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**CLINICAL RESEARCH**
*Heart failure/cardiomyopathy*

# Usefulness of clinical and NT-proBNP monitoring for prognostic guidance in destabilized heart failure outpatients

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**Aims** To study the relative prognostic value of N-terminal pro-B-type natriuretic peptide (NT-proBNP) monitoring in addition to clinical disease severity scores (CDSSs) in outpatients with destabilized heart failure (HF).

**Methods and results** Seventy-one outpatients with recently destabilized HF were recruited. At baseline, and at all following visits, a CDSS based on Framingham criteria was obtained, and NT-proBNP levels were measured in a blind fashion. CDSS did not correlate with NT-proBNP levels at any time ($P > 0.1$), although their relative changes correlated during follow-up ($P < 0.001$). Forty patients (56%) had clinical events (cardiovascular death and/or HF hospitalization) within 1 year of follow-up. Changes in CDSS from baseline were not predictive of subsequent events ($P > 0.1$ for all visits), whereas changes in NT-proBNP levels were predictive at several time points: week 2 ($P = 0.005$), week 3 ($P = 0.037$), week 4 ($P = 0.015$), and 6 months ($P = 0.026$). A change in NT-proBNP levels at follow-up week 2 (%) added independent prognostic information ($P < 0.001$, HR 0.982, 95% CI 0.972–0.992) to baseline CDSS ($P = 0.002$, HR 2.05, 95% CI 1.290–3.266), age ($P = 0.007$, HR 1.034, 95% CI 1.009–1.059), and left ventricular ejection fraction ($P = 0.013$, HR 0.942, 95% CI 0.898–0.987).

**Conclusion** Serial monitoring for per cent change in NT-proBNP concentrations offers superior prognostic information to clinical assessment among outpatients with recent destabilized HF.

**Keywords** B-type natriuretic peptide • Clinical score • Heart failure • Outpatient • Prognosis

## Introduction

Natriuretic peptides, particularly B-type natriuretic peptide (BNP) and its N-terminal cleavage equivalent (NT-proBNP), have emerged as powerful prognostic markers in the evaluation of heart failure (HF) patients.[1–4] It has been difficult, however, to incorporate the evaluation of natriuretic peptides into routine clinical practice. This is largely due to the heterogeneity of natriuretic peptide levels, even among individuals with similar signs and symptoms, and to the difficulty in combining information on natriuretic peptide levels with clinical findings for each individual patient.[5,6]

Natriuretic peptides have also been evaluated in monitoring and therapy guidance of HF patients. In hospitalized patients with acute HF, a reduction in BNP and NT-proBNP during hospitalization is associated with a better outcome.[7,8] In the HF clinic, patient follow-up is complicated by the lack of easily available and reliable indicators of the disease state. Recently, our group found that, in outpatients with HF destabilization, serial NT-proBNP changes at 3 months of follow-up correlated with adverse events.[9] This is

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an important finding, as a pilot study by Troughton *et al.*[10] suggested that outpatient NT-proBNP-guided therapy was better than treatment guided by a quantitative HF clinical disease severity score (CDSS), which was based on diagnostic Framingham criteria. However, the prognostic value of serial changes of this CDSS, with the addition of NT-proBNP monitoring, has not been properly evaluated in destabilized HF outpatients and may help to explain the putative superiority of NT-proBNP measurement over clinical assessment in the study by Troughton *et al*. The aim of this study was to compare the value of serial changes of NT-proBNP levels with information from CDSS monitoring for prognostic guidance in outpatients with recently destabilized HF.

