The utility of natriuretic peptide in the management of patients with acute and chronic heart failure: Insights from randomized controlled trials

July 2009

Gordon Moe
MD
Li Ka Shing Knowledge Institute
St. Michael's Hospital
University of Toronto
Toronto
Canada

Patients with heart failure (HF) experience significant morbidity and mortality and those admitted for acute decompensated HF are at particularly high risk for adverse events.

Hospitalization represents the major component of the high cost associated with the management of patients with HF. Accordingly, early and accurate diagnosis of the condition which leads to timely treatment is essential.

The natriuretic peptides (NP), particularly B-type NP (BNP) and N-terminal proBNP (NT-proBNP) have evolved into useful biomarkers of patients with suspected acute HF.

Two randomized controlled trials have now demonstrated that when compared to a conventional strategy, a management strategy that incorporates knowledge of blood BNP and NT-proBNP results reduces the direct medical costs and improves specific outcomes in patients presenting to the emergency department with dyspnea and suspected acute HF.

On the other hand, conflicting data exist on the utility of a NP-guided approach to ambulatory patients with chronic HF. The role of NP in the management of patients with stable chronic HF therefore remains to be defined.

Heart failure (HF) is a clinical syndrome that is associated with high mortality and significant morbidity [1, 2]. In the US, there are over 1 million hospitalizations for acute HF (AHF) [3].

Once a patient is hospitalized and discharged with a diagnosis of HF, the readmission rate for HF is 16 % and 53 % in 1 month and 1 year, respectively [2].

Rehospitalization predicts 1-year mortality [4], and the natural history of patients with chronic HF is adversely affected by repeated hospital admissions.

Accordingly, tremendous financial burden is incurred from managing patients with AHF. In the US, of the USD 30 billion spent on HF care in 2006, USD 18 billion was related to hospitalization [3]. These data highlight the need for clinical trials that would help develop strategies to manage AHF.

Natriuretic peptides as a biomarker for the management of heart failure

The diagnosis of HF is usually based on history, physical examination, chest radiograph and, if available, left-ventricular-function assessment. However, many studies have demonstrated that making a diagnosis of HF based on clinical assessment and standard testing may be inadequate [5-8].

There has therefore been a great effort to develop biomarkers that can offer incremental value to establish rapid and accurate diagnosis. To date, the only biomarkers that have been developed for clinical use in HF are the natriuretic peptides (NP).

Among the NP, BNP and the amino-terminal fragment of the prohormone, NT-proBNP, have evolved to be useful biomarkers of cardiac function as well as prognosis in HF and other cardiovascular (CV) disorders.

Studies have established a close association between the blood levels of BNP and NT-proBNP and the diagnosis of HF [7, 9-12] as well as an independent prediction of mortality and HF events [13-17]. Use of BNP/NT-proBNP as an adjunct to clinical evaluation in diagnosis of HF, particularly in the acute setting, has been recommended in the HF management guidelines [1, 18-22].

Does knowing blood BNP/NT-proBNP results influence outcomes and reduce healthcare cost in patients with suspected acute heart failure

Accompanying the observational data is increasing evidence from randomized controlled trials (RCT) supporting a concept that the provision of knowledge of plasma BNP/NT-proBNP levels may be translated to improved management of patients with AHF.

The Acute Shortness of Breath Evaluation (BASEL) study was a single-center prospective RCT of 452 patients presenting to an emergency department (ED) in Basel, Switzerland with acute dyspnea [23, 24].

Two hundred and twenty-five patients were randomized to a strategy with measurement of BNP levels and 227 were assessed in a standard manner. The use of BNP levels reduced the need for hospitalization.

The median time to discharge was 8.0 days in the BNP group and 11.0 days in the control group. The mean total cost was USD 5,410 in the BNP group vs. USD 7,264 in the control group.

Up until recently, studies, particularly those that studied NT-proBNP, had either involved small number of patients [25, 26], were conducted in single centers [9, 25, 26] or were not randomized in design [11].

The large-scale studies of BNP and NT-proBNP were conducted mostly in the US [9, 11] where per capita healthcare spending was high [27], and these data, while important, were not necessarily applicable to countries with publicly funded universal healthcare coverage systems.

These concerns prompted the design of the Canadian multicenter Improved Management of Patient with Congestive Heart Failure (IMPROVE-CHF) study.

This prospective RCT was designed to test the hypothesis that a strategy that included knowledge of NT-proBNP results improved the management of patients with suspected acute HF [12].

