Prognostic Value of N-terminal Pro-brain Natriuretic Peptide in Risk Stratification of Non-ST Elevation Myocardial Infarction / Unstable Angina

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CHAN ET AL.: *Prognostic Value of N-terminal Pro-brain Natriuretic Peptide in Risk Stratification of Non-ST Elevation Myocardial Infarction / Unstable Angina.* *The study evaluated the prognostic value of N-terminal pro-Brain Natriuretic Peptide (NTproBNP), and its incremental predictive power over traditional prognostic indicators, in the risk stratification of Non-ST elevation myocardial infarction / unstable angina (NSTEMI/UA). One hundred and seventy-seven NSTEMI/UA patients were recruited. NTproBNP level was obtained within 72 hours after index admission. Patients were followed for up to 1 year. The primary composite endpoint was defined as all-cause mortality, myocardial infarction (MI) / unstable angina (UA), and congestive heart failure (CHF) requiring hospitalization. At 1-year follow-up, patients with NTproBNP >331 ng/L had higher rate of primary composite endpoint, total mortality, MI/UA and CHF (35.4%, 11.1%, 19.2%, and 15.2% respectively) than those with NTproBNP≤331 ng/L (10.3%, 1.3%, 10.3%, and 0% respectively). NTproBNP cutoff of >331 ng/L was the independent predictor of composite endpoint at 1 year (HR 3.4; CI 1.6-7.5; p=0.002). In patients who were classified as low risk by traditional prognostic markers, the NTproBNP>331 ng/L also predicted a trend towards more adverse clinical outcome. In conclusion, in patients with NSTEMI/UA, NTproBNP cutoff of >331 ng/L was an independent prognostic marker in prediction of all cause mortality, MI/UA, and CHF requiring hospitalization at 1 year. It provided incremental and independent prognostic value over traditional prognostic markers. Measurement of NTproBNP in NSTEMI/UA patients should be considered for early risk stratification. (J HK Coll Cardiol 2011;19:45-56)*

NSTEMI, NTproBNP, Risk stratification, UA

摘要

此項研究旨在評估氨基末端前腦利納肽（NTproBNP）在非ST段抬高型心肌梗死/非穩定性心絞痛（NSTEMI/UA）中的預後價值，及其相比傳統預測指標而言所擁有的更強的預測力。共招募177位NSTEMI/UA患者，篩選入組72小時內查得其NTproBNP值，隨訪1年。基礎複合終點定義爲所有原因導致的死亡，心肌梗死（MI）/非穩定性心絞痛（UA）及需住院治療的充血性心力衰竭（CHF）。到1年的隨訪期時，NTproBNP>331 ng/L的患者在基礎複合終點，總死亡率，MI/UA和CHF中所佔比例（分別爲35.4%，11.1%，19.2%和15.2%）均高於那些NTproBNP≤331 ng/L的患者（分別爲10.3%，1.3%，10.3%和0%）。在隨訪1年時計算複合終點，臨界值NTproBNP>331 ng/L可作爲獨立的預測指標（HR 3.4；CI 1.6-7.5；p=0.002）。在那些傳統預測指標分類爲低危險性的患者中，其NTproBNP>331 ng/L同樣

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Received June 9, 2011; revision accepted July 15, 2011

能提示其趨向於不利的臨床預後。總而言之，在NSTEMI/UA患者中，隨訪1年時臨界值NTproBNP>331 ng/L可作爲一項獨立預測因數判斷所有原因的死亡率，MI/UA及需住院治療的CHF的預後。相比傳統預測指標而言，NTproBNP能提供更有效更獨立的預測價值。在NSTEMI/UA患者中測量NTproBNP應被列入早期危險度分層。

關鍵詞：非ST段抬高型心肌梗死（NSTEMI），氨基末端前腦利鈉肽（NTproBNP），危險度分層，非穩定性心絞痛（UA）

Introduction

In Non-ST elevation myocardial infarction/unstable angina (NSTEMI/UA), early coronary intervention in high-risk patients can achieve mortality reduction of 25% (6.5% to 4.9%) and MI reduction of 17% (9.1% to 7.6%).[1] The current guideline[2] recommends an early invasive strategy for high-risk groups. Early and accurate risk stratification in NSTEMI/UA is of paramount importance.

