Prognostic role of echocardiography and brain natriuretic peptide in symptomatic breathless patients in the community

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Aims
Brain natriuretic peptide (BNP), left ventricular (LV) systolic function, and mitral filling pattern (MFP) are prognostic indicators in patients with heart failure (HF). This study evaluated the potential role of E/Ea for predicting cardiovascular (CV) events in patients with suspected HF. This non-invasive measure of LV filling pressure has been shown to predict outcome in more advanced HF, but not in mild HF in the community.

Methods and results
Two hundred and twenty-eight elderly symptomatic general practice patients (dyspnoea/oedema) were recruited and underwent clinical evaluation, NT-proBNP assay, and comprehensive echocardiography. The Kaplan–Meier analysis of time to first CV hospitalization or CV death was performed for 1 year after presentation according to nominated thresholds of LV systolic function, NT-proBNP, MFP, and E/Ea ratio. Mean age was 70.3 ± 7.3 years, mean NT-proBNP was 111.4 ± 185.8, and 148 (65%) were female. Twenty-six patients (11%) experienced a CV event within 18 months of baseline (6 deaths and 20 admissions). Time to first CV event predicted by NT-proBNP (P, 0.0001), MFP (P = 0.009), and E:Ea (P = 0.0076), but not EF (P = 0.098). When NT-proBNP was elevated, E:Ea >15 identified a group of patients with lower survival (P < 0.0001).

Conclusion
Both E/Ea and NT-proBNP predicted hospitalization and when used in a two-step approach (NT-proBNP first, followed by E/Ea), the combination of both (elevated NT-proBNP and elevated E/Ea) identified those patients at highest risk, thus supporting a complementary approach for echocardiography and NT-proBNP in patients with HF symptoms.

Keywords
Echocardiography • Neurohormones • Diastole • Prognosis • Heart failure
echocardiography is increasingly being utilized for diagnosis of HF in community-based patients.17–18 Both BNP and echocardiography have been used to screen asymptomatic elderly and community-based individuals for the presence of LV dysfunction and when elevated BNP levels and/or systolic dysfunction are identified, both are associated with worse outcome.19–23

The Natriuretic Peptides in the Community (NPC) study24 was designed to prospectively evaluate the role of NT-proBNP in the diagnosis of HF in elderly community-based patients. The aim of this substudy was to prospectively evaluate the prognostic role of echocardiography and NT proBNP measurements for predicting subsequent hospitalization in these patients.

Methods

Subjects

This substudy includes 228 patients from a randomized clinical trial evaluating the utility of NT-proBNP in the diagnosis of HF in primary care, which recruited 305 symptomatic patients from primary care practices. The trial methods and results have been described elsewhere.24 Patients who presented to their general practitioner with signs and symptoms of HF (dyspnoea or oedema) were eligible for this study. General practitioners were responsible for the identification of referral of eligible patients who then attended a hospital study visit where, after providing written informed consent, a cardiological assessment, electrocardiography, chest radiography, blood collection for NT-proBNP measurement, and transthoracic echocardiography were performed. This substudy includes all those patients with complete diastolic evaluation including TDI (n = 228). It is smaller than the total cohort (n = 305) because this technology was not available at the commencement of the main study. The study was approved by the Auckland Ethics Committee and all patients provided written informed consent.

Panel standard diagnosis of heart failure

The diagnosis of HF was made by an expert panel of three cardiologists and one general physician independent of other study personnel and without the knowledge of the NT-proBNP result. The panel reviewed all clinical data for each patient including ECG, chest radiograph, and echocardiogram, but not NT-proBNP results in order to determine whether the clinical syndrome of HF was present using the European Society of Cardiology Working Group on Heart Failure diagnostic criteria.25 To meet the case definition of HF, patients were required to have appropriate symptoms (dyspnoea or oedema) with clinical signs of pulmonary or peripheral congestion in the presence of an underlying abnormality of cardiac structure and function. If doubt remained, response to treatment was considered.