The specific aims of IMPROVE-CHF were to evaluate: 1) whether NT-proBNP added incremental value to clinical judgment in diagnosing acute HF; and 2) whether a

management strategy that incorporated knowledge of NT-proBNP results would lead to cost-savings without compromising clinical outcomes.

Five hundred patients presenting with dyspnea to seven EDs in Canada were studied. Patients were screened consecutively. After enrollment, baseline medical history and clinical signs were documented.

A separate blood sample was collected for NT-proBNP measurement. At the end of the clinical evaluation and with knowledge of the results of standard diagnostic tests except for NT-proBNP, the ED physician was asked to commit to a diagnosis of whether a patient had HF or not and separately to estimate on a scale of 0-100 % the likelihood that acute HF was the cause of dyspnea.

Afterward, patients were randomly assigned to two groups based on management strategies that involved conventional measures (usual care) or conventional measures plus knowledge of NT-proBNP results (the NT-proBNP).

The results of NT-proBNP were made available only to the physicians who managed the patients in the NT-proBNP group and were provided immediately after randomization.

These physicians were provided with information to interpret the NT-proBNP results.

For adjudication, two cardiologists were provided with hospital records, including the discharge summary, results of laboratory and radiographic testing, echocardiograms if performed, clinical notes from the time of ED presentation to the 60-day follow-up and outcome of the telephone interview. Using all available data, the cardiologists assigned a diagnosis without knowing the NT-proBNP results. [9, 28].

For the diagnosis of AHF, adding NT-proBNP to clinical judgment enhanced accuracy, the area under the ROC curve increased from 0.83 to 0.90 (P <0.00001). Knowledge of NT-proBNP values reduced the primary end point, duration of ED visit, by 21 % (6.3 to 5.6 hours, P = 0.031).

The differences in initial hospitalizations, the hospital length of stay, the initial intensive care unit admissions and length of stay, and initial and 60-day mortality were not statistically significant.

However, a significant reduction in the number of patients rehospitalized by 60 days (13 % vs. 20 %; P = 0.0463) was observed. Direct medical cost of ED visits, hospitalizations and outpatient services were significantly reduced (USD 6129 to USD 5180 per patient, P = 0.023).

To gain insights into the contribution of outpatient use of diagnostic tests to the overall cost reduction, the proportion of patients who had undergone various advanced diagnostic tests was calculated and shown in FIGURE 1.

The frequency of outpatient use of these diagnostic tests was relatively low overall, but there was a tendency for less use of echocardiography, radionuclide ventriculography and computer tomography of the chest in the NT-proBNP group.

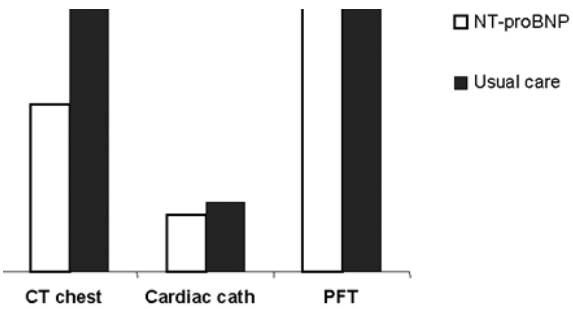

FIGURE 1: Use of diagnostic tests in the usual care and NT-proBNP-guided group

Using the IMPROVE-CHF data, our group have recently derived and validated a prediction model utilizing NT-proBNP and clinical variables to improve the diagnosis of AHF [29].

Physician estimates of probability of AHF in 500 ED patients from IMPROVE-CHF trial were classified into low (0-20 %), intermediate (21-79 %) or high (80-100 %) probability for AHF, then compared to the blinded adjudicated AHFS diagnosis.

Likelihood ratios were calculated and multiple logistic regression incorporated covariates into an AHFS prediction model, which was validated internally using bootstrapping and externally by applying the model to 573 patients from the N-terminal proBNP investigation of dyspnea in the emergency department (PRIDE) study [9].

Likelihood ratios for AHF with NT-proBNP were 0.11 (95 % CI, 0.06 to 0.19) for cut-point values < 300 pg/mL; rising to 3.43 (95 % CI, 2.34 to 5.03) for values 2700-8099 pg/mL and 12.80 (95 % CI, 5.21 to 31.45) for values ≥ 8100 pg/mL. Variables used to predict AHF were age, pretest probability and log NT-proBNP.

When applied to the external data using its adjudicated final diagnosis as the gold standard, the model appropriately reclassified 44 % of patients with intermediate clinical probability to either low or high probability of AHF with negligible (<3 %) inappropriate redirection.