# Methods

## Study population and design

The study population was obtained from two cardiology HF outpatient clinics. From September 2004 to October 2005, we evaluated all patients with established diagnosis of HF and symptoms of worsening [New York Heart Association (NYHA) class II–IV], yet not requiring emergency hospital admission, and impaired left-ventricular systolic function (left-ventricular ejection fraction $\leq$40% using echocardiography). The established inclusion criteria at the initial visit were objective evidence of destabilized HF and therapy with β-blockers at the maximum tolerated dose during the previous 3 months. An objective CDSS based on Framingham criteria was used to diagnose destabilized HF.[10] Major criteria were assigned values of 1, and minor criteria were assigned values of 0.5. A total score of 2 or more was taken to indicate destabilized HF[10,11] (*Table 1*). Patients were excluded in the presence of acute coronary syndrome within the last 3 months; pending cardiac transplant or revascularization; severe valvular disease eligible for surgical repair; or severe pulmonary (forced expiratory volume in 1 s of $<$1 L), hepatic or renal (plasma creatinine $>$200 μmol/L) disease. A total of 75 consecutive patients fulfilled these selection criteria. After enrolment, the study protocol included weekly follow-up visits for 4 weeks, and then at 3, 6, and 12 months. Four patients refused to participate because of inability to comply with the scheduled visits. Echocardiography was performed at baseline. CDSS was assessed by the same physician for each individual patient. The goal of treatment was to develop clinically compensated HF (clinical score $\leq$2). At every visit, a venous blood sample was taken to measure NT-proBNP levels but patients were assessed clinically by an investigator unaware of the patient's NT-proBNP levels. The study was approved by the Local Ethics Committee, and informed consent was obtained from each patient.

**Table 1 Heart failure clinical disease severity score**

| | Value |
|---|---|
| Major criteria | |
| Paroxysmal nocturnal dyspnoea | 1.0 |
| Basal crackles | 1.0 |
| Hepatojugular reflux positive | 1.0 |
| Third heart sound present | 1.0 |
| Minor criteria | |
| Orthopnoea | 0.5 |
| Reduction in exercise tolerance | 0.5 |
| Resting sinus tachycardia | 0.5 |
| Jugular venous pressure $>$4 cm | 0.5 |
| Hepatomegaly | 0.5 |
| Peripheral oedema | 0.5 |

## N-terminal pro-B-type natriuretic peptide assay

Serial blood samples were obtained at baseline, every week for 4 weeks, and then once every 3 months, unless a primary endpoint event occurred. All samples were obtained with patients at rest between 08:30 and 12:30 h. Serum was separated by centrifugation at 1500*g* and stored at $-80^{\circ}$C until analysis; all samples from the same patient were analysed in the same batch. NT-proBNP levels were measured by electrochemiluminescence immunoassay using an Elecsys 1010 analyser (Roche Diagnostics GmbH, Mannheim, Germany). The intra-assay coefficient of variation for NT-proBNP was 1.8% for 221 pg/mL and 3.1% for 4250 pg/mL; the inter-assay coefficient of variation was 5.5% for 187 pg/mL, 7.0% for 3120 pg/mL, and 7.3% for 12376 pg/mL.

## Endpoints and follow-up

The primary endpoint was either cardiovascular death or hospital admission for HF. After a primary endpoint was reached, the affected patient was excluded from subsequent study visits and NT-proBNP measurements. Patients were followed for 1 year, and the 1 year status was obtained in all patients. The database was closed when the last follow-up was obtained (October 2006).

## Statistical analysis

All data are expressed as mean values ($\pm$SD). Log-transformed NT-proBNP and clinical score values were used in all analyses to reduce the effects of skew in the distribution. At each follow-up visit, NT-proBNP and clinical score were evaluated as absolute value and relative change from baseline (%). Single-linear regression analysis was used to examine correlations between NT-proBNP and clinical score. Univariate analysis between baseline variables and events was examined using the non-paired *t*-test and the $\chi^2$ test, as appropriate. A Kaplan–Meier survival curve was calculated for the description of events during follow-up. Patients who reached the primary endpoint were censored at the time of occurrence. Two-way analysis of variance (ANOVA), using a general linear model (GLM) with repeated measures and Greenhouse–Geisser method, was used at each follow-up visit to examine the differences between patients who experienced subsequent events and those who did not. Analyses were performed separately for NT-proBNP and clinical score with two factors: outcome (two levels: events and no events) as between subject factor and follow-up visits (class variable with two levels: baseline and the evaluated visit) as the within subject factor. In order to approach the problem of informative missing data, we verified the results by repeating the ANOVA with a GLM analysis using the last observation carry forward (LOCF) method. The predictive value of NT-proBNP and clinical score at the selected follow-up visit was examined using a multivariable Cox proportional hazards regression analyses. The model was adjusted by baseline characteristics (age, sex, LVEF, NYHA class, clinical score, and NT-proBNP levels) and those with $P < 0.05$ in the univariable analysis. Log cumulative hazard plots, time-dependent covariates, and Schoenfeld residuals were used to evaluate adherence of the Cox proportional hazard assumptions, and these assumptions were verified by the

representation of $\ln(-\ln S(t))$ for every variable after its categorization. All tests were at two-sided, and *P*-value $<0.05$ was considered statistically significant. All data analyses were performed using SPSS 14.0 software (SPSS Inc., Chicago, IL, USA).