NT-proB type natriuretic peptide assay

Blood was collected using standard venepuncture technique into tubes containing EDTA. Samples were centrifuged and frozen at −70 °C. N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured by radioimmunoassay at the CardioEndocrine Research Laboratory, Christchurch, New Zealand.26 This laboratory usually reports NT-proBNP in pmol/L and thus these are the units used throughout this paper. To convert pmol/L to pg/mL, a multiplication factor of 8.457 is required. This assay compares well with the commercially available Roche (Elecsys 2010 platform) assay at levels commonplace in HF, but the assays differ at very low and very high values.27

Echocardiography methods

All patients were examined lying on their left side and images were digitally obtained (Philips HDI-5000, Phillips Ultrasound, Bothell, WA, USA). A full clinical echocardiogram was performed including: para-sternal M-mode recordings; biplane Simpson’s left ventricular volumes and ejection fraction (EF); left atrial area (apical four-chamber view); mitral valve pulsed wave Doppler (PWD); pulmonary venous PWD and isovolumic relaxation time (IVRT). Mitral valve inflow PWD was recorded with the sample volume between the leaflet tips and then recorded again during the Valsalva manoeuvre. IVRT recordings were made with a PWD sample volume placed in the LV outflow tract. All echocardiographic images were obtained according to a standardized protocol by specially trained research sonographers, without knowledge of the patients’ clinical details. In addition to the standard techniques described, tissue PWD was also performed by placing a 5 mm sample volume on the medial and lateral aspects of the mitral valve annulus. The signal was optimized and recorded at 100 mm/s sweep speed. The average of both measurements was used. None of the patients had haemodynamically significant valve disease.

Echocardiographic measurements

Triplicate measurements were made according to standard methods and included: (i) two-dimensional and m-mode measurements: left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension, left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left atrial area; (ii) Doppler measurements: mitral valve peak early filling velocity (E), peak late filling velocity (A), deceleration time (DT) of the mitral E wave, A wave duration (Adur), IVRT; pulmonary venous peak systolic velocity (S), peak diastolic velocity (D), atrial reversal velocity (AR), atrial reversal duration (ARdur); (iii) tissue Doppler measurements: mean of lateral and medial mitral annular E velocity (Ea), mitral annular A velocity (Aa), mitral annular S velocity (Sa). The following variables were calculated: E/A, ARdur – Adur, stroke volume (SV) = LVEDV–LVESV, ejection fraction (EF) = SV/LVEDV × 100%; E/Ea.

Differentiation between diastolic filling patterns

Each subject was classified into one of the following categories of filling patterns: normal filling; EA 1.0–2.0 and deceleration time 0.14–0.23 s; abnormal relaxation: EA < 1.0 and deceleration time > 0.23 s; pseudonormal filling; EA 1.0–2.0 and deceleration time 0.14–0.23 s, and EA < 1.0 and deceleration time > 0.23 s with valsalva and/or pulmonary atrial duration > A wave duration (at least 20 msec) 2; restrictive filling; EA > 2.0 and deceleration time < 0.14 s.

Statistical analysis

Comparisons between groups for continuous normally distributed variables were made using Student’s t-test and analysis of variance and non-parametric continuous data were analysed using Wilcoxon and Kruskall–Wallace tests, where appropriate. Differences between categorical variables were assessed using χ2 analysis. ANOVA was used to determine between group differences when there were more than two groups and post hoc Tukey’s test for within group differences. A P-value < 0.05 was accepted as indicating significance.

Time to first CV death/hospitalization analysis

The primary endpoint was a composite of cardiovascular death and/or hospitalization. Medical charts and general practice computer
databases were reviewed 18 months after recruitment into the study to collect data regarding each patient’s vital status and number of and reason for hospitalizations. Stratified survival analysis was performed using the Kaplan–Meier method. Where more than two categorical groups were tested (e.g. NT-proBNP level or diastolic filling pattern) $\chi^2$ was used to test overall significance. All tests were two-tailed and 5% significance level was maintained throughout. Procedures of the statistical analysis system (SAS) were employed in these analyses (SAS Institute, Cary, NC, USA).

**Analysis by NT-proBNP level**

The survival analyses were performed in different patients subgroups based upon the NT-proBNP level: less than $50$ pmol/L (HF diagnosis unlikely), $50–150$ pmol/L (HF diagnosis uncertain), and $>150$ pmol/L (HF diagnosis likely). This was done in order to compare the role of echocardiography within these groups of patients and to reflect the likely clinical scenarios in which physicians might use both echocardiography and NT-proBNP. These equate to $423$ pg/mL ($50$ pmol/L) and $1269$ pg/mL ($150$ pmol/L) (Table 1).

