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Prognostic Implications of the NT-ProBNP Level and Left Atrial Size in Non-Ischemic Dilated Cardiomyopathy

Hyungseop Kim, MD; Yun-Kyeong Cho, MD; Dong-Hwan Jun, MD; Chang-Wook Nam, MD; Seong-Wook Han, MD; Seung-Ho Hur, MD; Yoon-Nyun Kim, MD; Kwon-Bae Kim, MD

Background The ratio of peak early diastolic mitral inflow to annular velocity (E/E') and left atrial size could provide prognosis on congestive heart failure (CHF). N-terminal Pro B-type natriuretic peptide (NT-ProBNP) has also been useful for predicting adverse cardiac events. However, it is not clear how these parameters compare with conventional risk factors. Thus, we investigated whether E/E', left atrial dimension index (LADI) and NT-ProBNP would predict adverse events and add incremental value to conventional risk factors, even in non-ischemic advanced dilated cardiomyopathy (DCM).

Methods and Results Both NT-ProBNP and echocardiography were evaluated in 105 patients. The cardiac events were defined as the composite of cardiac death and re-admission for CHF. At follow up, cardiac events occurred in 24 patients who had high NT-ProBNP and showed higher LADI and E/E'. In multivariate analysis, both NT-ProBNP and LADI, but not E/E', remained as independent predictors; patients with both increased LADI and NT-ProBNP had a 27-fold higher risk of cardiac events than those without any risk factors (p=0.003). Moreover, LADI and NT-ProBNP showed a better incremental prognostic value over conventional risk factors (global chi-square increase from 7 to 17 to 49, p=0.003, p<0.001, respectively).

Conclusions Both NT-ProBNP and LADI might have the most predictable power, particularly in non-ischemic advanced DCM. (*Circ J* 2008; **72:** 1658 – 1665)

Key Words: Dilated cardiomyopathy; Left atrial dimension index; N-terminal Pro B-type natriuretic peptide; Tissue Doppler image

Congestive heart failure (CHF) is one of the most common causes of hospitalization resulting in high morbidity and mortality. Especially in dilated cardiomyopathy (DCM) with left ventricular (LV) systolic dysfunction, diastolic function also would decrease more frequently, and therefore the assessment of diastolic function should be included as an adjunct to standard evaluation in order to provide appropriate management. Both clinical factors such as age, hypertension and diabetes, and echocardiographic factors including ejection fraction (EF) and pulmonary vein flow or mitral inflow pattern have been considered as conventional risk factors for predicting the prognosis of DCM![1–5]

Among many echocardiographic factors, left atrial (LA) size has believed to have been correlated with LV filling pressure, has predicted cardiovascular (CV) adverse events in mild to moderate CHF, and the additional prognostic value of LA enlargement has also been observed particularly in elderly patients![6–8] As well as LA size, tissue Doppler image (TDI) has been applied for further evaluation of regional myocardial function and ventricular longitudinal contractility[9] The ratio of peak early diastolic mitral inflow to mitral annular velocity (E/E') could add independent and incremental prognostic information in CHF for adverse events, in addition to providing LV filling pressures![10,11] Likewise, a biochemical variable such as the N-terminal Pro B-type natriuretic peptide (NT-ProBNP) level was recognized and suggested to be included in guidelines or strategies for the diagnosis and treatment of CHF![12,13] Thus, the prognostic impact of NT-ProBNP on adverse cardiac events in CHF has been investigated recently![14–16]

Although both the E/E' ratio and NT-ProBNP have been suggested as factors for predicting LV filling pressure, poor correlations between these 2 markers might exist under specific conditions, for example, with or without cardiac diseases and high or low pulmonary capillary wedge pressure, when compared with the invasive measurement of LV filling pressure![7] Currently, the incremental value of echocardiographic and biochemical variables to conventional risk factors for predicting adverse outcomes of severely decreased LV systolic function still remains unclear. Most importantly, there are limited data on the prognostic power of these variables in non-ischemic DCM, whereas most studies about CHF focused on either ischemic or mixed ischemic and non-ischemic LV dysfunction.

We therefore investigated the incremental prognostic power of LA size, E/E' ratio and NT-ProBNP, and to what extent the prognosis of advanced LV dysfunction would be

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Division of Cardiology, Department of Internal Medicine, Keimyung University Dongsan Medical Center, Daegu, Korea
Mailing address: Hyungseop Kim, MD, Division of Cardiology, Department of Internal Medicine, Keimyung University Dongsan Medical Center, 194, Dongsan-dong, Jung-gu, Daegu, Korea. E-mail: khyungseop@dsmc.or.kr

dependent on these 3 variables in subjects with non-ischemic DCM.

