions initiated after monitoring BNP level at the 1-month follow-up relative to discharge are accompanied by decreasing readmission rates needs to be investigated in prospective trials. Because of the small number of cases, our results can best be viewed as hypothesis generating and should be confirmed in larger studies.

Conclusion

The increase in BNP level from hospital discharge to the 1-month follow-up was significantly higher in HF patients who were rehospitalized later on compared with those who were not rehospitalized. The magnitude of the rise in BNP level from discharge to the 1-month follow-up is therefore a useful prognostic tool for predicting rehospitalization in patients recently discharged after HF decompensation.

Corresponding address

H. R. Omar, MD
Internal Medicine Department, Mercy Medical Center
Clinton, IA, USA
hesham_omar2003@yahoo.com

Acknowledgements. The ESCAPE trial was conducted and supported by the NHLBI in collaboration with the ESCAPE Study Investigators. This article was prepared using a limited access dataset obtained from the NHLBI and does not necessarily reflect the opinions or views of the ESCAPE trial investigators or the NHLBI.

Compliance with ethical guidelines

Conflict of interest. H.R. Omar and M. Guglin declare that they have no competing interests.

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Chun S et al (2012) Lifetime analysis of hospitalizations and survival of patients newly admitted with heart failure. Circ Heart Fail 5(4):414–421
2. Butler J, Kalogeropoulos A (2008) Worsening heart failure hospitalization epidemic we do not know how to prevent and we do not know how to treat! J Am Coll Cardiol 52(6):435–437
3. Ross JS et al (2010) Recent national trends in readmission rates after heart failure hospitalization. Circ Heart Fail 3(1):97–103
4. Lindenauer PK et al (2007) Public reporting and pay for performance in hospital quality improvement. N Engl J Med 356(5):486–496
5. Omar HR, Guglin M (2016) Discharge BNP is a stronger predictor of 6-month mortality in acute heart failure compared with baseline BNP and admission-to-discharge percentage BNP reduction. Int J Cardiol 221:1116–1122
6. Verdiani V et al (2008) NT-ProBNP reduction percentage during hospital stay predicts long-term mortality and readmission in heart failure patients. J Cardiovasc Med (hagerstown) 9(7): 694–699
7. Bettencourt P et al (2002) 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 113(3):215–219
8. Omar HR, Guglin M (2016) Longitudinal BNP follow-up as a marker of treatment response in acute heart failure: Relationship with objective markers of decongestion. Int J Cardiol 221:167–170
9. Omar HR, Guglin M (2016) A single BNP measurement in acute heart failure does not reflect the degree of congestion. J Crit Care 33:262–265
10. Binanay C et al (2005) Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. JAMA 294(13):1625–1633
11. Zile MR et al (2008) Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. Circulation 118(14):1433–1441
12. Stevenson LW et al (2010) Chronic ambulatory intracardiac pressures and future heart failure events. Circ Heart Fail 3(5):580–587
13. Januzzi JL Jr. et al (2005) The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol 95(8): 948–954
14. Maisel A et al (2004) Primary results of the rapid emergency department heart failure outpatient trial (REDHOT). A multicenter study of B-type natriuretic peptide levels, emergency department decision making, and outcomes in patients presenting with shortness of breath. J Am Coll Cardiol 44(6):1328–1333
15. O'Donoghue M et al (2005) The effects of ejection fraction on N-terminal proBNP and BNP levels in patients with acute CHF: analysis from the proBNP investigation of dyspnea in the emergency department (PRIDE) study. J Card Fail 11(5 Suppl): S9–14
16. Watanabe S et al (2006) Myocardial stiffness is an important determinant of the plasma brain natriuretic peptide concentration in patients with both diastolic and systolic heart failure. Eur Heart J 27(7):832–838
17. Mueller C et al (2004) Use of B-type natriuretic peptide for the management of women with dyspnea. Am J Cardiol 94(12):1510–1514
18. McCullough PA et al (2002) B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) multinational study. Circulation 106(4):416–422
19. Jourdain P et al (2007) Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP multicenter study. J Am Coll Cardiol 49(16):1733–1739
20. Januzzi JL Jr. et al (2011) Use of amino-terminal pro-B-type natriuretic peptide to guide outpatient therapy of patients with chronic left ventricular systolic dysfunction. J Am Coll Cardiol 58(18):1881–1889
21. Redfield MM et al (2002) Plasma brain natriuretic peptide concentration: impact of age and gender. J Am Coll Cardiol 40(5):976–982
22. Wang TJ et al (2004) Impact of obesity on plasma natriuretic peptide levels. Circulation 109(5):594–600
23. Anwaruddin S et al (2006) Renal function, congestive heart failure, and amino-terminal pro–brain natriuretic peptide measurement: results from the proBNP investigation of dyspnea in the emergency department (PRIDE) study. J Am Coll Cardiol 47(1):91–97
24. Newton-Cheh C et al (2009) Association of common variants in NPPA and NPPB with circulating natriuretic peptides and blood pressure. Nat Genet 41(3):348–353
25. Dokainish H et al (2004) Optimal noninvasive assessment of left ventricular filling pressures: a comparison of tissue Doppler echocardiography and B-type natriuretic peptide in patients with pulmonary artery catheters. Circulation 109(20): 2432–2439