However, traditional prognostic markers in NSTEMI/UA like clinical vascular risk factors, ECG changes, cardiac enzyme elevation, stress test, left ventricular ejection fraction (LVEF), and clinical scoring systems (e.g. TIMI Score) have their limitations in predicting adverse cardiac outcome.

N-terminal pro-Brain Natriuretic Peptide's prognostic power surpasses that of conventional prognostic indicators, in risk stratification of NSTEMI/UA patients.

The aim of the study was to evaluate the prognostic value of N-terminal pro-Brain Natriuretic Peptide (NTproBNP) and its incremental predictive power over traditional prognostic indicators, in the risk stratification of NSTEMI/UA in a local population.

Method

Patient Selection

Patients admitted to our acute medical unit presenting with NSTEMI/UA, who were aged ≥18 years were included. Enrollment period was between December 2006 and February 2008. Patients with ST-Elevation Myocardial Infarction (STEMI), septicemia, shock at the time of recruitment, severe valvular heart disease, renal impairment with creatinine level >220 micromole/litre (μmol/L), history of admission for congestive heart failure, myocardial infarction/unstable angina within 3 months prior to index admission, history of coronary intervention within 3 months prior to index admission and advanced organ failure or malignancies with life-expectancy ≤1 year were excluded. Patients receiving cardiotoxic chemotherapeutic agents were also excluded. Patients who refused to consent or who were unable to consent were excluded.

Study Endpoints Definition

The primary composite endpoints were all cause mortality, MI/UA, and Congestive heart failure (CHF) requiring hospitalization. Patients were followed for up to 1 year after recruitment. NSTEMI/UA was diagnosed when patients presented with angina at rest, or crescendo angina, which lasted for ≥5 minutes (occurring within 24 hours of admission), and fulfilled one of the following criteria: 1) ST-segment depression ≥0.1 mV or T-wave inversion ≥0.1 mV; 2) elevated cardiac troponin T (TnT) ≥0.1 microgram/Litre (μg/L). CHF was defined according to the Modified Framingham clinical criteria.[3]

Laboratory Analysis

After informed consent, venous serum samples were collected in heparinised bottles, within 72 hours after admission. Serum was frozen at -20°C after centrifugation. Serum NTproBNP was determined with a sandwich immunoassay on an Elecsys 2010 (Roche Diagnostics). NTproBNP unit was expressed in nanogram per litre (ng/L). Serum creatinine kinase and cardiac troponin T were also obtained. If the first set of cardiac TnT was obtained within 6 hours of symptom onset and was negative, a second TnT would be repeated at ≥6 hours apart. Creatinine clearance was estimated by Cockcroft and Gault Equation.

Statistical Analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS 11.5) software (SPSS Inc., Chicago, Illinois). One-sample Kolmogorov-Smirnov Test was used to assess the normality of distribution of continuous variables. Differences between means for parametric variables were evaluated with independent sample T-test. Differences between means for nonparametric variables were evaluated with Mann-Whitney U test. Differences between categorical variables were evaluated with Chi-square test. The NTproBNP cutoff level was obtained from ROC analysis. Kaplan-Meier Survival analysis was used to assess the difference in event free survival. The relative risk and the 95% CI were calculated. The significance of differences in event rates between the two groups of patients with NTproBNP above and below cutoff level were assessed with log-rank test. Cox Regression analysis was used to assess the prognostic value of NTproBNP independent of other confounding variables. Hazard ratio comparing NTproBNP above and below the cutoff were calculated, with adjustment for statistically significant covariates (defined as $p<0.1$). Subgroup analysis was also performed in patients with LVEF≥55%, TIMI risk score ≤4 and negative TnT. All statistical tests were 2-tailed, and a P value of <0.05 was considered statistically significant.

Comparison with Other Traditional Prognostic Markers

The prognostic value of NTproBNP was assessed and compared with traditional prognostic markers including LVEF, Troponin T (TnT), TIMI Score, and the ten ACC/AHA Risk Factors (ACC Risk Factors) for NSTEMI/UA[2]: 1) Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy, 2) Elevated cardiac biomarkers, 3) New or presumably new ST-segment depression, 4) Signs or symptoms of CHF or new or worsening mitral regurgitation, 5) High-risk findings from noninvasive testing, (6) Hemodynamic instability, 7) Sustained ventricular tachycardia. 8) PCI within 6 months, 9) Prior CABG, 10) High risk score (e.g. TIMI), 11) Reduced left ventricular function (LVEF less than 40%).