We have therefore established a diagnostic prediction model for AHF utilizing both clinical assessment and NT-proBNP which appears to have excellent diagnostic accuracy, especially in cases with indeterminate likelihood for AHF.

Role of BNP/NT-proBNP in the management of chronic stable heart failure

While the provision of knowledge of BNP/NT-proBNP results appears to improve the management of patients with AHF, less data exists to support the routine use of serial NP testing in stable chronic HF. Troughton et al were the first to evaluate the strategy of NT-proBNP-guided therapy targeted to a specific value [30].

Sixty-nine patients with decompensated HF were randomized to therapy according to clinical algorithm or to NT-proBNP level with NT-proBNP levels > 1700 pg/mL, triggering intensification of therapy.

At follow-up, CV events were significantly improved in the NT-proBNP-guided group. Although the results of this study were promising, the sample size was small and the study was conducted in an era prior to contemporary HF therapy.

The second study is the Systolic Heart Failure Treatment Supported by BNP Multicenter Randomized Trial (STARS-BNP). This trial was designed to evaluate the benefit of BNP-guided therapy on clinical outcomes in patients followed in specialized HF clinics [31].

Patients were recruited from 17 university hospitals in France. A total of 220 patients with New York Heart Association (NYHA) functional class II to III symptoms were randomized to medical treatment (clinical group) or a goal of decreasing plasma BNP to <100 pg/mL (BNP group).

The primary end point was HF-related death or hospitalization for HF. During the first 3 months, drugs were adjusted more frequently in the BNP group. ACE inhibitors and β-blocker use increased more in the BNP group.

In a follow-up of 15 months, there were fewer deaths or HF hospitalizations in the BNP group. There were no significant differences in all-cause mortality or hospitalization.

The investigators conclude that a BNP-guided strategy with target BNP level reduces the risk of HF-related death or hospital stay and that the benefit is achieved through an increase in ACE inhibitor and β-blocker dosages.

The results of STARS-BNP, although very promising, warrant cautious interpretations for several reasons. First, the sample size of the trial was small. Second, the study was conducted in specialized HF clinics and the clinicians were familiar with the interpretation of BNP results.

These results may not be applicable to HF patients who are not managed in specialized clinics, or not by clinicians with expertise in the interpretation of BNP testing.

The Strategies for Tailoring Advanced Heart Failure Regimens in the Outpatient Setting: Brain Natriuretic Peptide Levels Versus the Clinical Congestion Score (STARBRITE) was a pilot study.

The study recruited 130 patients, randomized to 1) a Congestion Score Strategy and 2) a target BNP strategy.

The trial has not yet been published. Like in STARS-BNP, STARBRITE saw significantly increased use in ACE inhibitor (p=0.03) and a trend toward greater use in β-blockers (p=0.08) in the BNP group, but there was no significant difference in the primary end point of the number of days neither hospitalized nor dead from the date of the first clinic visit to 90 days.

The NTproBNP-AssisTed Treatment to LEssen Serial CARdiac REadmissions and Death (BATTLESCARRED) trial determined whether drug treatment according to plasma NT-proBNP is superior to intensive standardized clinical assessment; whether either of the regimens is superior to usual care; and whether age altered the relative efficacy of NT-proBNP-guided treatment.

The trial, which was conducted in New Zealand, randomized patients stratified by age to drug treatment directed by plasma NT-proBNP, intensive standardized clinical assessment or usual care [32]. The primary outcome was mortality.

The preliminary results were presented at a closed session at the European Society of Cardiology Congress 2007 in Vienna. The majority of subjects were in NYHA functional class II, 61 % were >75 years of age. The entry median plasma NT-proBNP level was 1900 pg/mL. Treating NT-proBNP to target levels appeared to confer some benefits to patients aged <75 years, but not in the overall group.

The Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF) was a prospective single-blinded trial of 824 elderly patients with HF [33].

Treatment strategies follow the published guidelines with the aim to reduce symptoms to NYHA class ≤ II (standard) or, also NT-proBNP levels below twice the upper limit of normal.

The primary end point was 18-month hospitalization-free survival. Therapy guided by NT-proBNP and symptom-guided therapy resulted in similar rates of survival free of all-cause hospitalizations (41 % vs. 40 %, respectively; hazard ratio, 0.91 (95 % CI, 0.72-1.14); P = 0.39). Quality-of-life metrics were similar in both strategies. Compared with the symptom-guided group, survival free of hospitalization for HF, a secondary end point, was higher among those in the NT-proBNP-guided group.