**Analysis by selected systolic and diastolic criteria**

Survival analysis was performed according to systolic function (EF < 45%) and diastolic function: diastolic filling pattern [restrictive filling, non-restrictive filling (pseudonormal and abnormal filling)] and using established E/Ea criteria ($<$8, 8–15, and $>$15).5

**Results**

**Baseline characteristics**

The mean age of the group was 70 years (range 40–95 years), 65% were female, 52% had a history of hypertension, 15% had type 2 diabetes, 14% prior acute myocardial infarction, and 14% reported chronic airways disease or asthma. NT-proBNP was elevated and baseline echocardiography revealed a group of patients with mildly dilated hearts, no significant systolic dysfunction, but with evidence of some advanced diastolic filling abnormalities and elevated filling pressure (Table 2). This group were not significantly different to the main clinical trial cohort (Table 3), nor was their outcome different to excluded subjects from the trial cohort [Hazard ratio 0.77 (95% CI: 0.44,1.33)].

**Time to first CV death/hospitalization**

During the 18 month follow-up period, 26 (11.4%) patients experienced a first CV event (20 hospitalizations and 6 deaths). The median time to first CV event was $339$ (range 0–545) days. Time to first event analysis is presented by NT-proBNP level, ejection fraction, diastolic filling pattern, and E/Ea (Figure 1). Vital status was unavailable for 13 patients.

<table>
<thead>
<tr>
<th>Table 1 Conversion of NT-proBNP levels</th>
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<td>Pmol/L</td>
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<td>1</td>
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<td>50</td>
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<td>100</td>
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<td>150</td>
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**NT-proBrain natriuretic peptide**

There was a tiered relationship between hospitalization and NT-proBNP level ($P < 0.0001$). NT-proBNP $\geq 150$ mmol/L was associated with worse outcome (10 CV events, event rate 26%) than NT-proBNP $< 150$ mmol/L (16 CV events, event rate 8.5%) hazard ratio 4.1 (95% CI: 1.9,9.1, $P = 0.0005$). NT-proBNP $> 50$ mmol/L was associated with worse outcome (20 CV events, event rate 19.6%) than NT-proBNP $< 50$ mmol/L (6 CV events, event rate 5.2%); hazard ratio 3.8 (95% CI: 1.5,9.4, $P = 0.004$) (Figure 1A).

**Ejection fraction**

Thirty-three subjects had an EF < 45% and this was associated with higher rates of CV hospitalization or death (18%) compared to patients with EF > 45% (10%); hazard ratio 2.0 (95% CI: 0.8,5.1, $P = 0.13$, log-rank $P = 0.098$) (Figure 1B).

**Diastolic filling pattern**

Eleven subjects (5.5%) displayed RFP at baseline and these patients had higher rates of CV events (27%) compared to patients with non-RFP (10%); hazard ratio 5.0 (95% CI: 1.5,17.3, $P = 0.010$). Both pseudonormal filling and abnormal relaxation were different

<table>
<thead>
<tr>
<th>Table 2 Baseline demographics and echocardiographic measurements</th>
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<tr>
<td>Age (years), mean ± SD</td>
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<tr>
<td>Gender (female:male)</td>
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<tr>
<td>N-terminal pro-BNP (pmol/L), median (IQ range)</td>
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<tr>
<td>Heart size</td>
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<tr>
<td>LV end-diastolic volume (mL)</td>
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<tr>
<td>LV end-systolic volume (mL)</td>
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<tr>
<td>Left atrial area (cm²)</td>
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<td>LV mass (g)</td>
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<tr>
<td>LV systolic parameters</td>
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<tr>
<td>Fractional shortening (%)</td>
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<tr>
<td>LV ejection fraction (%)</td>
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<tr>
<td>Stroke volume (mL)</td>
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<tr>
<td>Systolic annular velocity (Sa) (cm/s)</td>
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<tr>
<td>LV diastolic parameters</td>
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<tr>
<td>E wave velocity (ms)</td>
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<tr>
<td>A wave velocity (ms)</td>
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<tr>
<td>Deceleration time (ms)</td>
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<tr>
<td>Isovolumic relaxation time (ms)</td>
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<tr>
<td>Annular E velocity (Ea) (cm/s)</td>
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<tr>
<td>Annular A velocity (Aa) (cm/s)</td>
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<tr>
<td>E/Ea ratio</td>
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<tr>
<td>EA ratio</td>
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</tbody>
</table>