Methods

Subjects

We recruited patients with CHF symptoms who were referred to our CV center between April 2004 and December 2005. Inclusion criteria for non-ischemic DCM patients in the present study were: (1) an LVEF <45% without regional wall-motion abnormalities; (2) a LV diastolic dimension of >55 mm; (3) symptoms or signs of CHF according to Framingham criteria; and (4) absence of significant coronary artery stenosis on angiography. All patients underwent angiography to rule out an ischemic cause of CHF. Exclusion criteria included chronic renal dysfunction, severe lung disease, ischemic or valvular heart disease and non-sinus rhythm. Thus, a total of 105 patients (65 males, mean age: 61±15 years old) with non-ischemic DCM were enrolled. At the time of study enrollment, they did not show hemodynamic compromise and all patients received regular follow up at the outpatient clinic. The study protocol was approved by the Ethics Committee of the hospital and written informed consent was obtained from each patient.

Echocardiography

Comprehensive echocardiography was performed in all subjects, using a Vivid 7 digital ultrasound system (GE VingMed Ultrasound, Horten, Norway), and echocardiographic images were obtained in the standard parasternal and apical views. LV dimension and wall thickness as well as LA dimension (LAD) were measured according to the recommendations of the American Society of Echocardiography. LVEF was measured by modified biplane Simpson's method from apical 4- and 2-chamber views. The LAD index (LADI) was obtained by calculating LAD-to-body surface area. Mitral inflow velocity was derived from pulsed wave Doppler in the apical 4-chamber view; early transmitral inflow (E) velocity, its decelerating time (DT), late transmitral flow (A) velocity, and the isovolumic relaxation time were assessed. By using TDI, systolic (S'), early diastolic (E') and late diastolic (A') mitral annular velocity were obtained at the septal mitral annulus level in the apical 4-chamber view and the E/E' ratio was derived.

Serologic Measurements

Peripheral venous blood samples for NT-ProBNP were obtained immediately after the echocardiographic study. Blood samples were collected in EDTA-containing tubes and centrifuged within 1 h. The NT-ProBNP level was measured using an electrochemiluminescence immunoassay on a Modular analytics E170 (Roche Diagnostics) and the analytic range of NT-ProBNP extended from 5 to 35,000 pg/ml.

The following conventional parameters were also measured: lipid level, serum creatinine, C-reactive protein, troponin-I and hemoglobin. Glomerular filtration rate was estimated using the Modification of Diet in Renal Disease (MDRD) Study equation as follows: $186.3 \times (\text{serum creatinine})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female})$[18]

Follow-up

At study entry, a thorough medical history was recorded for all patients. The data obtained included: age, sex, and assessment of risk factors. The clinical risk factors such as hypertension, diabetes, smoking or previous stroke were investigated; information was acquired from medical records, directly from patients, or both.

The development of recurrent clinical events was defined as the composite of cardiac death and rehospitalization for worsening of CHF. Patients were followed up for a mean duration of 574±150 days. The follow up was performed by reviewing the medical records in the outpatient clinic and/or by telephone interviews.

Statistics Analysis

The data analyses were performed with the Statistical Package for Social Science (SPSS for windows 12.0, SPSS Inc, Cary, NC, USA) software. The baseline demographic and laboratory information is presented as mean ± standard deviation for the continuous variables and frequencies for the discrete variables. The categorical variables were analyzed using a chi-square test and the continuous variables were analyzed using an unpaired t-test. The NT-ProBNP was log-transformed to reduce the effect of extreme values because the relationship between the NT-ProBNP level and the end-point was not of a linear nature. Therefore, NT-ProBNP was logarithmically transformed before entering the analysis in order to perform the multiple analyses, which required a normal distribution. A receiver-operating characteristics (ROC) curve analysis was used to determine the cut-off values for the E/E' ratio, LADI and NT-ProBNP in terms of prediction for cardiac adverse events during the follow-up period. Univariate and multivariate Cox regression analyses were used to evaluate the prognostic value of the parameters, and was also performed using conventional risk factors, E/E' ratio, LADI and NT-ProBNP, so that sequential models were developed to examine the incremental prognostic value. The incremental values of E/E' ratio, LADI and NT-ProBNP over conventional risk factors were assessed by a modified stepwise process in 3 modeling steps in the same order as in a clinical practice. The incremental factors added to the model at each step were considered significant when the difference in log-likelihood associated with each model corresponded to $p<0.05$. In addition, cardiac event-free survival was determined according to the Kaplan–Meier method. The p values were 2-sided, and $p<0.05$ was considered to be significant.