# Results

## Study population and events

Seventy-one patients with destabilized HF were studied in two HF specialist clinics. *Table 2* shows the demographic and clinical data of the patients studied. At baseline, all patients were treated with β-blockers, angiotensin-converting enzyme-inhibitors (ACE-I)/angiotensin receptor blockers (ARBs), and a loop diuretic; 65% were on spironolactone and 41% were on digoxin. At the initial visit, the mean clinical score was $3.5 \pm 1.3$, and the median NT-proBNP concentration was 5370 pg/mL (range 1842–11450). Diuretics (loop diuretic, spironolactone, hydrochlorothiazide) and ACE-I/ARBs were intensified to achieve clinical stabilization. β-Blockers were not discontinued but occasionally dosages were reduced according to symptoms.

During the first year of follow-up, 40 patients (56%) had a primary endpoint (14 deaths and 26 hospitalizations due to HF). *Figure 1* shows the Kaplan–Meier analysis of event-free survival for the group as a whole. Two events occurred during the first 2 weeks, 30% of events occurred between weeks 2 and 4, 50% of events occurred between weeks 4 and 24, and 17% occurred between months 6 and 12. There were no differences in the baseline clinical score and NT-proBNP concentration between patients experiencing clinical events during follow-up and those who did not ($P = 0.3$ and $P = 0.9$, respectively; *Table2*).

## Clinical disease severity score and N-terminal pro-B-type natriuretic peptide: correlation

The absolute CDSSs did not correlate with NT-proBNP concentration either at baseline ($P = 0.61$, *Figure 2A*) or at subsequent

**Table 2 Baseline clinical characteristics**

| | All patients, *n* = 71 | No events, *n* = 31 | Events, *n* = 40 |
|---|---|---|---|
| Age, years | 61 ± 14 | 59 ± 15 | 63 ± 12 |
| Sex, male/female | 57/14 | 26/5 | 31/9 |
| Ichaemic aetiology | 34 (48) | 10 (32) | 24 (60)* |
| HF duration, months | 38 (9–92) | 38 (9–70) | 45 (9–105) |
| Risk factors | | | |
| Smoking, *n* (%) | 5 (7) | 2 (7) | 3 (7) |
| Arterial hypertension, *n* (%) | 40 (56) | 19 (61) | 21 (53) |
| Diabetes mellitus, *n* (%) | 23 (32) | 8 (26) | 15 (38) |
| Therapy (baseline) | | | |
| ACE-inhibitors, *n* (%) | 58 (82) | 15 (81) | 33 (82) |
| ARBs, *n* (%) | 13 (18) | 6 (19) | 7 (18) |
| Furosemide, *n* (%) | 71 (100) | 31 (100) | 40 (100) |
| β-Blockers, *n* (%) | 71 (100) | 31 (100) | 40 (100) |
| Spironolactone, *n* (%) | 46 (65) | 19 (61) | 27 (68) |
| Digoxin, *n* (%) | 29 (41) | 11 (36) | 18 (45) |
| NYHA, II/III/IV | 8/46/17 | 4/18/9 | 4/28/8 |
| Haemoglobin, g/L | 133 ± 18 | 136 ± 18 | 130 ± 17** |
| Serum creatinine, μmol/L | 115 ± 32 | 115 ± 35 | 115 ± 29 |
| Heart rate, b.p.m. | 81 ± 15 | 77 ± 13 | 84 ± 16 |
| Systolic blood pressure (mmHg) | 111 ± 18 | 112 ± 17 | 110 ± 19 |
| Left bundle branch block, *n* (%) | 30 (44) | 12 (40) | 18 (47) |
| LVEDD, mm | 65 ± 10 | 66 ± 12 | 65 ± 9 |
| IV septum, mm | 10 ± 3 | 10 ± 2 | 10 ± 4 |
| LVEF, % | 27 ± 9 | 28 ± 8 | 27 ± 11 |
| Baseline clinical score | 3.5 ± 1.1 | 3.3 ± 1.1 | 3.6 ± 1.1 |
| NT-proBNP, pg/mL | 7421 ± 6751 | 7083 ± 6070 | 7682 ± 7301 |