A, late mitral inflow velocity; Aa, late mitral annular velocity; ANOVA, analysis of variance; E, early mitral inflow velocity; E/Ea ratio, mitral inflow velocity/annular velocity; LV, left ventricle; NT-proBNP, N terminal pro brain natriuretic peptide; Sa, tissue Doppler mitral annular systolic velocity.
to the restrictive filling group ($P = 0.008$) but no difference was seen between the pseudonormal filling and abnormal relaxation groups (overall difference $P = 0.0089$) (Figure 1C).

**E/Ea ratio**

E/Ea was $\leq 8$ in 77 (34%) subjects, between 9 and 15 in 112 (49%) subjects, and $> 15$ in 39 (17%) subjects. There were 5 CV events in the group with $\text{E/Ea} \leq 8$ (6.4% event rate), 11 in the group with $\text{E/Ea} = 9–15$ (event rate 9.8%), and 10 in the group with $\text{E/Ea} > 15$ (event rate 25%) ($\chi^2 = 0.0069$). The hazard ratio for $\text{E/Ea} \geq 15$ was 3.6 (95% CI: 1.6, 8.0, $P = 0.0015$) and for $\text{E/Ea} > 8$ was 2.2 (95% CI: 0.84, 5.9, $P = 0.11$) (Figure 1D).

Higher E/Ea was associated with higher NT-proBNP level, older age, larger LV volumes, reduced FS, EF, and Sa (all consistent with depressed systolic function), larger LA area, short deceleration time, higher EA ratio, and lower tissue Doppler velocities.

### Table 3 Characteristics of included and excluded patients

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<thead>
<tr>
<th></th>
<th>Excluded</th>
<th>Included</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>77</td>
<td>228</td>
<td>—</td>
</tr>
<tr>
<td>NT-proBNP (pmol/L), median (IQ range)</td>
<td>49 (22,109)</td>
<td>78 (26,203)</td>
<td>0.11</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.1 ± 74.9</td>
<td>70.3 ± 73.1</td>
<td>0.34</td>
</tr>
<tr>
<td>LV end-diastolic volume (mL)</td>
<td>90.3 ± 33.8</td>
<td>92.8 ± 35.9</td>
<td>0.64</td>
</tr>
<tr>
<td>LV end-systolic volume (mL)</td>
<td>41.9 ± 27.7</td>
<td>40.6 ± 27.5</td>
<td>0.76</td>
</tr>
<tr>
<td>FS (%)</td>
<td>30.6 ± 7.9</td>
<td>31.9 ± 8.5</td>
<td>0.41</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>55.2 ± 10.7</td>
<td>58.4 ± 11.8</td>
<td>0.06</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>49.4 ± 14.2</td>
<td>52.7 ± 16</td>
<td>0.24</td>
</tr>
</tbody>
</table>

**Figure 1** Time to first hospitalization by NT-proBNP level, ejection fraction, diastolic filling pattern, and E/Ea ratio. Time to first hospitalization by NT-proBNP (A): grey line NT-ProBNP $< 50$ pmol/L, dashed line NT-ProBNP 50–150 pmol/L, black line NT-ProBNP >150 pmol/L; ejection fraction (B): grey line EF $\geq 45\%$, black line EF $< 45\%$; diastolic filling pattern (C): grey line abnormal relaxation, dashed line pseudonormal filling, black line restrictive filling; and E/Ea (D): grey line E/Ea $< 8$, dashed line E/Ea 8–15, black line E/Ea $> 15$. Abbreviations: E/Ea ratio = mitral inflow velocity/annular velocity, NT-proBNP = N terminal pro brain natriuretic peptide.
(consistent with advanced diastolic filling abnormalities and significantly elevated filling pressure) (Table 4).