Results

Subjects

The baseline characteristics of the study subjects are showed in Table 1. Among the 105 patients referred, 24 patients (23%) had adverse cardiac events during follow-up periods. Five patients (21%) died and all 5 deaths had a cardiac origin cause. Nineteen (79%) had recurrent CHF leading to re-admission to hospital. The patients with cardiac events were found to have a significantly higher value of log NT-ProBNP, compared to those without events. However, there were no differences in age, diabetes and hypertension, and there were also no significant differences in the treatment with medication and laboratory results such as lipid profile between the 2 groups.

Echocardiography Study

Among the conventional echocardiographic parameters, an increased LADI was noted in those with cardiac events (Table 2). Regarding the Doppler study for mitral inflow, in those patients with cardiac events, it showed the restrictive filling pattern, which was demonstrated by increased E-

Table 1 Baseline Characteristics of the Study Subjects According to the Cardiovascular Events

	Subjects without events (n=81)	Subjects with events (n=24)	p value
Age (years)	61±15	61±15	0.954
M/F	49/32	16/8	0.639
History			
Hypertension (%)	26/81 (32%)	9/24 (38%)	0.630
Diabetes (%)	18/81 (22%)	5/24 (21%)	1.000
Prior CHF (%)	28/81 (35%)	7/24 (29%)	0.806
NYHA class			0.696
II (%)	12 (15%)	2 (8%)	0.515
III (%)	23 (28%)	8 (33%)	0.621
IV (%)	46 (57%)	14 (59%)	1.000
Log NT-ProBNP	3.29±0.61	3.84±0.26	<0.001
C-reactive protein (mg/L)	1.56±3.01	1.51±2.94	0.938
Creatinine (mg/dl)	1.21±0.54	1.19±0.32	0.859
eGFR ($ml \cdot min^{-1} \cdot 1.73\,m^{-2}$)	66.07±20.11	66.38±21.13	0.949
Hemoglobin (g/dl)	13.76±2.00	13.22±2.00	0.243
Total cholesterol (mg/dl)	182.30±44.19	176.73±54.36	0.721
Triglyceride (mg/dl)	136.74±96.63	94.30±30.81	0.144
HDL-cholesterol (mg/dl)	44.61±11.59	43.78±7.28	0.815
LDL-cholesterol (mg/dl)	121.48±38.25	119.48±54.50	0.889
Medication			
Aspirin (%)	57 (70%)	18 (75%)	0.799
β-blockers (%)	58 (72%)	14 (58%)	0.223
Calcium-blockers (%)	2 (3%)	1 (4%)	0.545
ACEI or ARB (%)	68 (84%)	21 (88%)	1.000
Diuretics (%)	65 (85%)	21 (88%)	1.000
Spironolactone (%)	24 (30%)	7 (29%)	1.000

CHF, congestive heart failure; NYHA, New York Heart Association; NT-ProBNP, N-terminal Pro B-type natriuretic peptide; eGFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2 Echocardiographic Parameters of the Patients According to the Cardiovascular Events

	Subjects without events (n=81)	Subjects with events (n=24)	p value
LV structures			
LVPWD (cm)	0.93±0.20	0.91±0.37	0.641
IVSD (cm)	0.88±0.20	0.86±0.28	0.808
LVEDD (cm)	6.48±0.74	6.79±0.62	0.143
LVESD (cm)	5.50±0.92	5.75±0.64	0.133
LVEDV (ml)	150.13±51.14	158.41±41.17	0.572
LVESV (ml)	125.45±42.54	130.06±31.43	0.386
LVMI (g/m^2)	160.62±42.03	176.55±58.94	0.350
LADI (cm/m^2)	2.77±0.47	3.10±0.54	0.004
LV ejection fraction (%)	27.69±6.94	25.67±7.00	0.214
Mitral inflow study			
Mitral E wave (cm/s)	71.81±24.53	83.13±19.80	0.041
Mitral A wave (cm/s)	75.71±28.14	63.50±36.23	0.128
E/A ratio	1.11±0.73	1.86±1.45	0.047
DT (ms)	186.25±71.33	155.78±49.59	0.026
Isovolumic relaxation time (ms)	118.14±33.38	108.91±42.75	0.287
Tissue Doppler velocity			
S' (cm/s)	4.27±1.44	3.96±1.07	0.332
E' (cm/s)	4.48±1.48	4.78±1.81	0.411
A' (cm/s)	5.55±1.68	4.89±1.71	0.146
E/E' ratio	17.19±7.75	21.01±7.69	0.036