Results

A total of 329 patients were screened. One hundred and fifty-one patients were excluded during initial screening for various reasons including: renal impairment with creatinine >220 μmol/L (60), delayed recruitment (when NTproBNP sampling time could not be obtained within 72 hours after index admission) (31), inability/refusal to consent (26), history of MI, UA, CHF or coronary revascularisation within 3 months of index admission (22), coexisting advanced medical illness with life-expectancy ≤1 year (e.g. malignancies) (7), severe valvular heart disease (4), and expected loss of follow-up (non-local citizen) (1). One patient was excluded retrospectively due to septicemic shock at the time of NTproBNP sampling.

Baseline Characteristics

A total of 177 patients were included in the study. The baseline characteristics of patients were listed in Table 1. The median time between NTproBNP sampling and symptom onset was 36 hours. The mean LVEF of our study population was 52.2±12.4%. The median NTproBNP level in patients with unstable angina and NSTEMI was 262 ng/L and 874.6 ng/L respectively. The mean TIMI risk score was 3.7±1.4. Forty-four (24.9%) patients had TIMI risk score >4. The mean ACC risk factors was 2.1±1.4.

Assessment of NTproBNP Cutoff

The Receiver-Operator Curve (ROC) analysis yielded an area under curve of 0.746. (SE: 0.042; CI 0.663-0.83; $p<0.001$) (Figure 1). NTproBNP cutoff of 331 ng/L yielded a sensitivity of 81.4% and a specificity of 52.2% in predicting primary composite endpoints at 1 year. The positive and negative predictive values were 35.4% and 90% respectively.

Outcome Measures

At 1 year follow-up, a total of 43 (24.3%) patients reached primary composite endpoint of all cause mortality, MI/UA or CHF requiring hospitalization. Twelve patients (6.8%) reached mortality endpoint. Seven patients (4%) died of cardiac cause. Five patients (2.8%) died of noncardiac causes (namely intracranial

hemorrhage, ischemic stroke, chronic obstructive airway disease, pneumonia and unknown cause). Twenty-seven patients (15%) had MI/UA. Fifteen patients (8.5%) had CHF requiring hospitalization at 1 year (Table 2).

Among patients with NTproBNP ≤331 ng/L, the 1-year incidences of primary composite endpoint, total mortality, MI/UA and CHF rate were lower (10.3%, 1.3%, 10.3%, and 0% respectively, p all ≤0.01) than that in patients with NTproBNP >331 ng/L (35.4%, 11.1%, 19.2%, and 15.2% respectively, p all ≤0.01). In patients with NTproBNP >331 ng/L, there was a trend towards higher cardiac mortality (OR 4.97; CI 0.6-42.2; p=0.136) and MI/UA (OR 2.08; CI 0.9-5; p=0.1) at

Table 1. Baseline characteristics

Epidemiological factors (n=177)	
Age (years)	68.4±13.1
Gender (Male/Female)	112/65
Creatinine clearance (ml/min)	62±28
Creatinine (μmol/L)	90.7±24.9
Body weight (kg)	61.9±13.3
NTproBNP time from admission (hours)#*	22 (15-36)
NTproBNP time from symptom onset (hours)#*	36 (23-54)
Peak creatinine kinase (IU/L)#	150 (78.5-334)
Patients with angina	153 (86.4%)
Dynamic ECG changes	133 (75%)
Patients with Non-ST elevation myocardial infarction (NSTEMI)	72 (40.7%)
Patients with unstable angina	105 (59.3%)
Left ventricular ejection fraction (%)	52.2±12.4
Patients with left ventricular ejection fraction ≤40%	31 (17.5%)
NTproBNP (ng/L)#	591.8 (95.6-1757.5)
NTproBNP in unstable angina patients (ng/L)#	262 (76.3-1285.5)
NTproBNP in NSTEMI patients (ng/L)#	874.6 (219.9-3237.3)
TIMI score	3.7±1.4
Patients with TIMI risk score >4	44 (24.9%)
ACC risk factors	2.1±1.4
Patients with ACC risk factors≥1	159 (89.8%)
Patients received percutaneous coronary intervention at 1 year	72 (40.7%)
Patients received coronary artery bypass grafting at 1 year	2 (1.1%)

Continuous variables are expressed in mean ± standard deviation unless otherwise specified.