Therapy guided by NT-proBNP improved outcomes in patients aged 60-75 years but not in those aged 75 years or older (P <0.02 for interaction). These findings therefore suggest that therapy guided by NT-proBNP does not improve overall clinical outcomes or quality of life.

In conclusion, data to date supports the use of adjunctive natriuretic peptide testing in the management of patients with acute dyspnea and suspected AHFHFS. In these patients, addition of NP testing to careful clinical evaluation reduces medical cost without adverse effects on clinical outcomes. At present, there is less data to support the routine use of serial NP testing in patients with chronic stable HF.

References

1. Arnold JM, Liu P, Demers C, Dorian P, Giannetti N, Haddad H, Heckman GA, Howlett JG, Ignaszewski A, Johnstone DE, Jong P, McKelvie RS, Moe GW, Parker JD, Rao V, Ross HJ, Sequeira EJ, Svendsen AM, Teo K, Tsuyuki RT, White M. Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: diagnosis and management. Can J Cardiol 2006; 22: 23-45.

2. Johansen H, Strauss B, Arnold JM, Moe G, Liu P. On the rise: The current and projected future burden of congestive heart failure hospitalization in Canada. Can J Cardiol 2003; 19: 430-35.

3. Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, Haase N, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell CJ, Roger V, Rumsfeld J, Sorlie P, Steinberger J, Thom T, Wasserthiel-Smoller S, Hong Y. Heart disease and stroke statistics - 2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007; 115: e69-171.

4. Pulignano G, Del SD, Tavazzi L, Lucci D, Gorini M, Leggio F, Porcu M, Scherillo M, Opasich C, Di LA, Senni M, Maggioni AP. Clinical features and outcomes of elderly outpatients with heart failure followed up in hospital cardiology units: data from a large nationwide cardiology database (IN-CHF Registry). Am Heart J 2002; 143: 45-55.

5. Remes J, Miettinen H, Reunanen A, Pyorala K. Validity of clinical diagnosis of heart failure in primary health care. Eur Heart J 1991; 12: 315-21.

6. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. JAMA 1989; 261: 884-88.

7. McCullough PA, Nowak RM, McCord J, Hollander JE, Herrmann HC, Steg PG, Duc P, Westheim A, Omland T, Knudsen CW, Storrow AB, Abraham WT, Lamba S, Wu AH, Perez A, Clopton P, Krishnaswamy P, Kazanegra R, Maisel AS. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study. Circulation 2002; 106: 416-22.

8. Thomas JT, Kelly RF, Thomas SJ, Stamos TD, Albasha K, Parrillo JE, Calvin JE. Utility of history, physical examination, electrocardiogram, and chest radiograph for differentiating normal from decreased systolic function in patients with heart failure. Am J Med 2002; 112: 437-45.

9. Januzzi JL, Jr., Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, Tung R, Cameron R, Nagurney JT, Chae CU, Lloyd-Jones DM, Brown DF, Foran-Melanson S, Sluss PM, Lee-Lewandrowski E, Lewandrowski KB. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol 2005; 95: 948-54.

10. Maisel A, Hollander JE, Guss D, McCullough P, Nowak R, Green G, Saltzberg M, Ellison SR, Bhalla MA, Bhalla V, Clopton P, Jesse R. 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 2004; 44: 1328-33.

11. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Clopton P, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002; 347: 161-67.

12. Moe GW, Howlett J, Januzzi JL, Zowall H. N-terminal pro-B-type natriuretic peptide testing improves the management of patients with suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. Circulation 2007; 115: 3103-10.

13. Januzzi JL, van KR, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, Pinto YM, Richards M. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J 2006; 27: 330-37.

14. Januzzi JL, Jr., Sakhuja R, O'Donoghue M, Baggish AL, Anwaruddin S, Chae CU, Cameron R, Krauser DG, Tung R, Camargo CA, Jr., Lloyd-Jones DM. Utility of amino-terminal pro-brain natriuretic peptide testing for prediction of 1-year mortality in patients with dyspnea treated in the emergency department. Arch Intern Med 2006; 166: 315-20.

15. Anand IS, Fisher LD, Chiang YT, Latini R, Masson S, Maggioni AP, Glazer RD, Tognoni G, Cohn JN. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). Circulation 2003; 107: 1278-83.

16. Fisher C, Berry C, Blue L, Morton JJ, McMurray J. N-terminal pro B type natriuretic peptide, but not the new putative cardiac hormone relaxin, predicts prognosis in patients with chronic heart failure. Heart 2003; 89: 879-81.