LV, left ventricular; LVPWD, LV posterior wall dimension; IVSD, interventricular septal dimension; LVEDD, LV end-diastolic dimension; LVESD, LV end-systolic dimension; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; LVMI, LV mass index; LADI, left atrial dimension index; E, early transmitral inflow; A, late transmitral inflow; DT, decelerating time; S', systolic mitral annular velocity; E', early diastolic mitral annular velocity; A', late diastolic mitral annular velocity; E/E' ratio, ratio of peak early diastolic mitral inflow to annular velocity.

velocity, decreased A-velocity, shortened DT and a typical E/A ratio of more than 1.5. However, the TDI revealed that the S', E' and A' were not significantly decreased, while the E/E' ratio was higher in the cardiac event group.

Prognosis of DCM

The univariate and multivariate predictors of cardiac events are listed in Table 3. After all, the variables showing the significant predicting value for the adverse outcomes on univariate Cox regression analysis were entered into a for-

Table 3 Results of Cox-Hazard Univariate and Multivariate Predictors of Outcomes

	Univariate HR (95%CI)	*p value*	*Multivariate HR (95%CI)*	*p value*
LADI	*3.985 (1.780–8.922)*	*0.001*	*3.332 (1.356–8.185)*	*0.009*
DT	*0.994 (0.987–1.001)*	*0.096*	*1.003 (0.990–1.016)*	*0.656*
Mitral E wave	*1.017 (1.000–1.034)*	*0.044*	*1.005 (0.971–1.040)*	*0.768*
E/A ratio	*1.671 (1.185–2.355)*	*0.003*	*1.401 (0.796–2.467)*	*0.242*
E/E' ratio	*3.665 (1.549–8.669)*	*0.003*	*0.973 (0.899–1.053)*	*0.494*
Log NT-ProBNP	*11.104 (3.419–36.057)*	*<0.001*	*8.304 (1.795–38.412)*	*0.007*

HR, hazard ratio; CI, confidence interval. Other abbreviations see in Tables 1,2.

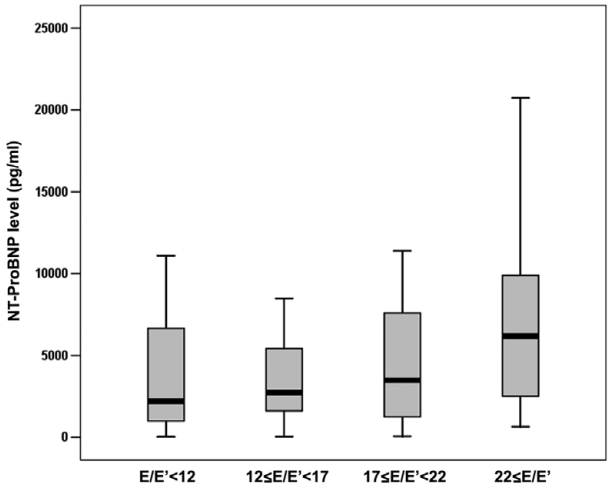

Fig 1. Level of N-terminal Pro B-type natriuretic peptide (NT-ProBNP) according to the quartile ratio of peak early diastolic mitral inflow to annular velocity (E/E' ratio).

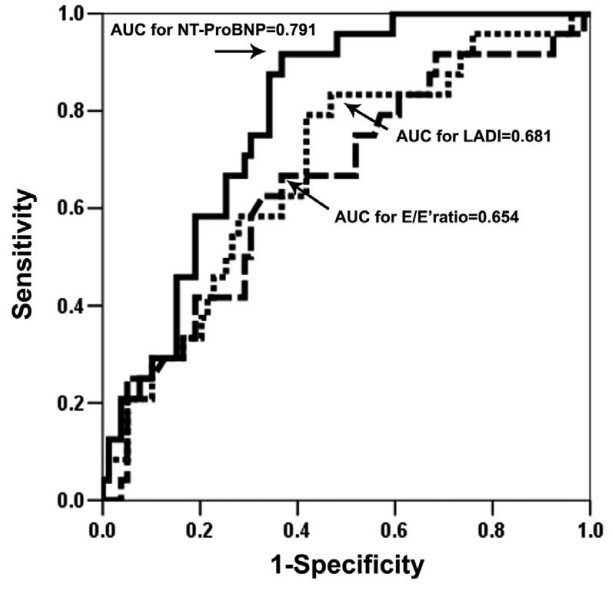

Fig 2. Receiver-operating characteristics (ROC) curves of N-terminal Pro B-type natriuretic peptide (NT-ProBNP), left atrial dimension index (LADI) and the ratio of peak early diastolic mitral inflow to annular velocity (E/E' ratio) against the adverse cardiovascular events in 105 patients with dilated cardiomyopathy.