Variables expressed in median (25th/75th centile). All dichotomous variables are expressed in number (percentage); *NTproBNP time from admission=Time between NTproBNP sampling and admission; NTproBNP time from symptom onset=Time between NTproBNP sampling and symptom onset.

1 year, although it did not reach statistical significance. NTproBNP cutoff of >331 ng/L predicted 1-year composite endpoint with a sensitivity of 81.4% and specificity of 52.2%. It also provided a high negative predictive value of 90% in predicting composite endpoint at 1 year.

Major predictors of primary composite endpoint assessed in univariate and multivariate analysis were summarized in Tables 3a, 3b and 4. NTproBNP, Age, creatinine clearance, ST segment depression, ACC risk factors, TIMI score, CHF during index admission, hypertension, history of CHF, history of stroke, use of calcium channel blockers, nitrates, diuretics, and previous use of aspirin were found to be predictors of primary composite endpoint in univariate analysis. However, in multivariate analysis, NTproBNP>331 ng/L remained to be the independent predictor of primary composite endpoint.

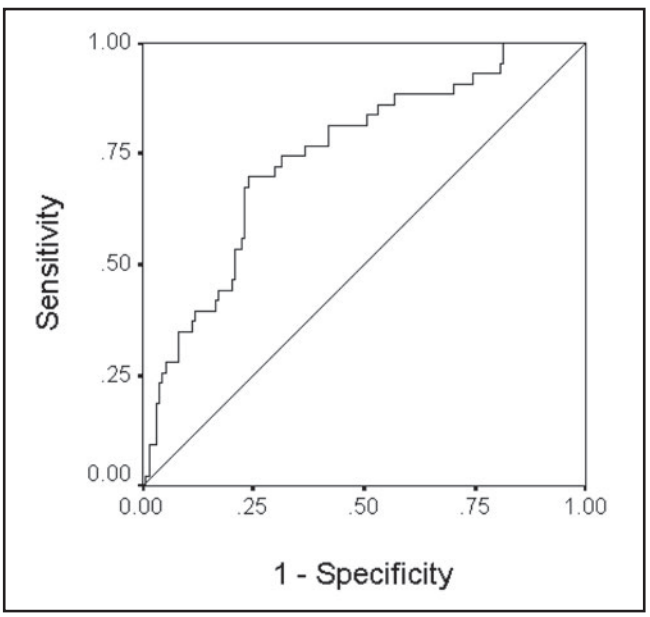

Figure 1. *Receiver-operator curve analysis. NTproBNP cutoff of >331 ng/L yielded a sensitivity of 81.4% and a specificity of 52.2% in prediciting primary composite endpoints at 1 year. The positive and negative predictive values were 35.4% and 90% respectively.*

Survival Analysis

Patients with NTproBNP≤331 ng/L demonstrated higher event free survival at 1 year in Kaplan Meier analysis (Log Rank 13.97; p=0.0002) (Figure 2). The composite endpoint event free survival at 1 year (HR 2.5; CI 1.1-5.8; p=0.028) (Figure 3) was higher in patients with NTproBNP >331 ng/L in Cox Regression analysis. NTproBNP was the independent prognostic indicator after adjusting for confounding variables including age, diabetes mellitus (DM), hypertension (HT), smoking status, creatinine clearance, CHF during index admission, history of MI/UA, history of CVA, ACC risk factors and the time between NTproBNP sampling and symptom onset. NTproBNP >331 ng/L predicted primary composite endpoint with a HR of 3.4 (CI 1.6-7.5; p=0.002). The prognostic value of NTproBNP was still retained after adjusting for revascularisation strategy.

Table 2. Outcome at 1 year

	NTproBNP		Odds ratio	Confidence interval	p value
	≤331 ng/L (n=78)	>331 ng/L (n=99)			
Composite endpoint	8 (10.3%)	35 (35.4%)	4.79	2.1-11.1	<0.001
Mortality	1 (1.3%)	11 (11.1%)	9.6	1.2-76.3	0.01
Cardiac mortality	1 (1.3%)	6 (6.1%)	4.97	0.6-42.2	0.136
Recurrent myocardial infarction/ unstable angina	8 (10.3%)	19 (19.2%)	2.08	0.9-5.0	0.1
Congestive heart failure 1 year	0 (0%)	15 (15.2%)	–	–	<0.001