**Two-tiered approach with NT-proBNP and E/Ea**

When the groups were divided on the basis of NT-proBNP level (< or > 50 pmol/L), and then the patients with elevated NT-proBNP were divided into two groups on the basis of E/Ea (< or > 15), there was a significant difference in the time to first CV event (P < 0.0001). The low NT-proBNP group (n = 116) had the same outcome as the high NT-proBNP/low E/Ea group (n = 73), but both had significantly lower CV event rates than the high NT-proBNP/high E/Ea group (n = 39) (Figure 2).

**Discussion**

In this study, E/Ea, an echocardiographic surrogate of LA pressure, was closely linked to future cardiovascular events (death or hospitalization) in community patients with symptoms of breathlessness and/or oedema. Although other studies have demonstrated the link between diastolic parameters and outcome in established HF, we believe this may be the first study to do so in this particular patient cohort. Although restrictive filling was predictive of outcome, no difference between the pseudonormal and abnormal filling groups was observed. However, E/Ea identified three distinct groups each with associated and incremental event-free survival rates.

Other traditional echocardiographic variables, such as EF and mitral filling pattern, as well as NT-proBNP also predicted hospitalization, but in multivariable analysis, only E/Ea and age predicted CV events. The prognostic role of NT-proBNP and BNP in primary care patients with suspected HF has been previously demonstrated. The current study has extended these findings and
better differentiated the combined role of neurohormonal and echocardiographic assessment. When the event rates were compared across the patient cohort divided on the basis of neurohormone level, both E/Ea and NT-proBNP were independent predictors, depending upon the neurohormone level. These results support a complementary role for the two techniques.

When used in a pragmatic, two-tiered approach (NT-proBNP assay followed by E/Ea), the prognostic role of both may be optimized. In this setting, the addition of E/Ea identified two sub-groups of patients within the group with elevated NT-proBNP level—patients with low E/Ea had similar outcome as patients with normal NT-proBNP and patients with elevated E/Ea with higher hospitalization. The subjects with the highest E/Ea had much higher NT-proBNP levels and also more systolic dysfunction. Echocardiographic measurements and neurohormone levels should not be considered independently as they are almost certainly inter-related and indeed demonstrated in patients with symptomatic systolic HF.36

E/Ea correlates with filling pressures in several studies4–6,37,38 and has been previously linked to prognosis in patients with established cardiovascular disease39,40 and has been used in both atrial fibrillation41 and supraventricular tachycardia.37 In the current study, E/Ea even predicted CV events in those patients in whom HF was not considered the primary cause of symptoms. E/Ea may have identified a group of patients with elevated filling pressures but without definitive clinical HF. E/Ea is related to left atrial pressure and thus some of the non-HF patients may have had some degree of increased filling pressure. This is supported by the fact that both E/Ea,4–6 and deceleration time41–47 are related to left ventricular filling pressure. BNP is also closely correlated with deceleration time.48,49 BNP is a marker of haemodynamic stress and it may be that E/Ea is similarly reflective of haemodynamic stress in these patients.

In a recently published study performed in patients hospitalized for HF symptoms, a similarly incremental prognostic utility for BNP and E/Ea was demonstrated.50 The current study is at the other end of the disease spectrum. In a similar cohort of patients, traditonal mitral valve and pulmonary venous diastolic parameters did not add significantly to clinical assessment and assessment of systolic function.38 This study was similar in many ways to our study with the exception that neither BNP nor tissue Doppler measurements were available. Mitral valve filling pattern is a powerful prognostic indicator in patients with advanced HF, but its categorical nature and low prevalence of advanced filling patterns in newly diagnosed HF may render it of limited use in newly diagnosed HF. Since E/Ea is a continuous variable, this may explain its superior prognostic differentiation.

Conclusion
This study has demonstrated the complementary roles of neurohormone assay and echocardiography as predictive markers of CV outcome in symptomatic patients in the community. Both techniques identify different subgroups of patients with different associated prognosis. These data would support a two-step approach that incorporates both NT-proBNP levels with echocardiographic diastolic assessment and may identify those at highest risk of subsequent cardiovascular death or hospitalization.

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