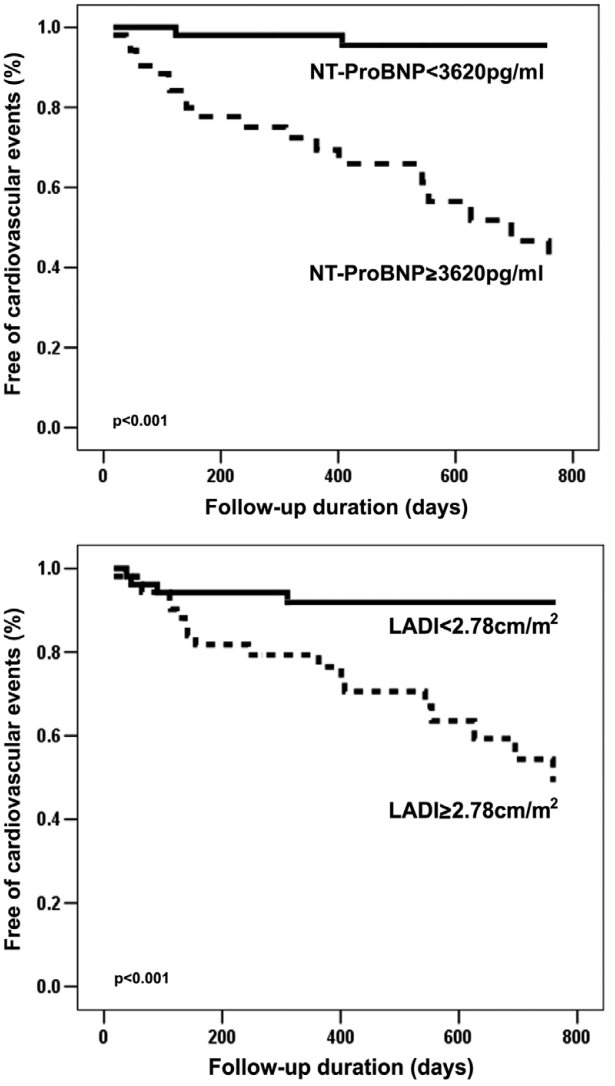

Fig 3. Event-free Kaplan–Meier curves for subgroups according to the level of N-terminal Pro B-type natriuretic peptide (NT-ProBNP) (Upper) and left atrial dimension index (LADI) (Lower).

ward multivariate analysis, and LADI and log NT-ProBNP still remained as independent predictors. In terms of the relationship between the E/E' ratio and the NT-ProBNP level, NT-ProBNP was elevated gradually in slow increments when the level of the E/E' ratio was less than 22, whereas it rapidly increased in steep increments when the level of the E/E' ratio was greater than 22 (Fig 1).

Fig 2 shows the area under the ROC curves for LADI and NT-ProBNP, for the prediction of cardiac events (0.681:

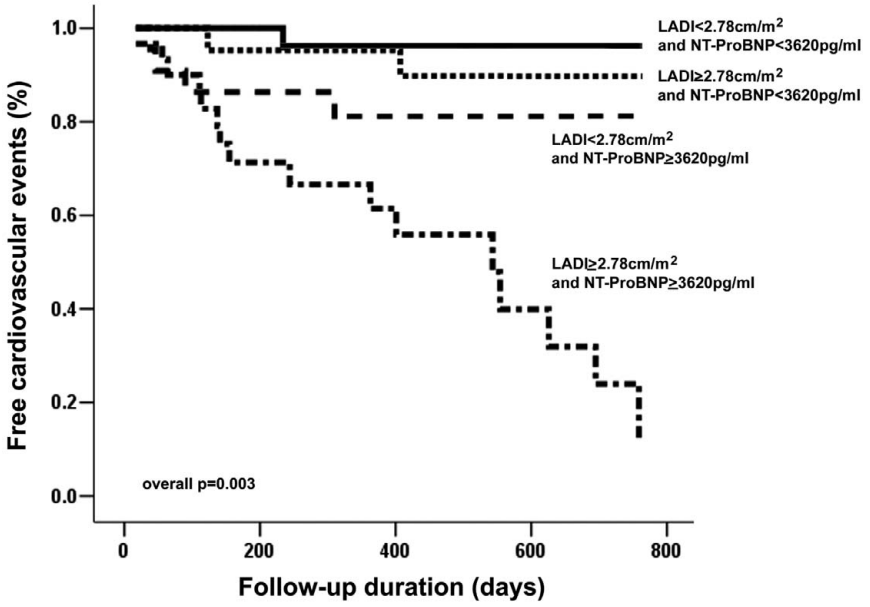

Fig 4. Event free Kaplan–Meier curves for subgroups stratified by both combination of N-terminal Pro B-type natriuretic peptide (NT-ProBNP) and left atrial dimension index (LADI).

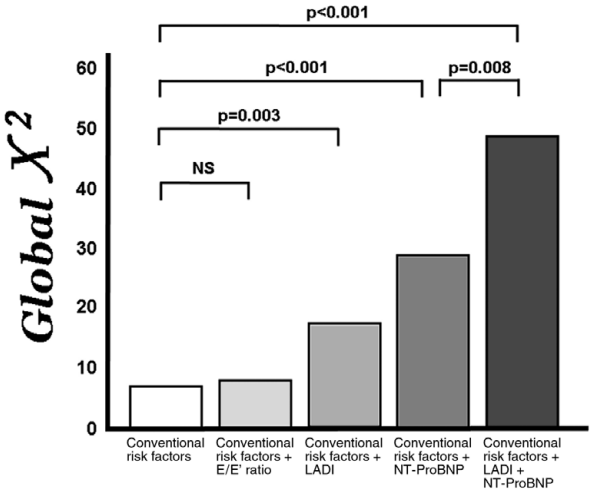

Fig 5. Incremental prognostic values of the ratio of peak early diastolic mitral inflow to annular velocity (E/E' ratio), left atrial dimension index (LADI) and N-terminal Pro B-type natriuretic peptide (NT-ProBNP) to the conventional risk factors.

95% confidence interval (CI), 0.562–0.801 for LADI; 0.791: 95% CI, 0.703–0.878 for NT-ProBNP). However, the area under the ROC curves for the E/E' ratio (0.654: 95% CI, 0.528–0.780) was smaller than that for LADI or NT-ProBNP. The optimal values of LADI and NT-ProBNP for predicting cardiac events were defined as the concentration with the largest sum of sensitivity plus specificity for each of the curves. As such, for LADI, the optimal level was 2.78 cm/m^2, while for NT-ProBNP, the optimal concentration was 3,620 pg/ml. The sensitivity and specificity in patients with a LADI at 2.78 cm/m^2 were 79.2% and 58.2%, respectively, while the sensitivity and specificity of cardiac events in patients with a serum level of NT-ProBNP at 3,620 pg/ml were 91.7% and 63.3%, respectively.

By using these cut-off levels for NT-ProBNP and LADI, the patients who had a level of NT-ProBNP less than 3,620 pg/ml and a LADI less than 2.78 cm/m^2 showed a more favorable prognosis during the follow-up period (Fig 3). Compared with the event-free curve for the NT-ProBNP level, there was no difference in the occurrence of cardiac events between the 2 groups within the initial 3 months over the course of the study period in the curve for LADI; thereafter it was markedly different between the 2 groups over the rest of the follow-up period.

To further analyze the prognostic power of LADI and NT-ProBNP to obtain useful information on predicting cardiac events, the subjects were classified into 4 groups according to the value of LADI and NT-ProBNP: group I; LADI <2.78 cm/m^2 and NT-ProBNP <3,620 pg/ml, group II; LADI ≥2.78 cm/m^2 and NT-ProBNP <3,620 pg/ml, group III; LADI <2.78 cm/m^2 and NT-ProBNP ≥3,620 pg/ml, group IV; LADI ≥2.78 cm/m^2 and NT-ProBNP ≥3,620 pg/ml. The patients with both an increased LADI and NT-ProBNP level had a 27-fold higher risk of experiencing cardiac events than those patients with no risk factors (hazard ratio 27.2, 95% CI 3.2–233.7, p=0.003) (Fig 4). Moreover, with respect to the incremental value, in the global chi-square analysis showing improvement with an increment of 10 by adding LADI and of 32 by adding NT-ProBNP in sequence, the value of both LADI and NT-ProBNP added the incremental prognostic value to conventional risk factors such as age, hypertension and diabetes. In contrast, the E/E' ratio alone did not have the incremental power over the conventional risk factors; it was suggested that both the LADI and NT-ProBNP level could be related to CV prognosis more than the E/E' ratio (Fig 5).