Data are expressed as mean ± SD or median (quartiles), and number (%).
ACE-I, angiotensin-converting enzyme-inhibitors; ARB, angiotensin II receptor blockers; NYHA, New York Heart Association; LVEDD, left ventricle end-diastolic diameter; IV, interventricular; LVEF, left ventricular ejection fraction.
*$P = 0.020$ and **$P = 0.09$ between patients with and without events during follow-up.

visits ($P > 0.05$). However, a positive association was found between relative NT-proBNP and CDSS changes (compared with baseline) at week 1 ($r = 0.47$, $P < 0.001$), week 2 ($r = 0.55$, $P < 0.001$, *Figure 2B*), week 3 ($r = 0.55$, $P < 0.001$), week 4 ($r = 0.62$, $P < 0.001$), week 12 ($r = 0.45$, $P < 0.001$), and week 24 ($r = 0.46$, $P = 0.001$).

## Clinical disease severity score monitoring and events

In the analysis of CDSS at each follow-up visit (*Figure 3*), there were no differences in either absolute value (*Figure 3A*) or in relative changes from baseline (*Figure 3B*) between patients who experienced clinical events and those who did not ($P > 0.1$ for all analyses).

During the first year of follow-up, a total of 58 patients (82%) achieved clinical stabilization, defined as a CDSS <2. All but one patient (92%) whose CDSS could not be lowered below 2 at any time had a clinical event. However, clinical stabilization during follow-up was not associated with an entirely benign course; 28 out of 58 (48%) stabilized patients also had clinical events (70% of all events).

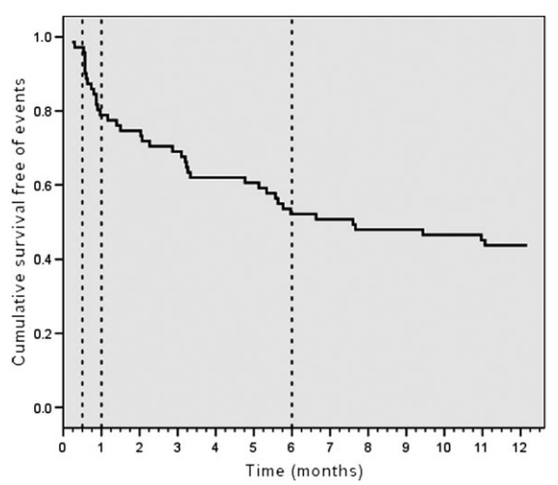


**Figure 1** Kaplan–Meier analysis of event-free survival. Dotted lines indicate 2 weeks, 1 month, and 6 months.

## N-terminal pro-B-type natriuretic peptide monitoring and events

In the analysis of NT-proBNP levels at each follow-up visit (*Figure 4*), absolute NT-proBNP values were not predictive of subsequent events (*Figure 4A*), although relative NT-proBNP changes were predictive at several time points, week 2 ($P = 0.005$), week 3 ($P = 0.037$), week 4 ($P = 0.015$), and 6 months ($P = 0.026$) (*Figure 4B*). Indeed, the ANOVA with a GLM analysis using the LOCF method showed similar *P*-values at each follow-up visit. The relative change in NT-proBNP levels at 2 weeks was the first measurement predictive of clinical events ($P = 0.005$). At 2 weeks, there was a 17% reduction in the risk of subsequent events per each 10% reduction in NT-proBNP levels (per cent, $P < 0.001$, HR 0.829, 95% CI 0.758–0.906). NT-proBNP reduction below the median (of 26%) at 2 weeks was associated with a higher event rate irrespective of CDSS at baseline, with a 23% excess event rate in patients with low score (score ≤3) and 19% excess event rate in those with higher score, compared with NT-proBNP reduction >26%. As well, an absence in the decline of NT-proBNP levels during the first 2 weeks of follow-up was associated with a subsequent lack of clinical stabilization during follow-up ($P = 0.001$). The GLM analysis with LOCF for the entire follow-up showed that both the outcome factor