17. Harrison A, Morrison LK, Krishnaswamy P, Kazanegra R, Clopton P, Dao Q, Hlavin P, Maisel AS. B-type natriuretic peptide predicts future cardiac events in patients presenting to the emergency department with dyspnea. Ann Emerg Med 2002; 39: 131-38.

18. Executive summary: HFSA 2006 Comprehensive Heart Failure Practice Guideline. J Card Fail 2006; 12: 10-38.

19. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC, Jr., Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult - Summary Article: A Report of the American

College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): Developed in Collaboration With the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: Endorsed by the Heart Rhythm Society. Circulation 2005;112: 1825-52.

20. Nieminen MS, Bohm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, Hasin Y, Lopez-Sendon J, Mebazaa A, Metra M, Rhodes A, Swedberg K, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie MR, Dean V, Deckers J, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, Morais J, Oto A, Smiseth OA, Garcia MA, Dickstein K, Albuquerque A, Conthe P, Crespo-Leiro M, Ferrari R, Follath F, Gavazzi A, Janssens U, Komajda M, Morais J, Moreno R, Singer M, Singh S, Tendera M, Thygesen K. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J 2005; 26: 384-416.

21. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001; 22: 1527-60.

22. Arnold JM, Howlett JG, Dorian P, Ducharme A, Giannetti N, Haddad H, Heckman GA, Ignaszewski A, Isaac D, Jong P, Liu P, Mann E, McKelvie RS, Moe GW, Parker JD, Svendsen AM, Tsuyuki RT, O'Halloran K, Ross HJ, Rao V, Sequeira EJ, White M. Canadian Cardiovascular Society Consensus Conference recommendations on heart failure update 2007: Prevention, management during intercurrent illness or acute decompensation, and use of biomarkers. Can J Cardiol 2007; 23: 21-45.

23. Mueller C, Scholer A, Laule-Kilian K, Martina B, Schindler C, Buser P, Pfisterer M, Perruchoud AP. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. N Engl J Med 2004; 350: 647-54.

24. Mueller C, Laule-Kilian K, Schindler C, Klima T, Frana B, Rodriguez D, Scholer A, Christ M, Perruchoud AP. Cost-effectiveness of B-type natriuretic peptide testing in patients with acute dyspnea. Arch Intern Med 2006; 166: 1081-87.

25. Bayes-Genis A, Santalo-Bel M, Zapico-Muniz E, Lopez L, Cotes C, Bellido J, Leta R, Casan P, Ordonez-Llanos J. N-terminal probrain natriuretic peptide (NT-proBNP) in the emergency diagnosis and in-hospital monitoring of patients with dyspnoea and ventricular dysfunction. Eur J Heart Fail 2004; 6: 301-08.

26. Lainchbury JG, Yandle TG, Campell E, Richards M. Brain natriuretic peptide and N-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath (abstract). J Am Coll Cardiol 2003; 41: 184A.

27. Lasser KE, Himmelstein DU, Woolhandler S. Access to care, health status, and health disparities in the United States and Canada: results of a cross-national population-based survey. Am J Public Health 2006; 96: 1300-07.

28. Jernberg T, Stridsberg M, Venge P, Lindahl B. N-terminal pro brain natriuretic peptide on admission for early risk stratification of with chest pain and no ST-segment elevation. J Am Coll Cardiol 2002; 40: 437-45.

29. Steinhart B, Thorpe KE, Bayoumi AM, Moe G, Januzzi JL, Mazer CD. Improving the diagnosis of acute heart failure using a validated prediction model. J Am Coll Cardiol 2009 (in press).

30. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Lancet 2000; 355: 1126-30.

31. Jourdain P, Jondeau G, Funck F, Gueffet P, Le HA, Donal E, Aupetit JF, Aumont MC, Galinier M, Eicher JC, Cohen-Solal A, Juilliere Y. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. J Am Coll Cardiol 2007; 49: 1733-39.

32. Lainchbury JG, Troughton RW, Frampton CM, Yandle TG, Hamid A, Nicholls MG, Richards AM. NTproBNP-guided drug treatment for chronic heart failure: design and methods in the "BATTLESCARRED" trial. Eur J Heart Fail 2006; 8: 532-38.

33. Brunner-La Rocca HP, Buser PT, Schindler R, Bernheim A, Rickenbacher P, Pfisterer M. Management of elderly patients with congestive heart failure--design of the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF). Am Heart J 2006; 151: 949-55.