Discussion

While most of the previous studies focused on either ischemic or mixed ischemic and non-ischemic LV function, the present study excluded the ischemic etiologies of CHF. There were few and limited data for the incremental value of the E/E' ratio and LA size compared to NT-ProBNP in non-ischemic heart diseases. Thus, we extended these echocardiographic parameters in the current study because the role of these parameters for predicting the adverse of a cardiac event, particularly in non-ischemic DCM with advanced

LV dysfunction, seems unclear. To the best of our knowledge, this is the first study that has examined the prognostic power of the NT-ProBNP level and echocardiographic factors in non-ischemic DCM patients.

As expected, the lower EF and S' in TDI, reflecting LV systolic dysfunction, were not important contributors to adverse events in DCM. Diastolic echoparameters such as mitral E and the E/A ratio were significantly different between the 2 groups because both systolic and diastolic dysfunction would co-exist in the majority of patients with CHF. Along with those parameters, the E/E' ratio was also increased in patients who experienced cardiac events, which had been reported to represent the LV end-diastolic pressure and to predict further CV events. And also, the more enlarged LAD and higher LADI in the event group could support the additional evidence of the diastolic functional role in addition to the LV end-diastolic pressure, because LAD or LADI had a good correlation with diastolic dysfunction over a long-term duration in previous studies![19,20]

With those echocardiographic parameters, NT-ProBNP was significantly higher in the cardiac event group, as was also evidenced by a recent study[21] NT-ProBNP is a neurohormone, which is released mainly from ventricular myocytes and has been used as a marker of LV dysfunction. The degree of its elevation in the CV diseases shows a somewhat different level according to the types of heart diseases, as was influenced by many other factors. Some studies revealed that combined systolic and diastolic dysfunction, or diastolic dysfunction would like to show a better correlation with NT-ProBNP than only systolic dysfunction[22,23] Moreover, this variable heterogeneity of the NT-ProBNP level in patients with systolic CHF would seem to reflect the severity of diastolic abnormality, right ventricular function and mitral regurgitation in addition to LVEF, age and renal function[24,25] Interestingly, another recent report has demonstrated that the NT-ProBNP level was shown to correlate closely with LV end-diastolic wall stress more than any other echocardiographic or hemodynamic factors, including LV end-diastolic filling pressure in DCM or CHF[26] Thus, it might suggest that the usefulness of the NT-ProBNP level in predicting morbidity and mortality accurately in CHF might be explained by the link with LV end-diastolic wall stress, which is one of the primary determinants of myocardial oxygen consumption[27] In the present study, for the relationship between NT-ProBNP level and TDI in only non-ischemic DCM, TDI components of mitral annulus velocity, which is mainly relevant to ischemia or infarction, had less considerable influence on the prognosis of non-ischemic DCM. The lack of predictability of TDI leads to the suggestion that TDI would reflect primarily systolic dysfunction caused by ischemic heart diseases rather than non-ischemic diseases, although there would be a significant correlation or inter-relationship between systolic (S') and diastolic (E' and A') TDI of mitral annulus caused by the close physiologic interaction between systolic shortening and diastolic lengthening[28,29] Similarly, in a previous study[21] with regards to comparing the prognostic impact of echocardiographic factors against NT-ProBNP in CHF with systolic dysfunction, although it was not all the non-ischemic etiology of CHF, the NT-ProBNP level provided the most informative predictor of outcome by multivariate analysis more than the E/E' ratio or restrictive filling patterns.

In this study, in terms of the prognosis of long-term duration, LADI and NT-ProBNP, with the E/E' ratio as an exception, were independent factors, even after adjusting for other parameters in the Cox-hazard analysis. Furthermore, on Kaplan–Meier analysis, the adverse cardiac events occurred much more in the patients with higher LADI ($\geq$2.78 cm/m^2) and/or increased NT-ProBNP ($\geq$3,620 pg/ml), both of which were suggested to be informative factors for predicting for prognosis. However, based on the results of this study, it seems that the role of LADI and NT-ProBNP on prognosis during the follow up period provided different results. The power of LADI for predicting cardiac events in the early course of disorder was lower at this stage rather than later in the course, as was shown in Fig 3. In contrast, the NT-ProBNP level showed more a favorable discriminating power for prognosis over the entire period, even in the early course. The slow and incomplete ventricular filling with increased chamber stiffness is believed to cause the alteration of LV diastolic mechanics leading into LA enlargement, which has been considered as chronic LA dysfunction![19] However, LA enlargement correlates well with the duration or severity of diastolic heart failure[30] Moreover, acute changes of LV function could easily affect the elevation of the NT-ProBNP level rather than LA function or volume, the changes of which would require chronic adaptation, resulting in the remodeling of LA. Thus, it was speculated that the LAD or LADI might contribute independently to the adverse prognosis and worsening of CHF, particularly in the late course, although current available data rarely specifically report on the potential roles of those risk factors regarding prediction for prognosis.