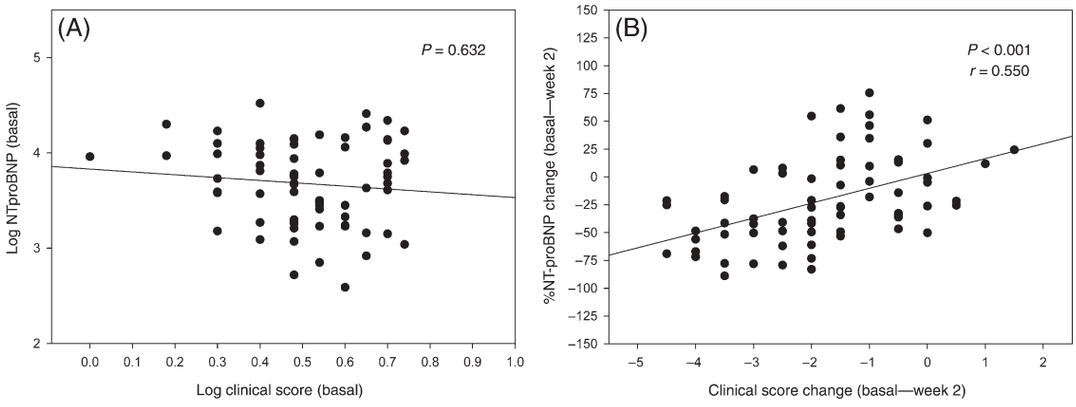


**Figure 2** (*A*) Correlation between clinical score and N-terminal pro-B-type natriuretic peptide concentration as an absolute value at baseline; (*B*) correlation between relative changes in N-terminal pro-B-type natriuretic peptide levels and clinical scores from baseline to week 2.

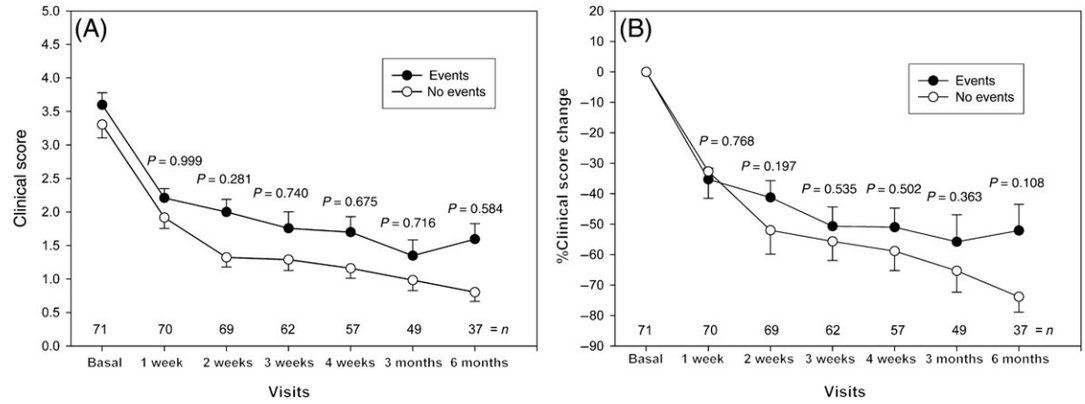


**Figure 3** General linear model with repeated measures analysis of variance for clinical score at each follow-up visit, between patients with (black dots) and without subsequent events (white dots), as absolute value (*A*) and relative change from baseline (*B*).

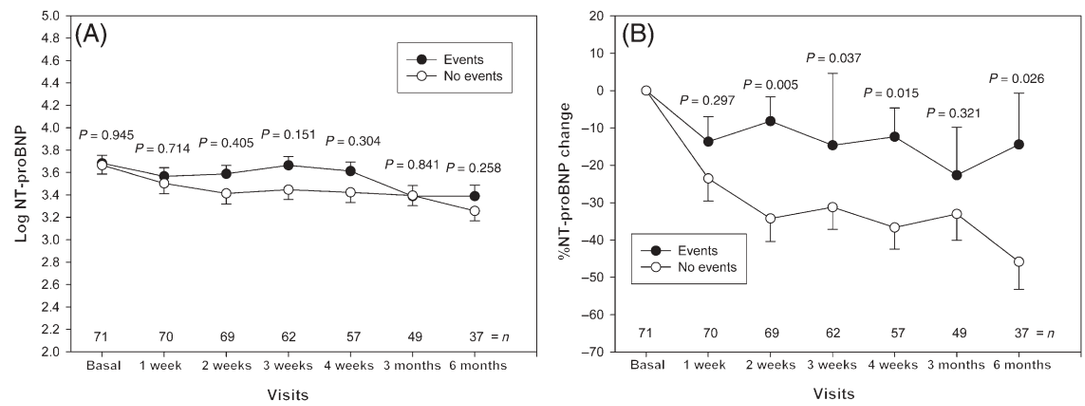


**Figure 4** General linear model with repeated measures analysis of variance for N-terminal pro-B-type natriuretic peptide levels at each follow-up visit, between patients with (black dots) and without subsequent events (white dots), as absolute concentration (*A*) and relative change from baseline (*B*).

($P = 0.008$) and its interaction with time ($P = 0.042$) were significant.

## Multivariable analysis

As shown in *Table 3*, the relative change in NT-proBNP levels at 2 weeks added significant prognostic information for the prediction of subsequent clinical events, as well as baseline CDSS, age, and LVEF. *Figure 5* shows that the presence of CDSS >3 at baseline and/or NT-proBNP reduction <26% at 2 weeks were associated with a lower event-free survival.

# Discussion

This study has important clinical implications that are easily applicable in the clinical management of HF patients. The main findings of this study are (i) absolute NT-proBNP levels do not necessarily correlate with CDSSs reflecting clinical status; however, changes in NT-proBNP levels during follow-up do correlate with changes in clinical status; (ii) for patients with HF destabilization, relative changes in NT-proBNP levels are better predictors of future clinical events than CDSS changes; (iii) the relative change (in percentage terms) in NT-proBNP levels at 2 weeks of follow-up is a strong predictor of clinical events, even better than achieving apparent clinical stabilization using subjective clinical measures; and (iv) NT-proBNP monitoring added independent prognostic information to clinical scoring in patients with destabilized HF. These results establish an important foundation for the numerous clinical trials that will now examine the potential utility of therapeutic efforts towards lowering NT-proBNP values with the hope to improve longer term outcomes in chronic HF.

It is well known that there is heterogeneity in natriuretic peptide levels among individuals with HF, and this has caused some

**Table 3 Multiple Cox analysis: adjusted models at week 2 for prediction of events**

| | $\chi^2$-value | *P*-value | HR (CI 95%) |
|---|---|---|---|
| NT-proBNP per cent change not included | 14.2 | | |
| Baseline clinical score, per unit | | 0.001 | 2.132 (1.342–3.386) |
| Clinical score change, per cent | | 0.018 | 0.988 (0.978–0.998) |
| Age, per year | | 0.025 | 1.028 (1.003–1.051) |
| LVEF, per cent | | 0.031 | 0.952 (0.912–0.996) |
| Baseline NT-proBNP | | 0.643 | 1.000 (1.000–1.000) |
| NT-proBNP per cent change included | 27.8 | | |
| NT-proBNP change, per cent | | <0.001 | 0.982 (0.972–0.992) |
| Baseline clinical score, per unit | | 0.002 | 2.052 (1.290–3.266) |
| Age, per year | | 0.007 | 1.034 (1.009–1.059) |
| LVEF, per cent | | 0.013 | 0.942 (0.898–0.987) |
| Baseline NT-proBNP | | 0.530 | 1.000 (1.000–1.000) |
| Clinical score change, per cent | | 0.422 | 0.995 (0.984–1.007) |

Adjusted by sex, ischaemic aetiology and NYHA class.