On the contrary to LADI and NT-ProBNP, the E/E' ratio could not have sufficient power for predicting cardiac adverse events, even although it reached significance in the univariate analysis. Actually, in advanced LV systolic dysfunction, the TDI of mitral annulus velocity was much reduced and was within a narrow range under 5–6 cm/s, and the E/E' ratio, per se, would correlate with the LV end-diastolic pressure, not with systolic or diastolic function. In addition, the TDI-derived E' and A' velocity or the E/E' ratio are relatively load-independent measures of diastolic function, and preferably correlate well with systolic function such as LVEF and tau![7,31,32] although they have been validated as an accurate, non-invasive index of LV filling pressure. Thus, in non-ischemic DCM with the same severity of systolic EF or TDI-S', diastolic TDI-components are not markedly important in the prognosis for tissue Doppler velocity, as they would not provide useful information on the natural course of DCM. Therefore, this narrow range of TDI would result in its less significance in the severely decreased systolic function, and adding the E/E' ratio to conventional risk factors could not significantly increase the incremental predictive power. In addition, a modest increase of LV filling pressure of less than 22, assessed by the E/E' ratio, would fail to demonstrate the severity of an increased of NT-ProBNP. Thus, NT-ProBNP would not be correlated in proportion to the E/E' ratio and the steep uprise of the NT-ProBNP level could not be explained by the increased E/E' ratio alone. Although the E/E' ratio might be a useful parameter in patients with CHF symptoms, it has much more limited value than LADI and NT-ProBNP in providing the incremental value to conventional risk factors in patients with advanced DCM. Our results are in agreement with previous findings, as the NT-ProBNP level was demonstrated to represent the severity and prognosis of CHF including diastolic and/or systolic components rather than be associated with LV filling pressure, compared with

TDI.[17] Therefore, LADI and NT-ProBNP would be the most significant predictable factors over other factors including the E/E' ratio in patients who have non-ischemic, advanced DCM and would become an indicator of global cardiac function.

However, our study has some limitations. The invasive hemodynamic parameters could not be obtained in this study. The assessment of diastolic function would require the invasive catheterization of LV to obtain pressure-volume curves, because the elevated E/E' ratio might not be equal to the diastolic dysfunction but might mean only a high LV end-diastolic pressure. Indeed, the whole definition of diastolic dysfunction based on echocardiography is difficult and there is no ideal method to evaluate diastolic function accurately. However, the non-invasive parameters such as the E/E' ratio or mitral inflow by using echocardiography have been currently recognized as useful markers for diastolic dysfunction.[33] A further limitation is that the TDI for only septal mitral annular velocity was measured, and thus, mean values of other sites could not be obtained. Taken together, the strain or strain rate was not studied. However, there is no general consensus about the appropriate sites for mitral annular tissue velocity, as was reported by previous studies[31,34,35] and thus, a variety of sites have been used to study TDI analysis. However, medial TDI is less affected by the translational movement of the heart and is easy to obtain for appropriate Doppler beam alignment, although the TDI from the lateral mitral annulus is higher than the TDI from the medial mitral annulus. These were supported by previously published studies demonstrating that septal TDI would correlate well with LA size or volume, and provide better diagnostic utility.[36,37] Therefore, in non-ischemic DCM, not coronary artery diseases, septal TDI might be enough to represent mitral annular motion.

In conclusion, we have shown that further risk stratification could be demonstrable by assessing both the LADI and NT-ProBNP levels simultaneously. The current study on advanced DCM provides a strong rationale for the evaluation of LADI and NT-ProBNP than the E/E' ratio, although the E/E' ratio would be a useful prognostic factor for recognising further CV events in the advanced LV dysfunction of non-ischemic DCM. When these 2 factors are combined for the prediction of prognosis, the subjects could be more easily stratified even in the early course, whereas a lower power of the E/E' ratio for prognosis was noted in the present study. Therefore, NT-ProBNP could be used complementary to LADI in DCM, as it is rapid and easy to obtain these binary risk factors.

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