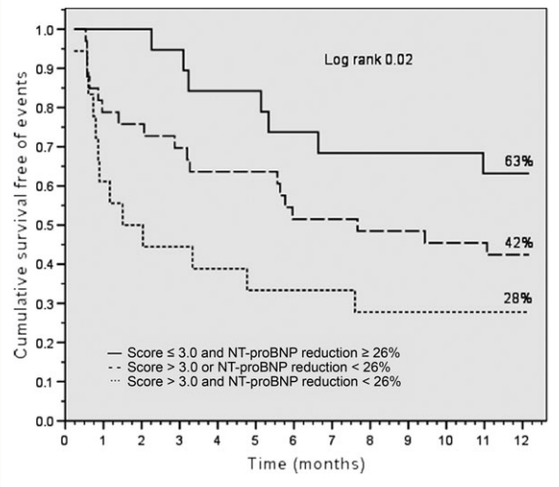


**Figure 5** Kaplan–Meier survival curves according to the presence of baseline clinical disease severity score >3.0 and/or N-terminal pro-B-type natriuretic peptide reduction <26% at week 2.

confusion in the interpretation of results. In our study, absolute NT-proBNP levels did not correlate with clinical scores at any time, in agreement with the inter-individual heterogeneity previously described.[5,6] In contrast, relative changes in NT-proBNP levels correlated with changes in clinical score. This finding is in accordance with the poor correlation seen between NT-proBNP levels and invasive haemodynamic parameters in destabilized HF, and with the positive association observed between relative NT-proBNP changes and haemodynamic improvements assessed invasively[12,13] or by echo Doppler.[14] Our study also shows for the first time that, despite inter-individual variation in NT-proBNP levels, intra-individual NT-proBNP changes are more relevant for monitoring events than more subjective measures of clinical status in an outpatient setting.

Interestingly, although clinical disease severity scoring was useful at HF decompensation, NT-proBNP monitoring, but not clinical monitoring, added significant prognostic information. Illustrating this fact, among subjects with clinical stabilization (score ≤2) during follow-up, 48% experienced clinical events (representing 70% of all clinical events observed in the study). Thus, clinical acumen retains its fundamental role at the time of HF decompensation for graduating its severity, but NT-proBNP monitoring is better for determining risk stratification in response to treatment.

In hospitalized patients with acute HF, the lack of a decrease in natriuretic peptide levels or a high discharge natriuretic peptide value may be independently associated with a worse outcome.[7,8,15] In the outpatient setting, most studies have evaluated patients with chronic stable HF[16,17]; Anand *et al.*[16] reported that changes in BNP levels over time were associated with corresponding changes in morbidity and mortality, and that increasing NT-proBNP levels over time independently predicted greater short-tem mortality and morbidity,[16] although in this analysis, the value of NT-proBNP measurement relative to standard forms of clinical evaluation was not assessed. Among a generally more unstable group of outpatients with recently destabilized HF, we now show that monitoring relative changes in NT-proBNP levels was more useful than clinical monitoring for predicting long-term clinical events after HF decompensation. As NT-proBNP changes reflect not only clinical status, but also changes in parameters such as ejection fraction, ventricular volumes, filling pressures, or neurohormonal status,[13,18,19] and numerous therapeutic interventions for HF have known effects on NT-proBNP concentrations, it may be that such monitoring of the relative change in NT-proBNP levels from destabilized status will allow for the optimization of HF monitoring therapy.[10,20,21] As well, an important observation from our study is the ascertainment of an appropriate sampling strategy to guide prognostication. In agreement with suggested strategies for sampling of natriuretic peptide in treated HF,[22,23] we have ascertained that as early as week 2 from the establishment of clinical stability, prognostically meaningful results from NT-proBNP testing may be gained. Our results set an important foundation for the current studies now examining the role of NT-proBNP-guided therapy in outpatients with severe HF.

Limitations of our study include the fact that we compared the prognostic impact of NT-proBNP testing against a CDSS, rather than clinician judgement for assessing prognosis. As clinical judgement is often inferior to natriuretic peptide testing for the assessment of clinical stability, the use of a more objective scoring system, such as the one used in this study, would only be expected to result in data favouring clinical assessment, rather than

NT-proBNP. Furthermore, in our study, we did not specifically adjust HF therapies to lower NT-proBNP values; thus, although the magnitude of the declining slope at 2 weeks is associated with better outcomes than a particular threshold value of NT-proBNP, it remains yet unclear whether there may be a 'target' NT-proBNP concentration below which event rates would be expected to be dramatically reduced, or which methods should be applied to achieve such a target NT-proBNP. Given the generally marked elevation of NT-proBNP concentrations in our subjects, it is theoretically possible that relative/per cent changes would be less relevant if a lower value of NT-proBNP was achieved over time. We have to acknowledge the problem of non-available data at post-baseline visits in patients with events, which in this study was approached and validated by repeating the ANOVA with a GLM analysis using the LOCF method.

In conclusion, in outpatients with destabilized HF, monitoring the relative change in NT-proBNP levels over time was better for predicting prognosis than clinical evaluation, although the severity of HF decompensation, as measured by the HF CDSS at the initial visit, did add prognostic information. As a consequence, the combination of baseline clinical scoring and NT-proBNP monitoring at 2 weeks could be a useful tool for prognosis and therapy guidance in patients with destabilized HF.

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**CLINICAL VIGNETTE**

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# Right ventricle-dependent coronary circulation demonstrated with 64-slice computed tomography

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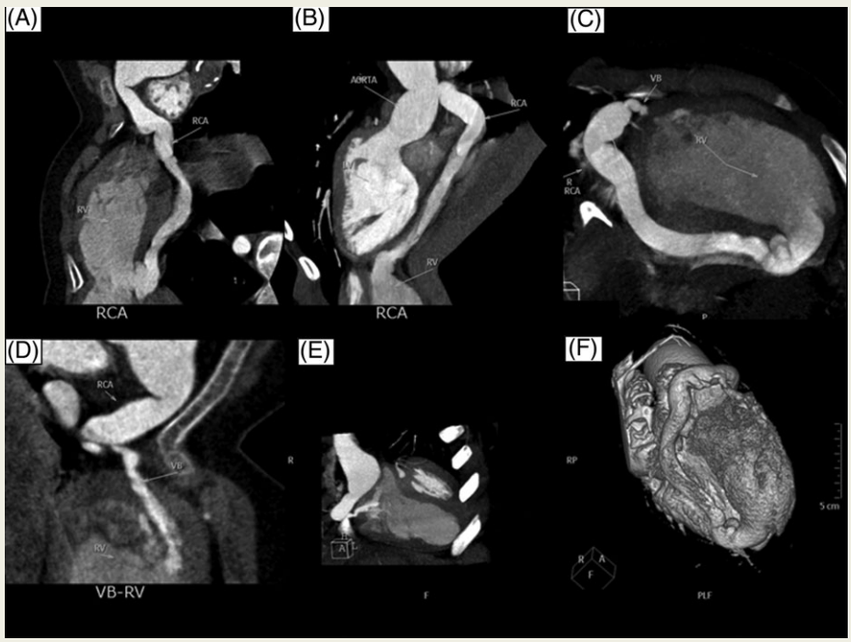


A 12-year-old female patient, who had emergency left modified Blalock–Taussig shunt operation during neonate and a total cavo-pulmonary shunt operation performed at the age of 5 years following a diagnosis of pulmonary atresia with intact ventricular septum (PAIVS), was under regular follow-up. At her last visit, she was admitted with exercised-induced anginal symptoms. Multi-slice computed tomography (MSCT) was performed for shunt and coronary circulation evaluation. The MSCT of the patient revealed right ventricle-dependent coronary circulation (RVDCC) associated with right coronary artery draining to right ventricle with large fistulas and enlarged right ventricle (Panels A–D).

PAIVS is a rare congenital disease with a reported incidence of four to seven per 100 000 live births. Coronary artery abnormalities are common in PAIVS and have serious effects on surgical management and outcome. It has been shown that the poor prognosis in neonates with PAIVS is generally related to either the presence of a small right ventricle and/or RVDCC. Identification of a ventriculo-coronary connection is one of the weakest areas of echocardiography and often represents a diagnostic dilemma. MSCT imaging seems to be an effective and alternative diagnostic modality in detection of coronary artery fistulas because of its excellent performance in determining coronary anatomy.

Panels A–C. Curved multi-planar reconstructed multi-slice computed tomography images demonstrating right ventricle-dependent coronary circulation with large fistula of right coronary to right ventricle.

Panels D and E. Curved multi-planar reconstructed multi-slice computed tomography images demonstrating right coronary ventricular branch fistulas to right ventricle.

Panel F. Post-processed three-dimensional volume rendered images demonstrating large right coronary artery with direct communication to right ventricle.