Table 3a. Univariate predictors of primary composite endpoint (continuous variables)

	Composite endpoint		p value
	0 (n=134)	+ (n=43)	
Age (years)	66.8±13	73.4±12	0.004
Creatinine clearance (ml/min)	64.7±28.8	54.1±24.1	0.029
ST depression (mm)	1±1	2±2	0.012
ACC risk factors	1.9±1.3	2.6±1.6	0.021
TIMI score	3.5±1.4	4.4±1.4	<0.001
NTproBNP time* (hours)	35 (22-52)	44 (26-91)	0.087
NTproBNP (ng/L)#	314.6 (84.6-1081.3)	1543 (773.9-4564)	<0.001

0=negative; +=positive

*NTproBNP time=NTproBNP sampling time from symptom onset; #values expressed in median (25th/75th centiles)

Table 3b. Univariate predictors of primary composite endpoint (dichotamous variables)

	Composite endpoint		Odds ratio	Confidence interval (95%)	p value
	0 (n=134)	+ (n=43)			
CHF adm	19 (14.2%)	13 (30.2%)	2.6	1.2-5.9	0.017
Diabetes mellitus	45 (33.6%)	22 (51.2%)	2.1	1.0-4.2	0.039
Hypertension	77 (57.5%)	35 (81.4%)	3.2	1.4-7.5	0.005
History of congestive heart failure	7 (5.2%)	7 (16.3%)	3.5	1.2-10.7	0.044
History of stroke	11 (8.2%)	9 (20.9%)	3.0	1.1-7.7	0.029
Previous aspirin use	67 (50%)	29 (67.4%)	2.0	1-4.3	0.046
Enoxaparin	113 (84%)	40 (93%)	2.5	0.7-8.8	0.15
Aspirin	133 (99.3%)	42 (97.7%)	0.3	0.2-5.2	0.43
Clopidogrel	124 (92.5%)	37 (86%)	0.5	0.2-1.5	0.22
ACEI	112 (83.6%)	36 (83.7%)	1.0	0.4-2.6	0.98
Statin	120 (89.6%)	38 (88.4%)	0.9	0.3-2.6	0.78
Betablockers	112 (83.6%)	39 (90.7%)	1.9	0.6-5.9	0.25
Calcium channel blockers	20 (14.9%)	14 (32.6%)	2.8	1.2-6.1	0.011
Nitrates	57 (42.5%)	28(65.1%)	2.5	1.2-5.2	0.01
Diuretics	35 (26.1%)	18 (41.9%)	2.0	1.0-4.1	0.05
NTproBNP>331 ng/L	64 (47.8%)	35 (81.4%)	4.8	2.1-11.1	<0.001

0=negative; +=positive; CHF adm = congestive heart failure in index admission; ACEI=angiotensin-converting enzyme inhibitors

Table 4. Multivariate parameters in Cox Regression analysis: Predictors of primary composite endpoint

	HR	Multivariate analysis Confidence (95%)	p value
Age	1.0	0.98-1.04	0.463
Chronic smoker	1.1	0.4-2.8	0.915
CHF adm	1.1	0.4-2.0	0.851
NTproBNP time (hours)	1.0	0.998-1.003	0.714
History of MI/UA	1.2	0.6-2.3	0.551
Creatinine clearance	1.0	0.99-1.02	0.594
Diabetes mellitus	1.5	0.8-2.8	0.179
History of stroke	2.0	0.9-4.1	0.080
Hypertension	2.0	0.9-4.4	0.084
ACC risk factors	1.3	1.1-1.7	0.016
NTproBNP>331 ng/L	2.5	1.1-5.8	0.028

CHF adm=congestive heart failure in index admission; NTproBNP time=NTproBNP sampling time from symptom onset; ACC risk factors=The ten American College of Cardiology/ American Heart Association Risk Factors for Non-ST Elevation Myocardial Infarction/ Unstable Angina: 1) Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy, 2) Elevated cardiac biomarkers, 3) New or presumably new ST-segment depression, 4) Signs or symptoms of CHF or new or worsening mitral regurgitation, 5) High-risk findings from noninvasive testing, 6) Hemodynamic instability, 7) Sustained ventricular tachycardia, 8) PCI within 6 months, 9) Prior CABG, 10) High risk score (e.g. TIMI), 11) Reduced left ventricular function (LVEF less than 40%).

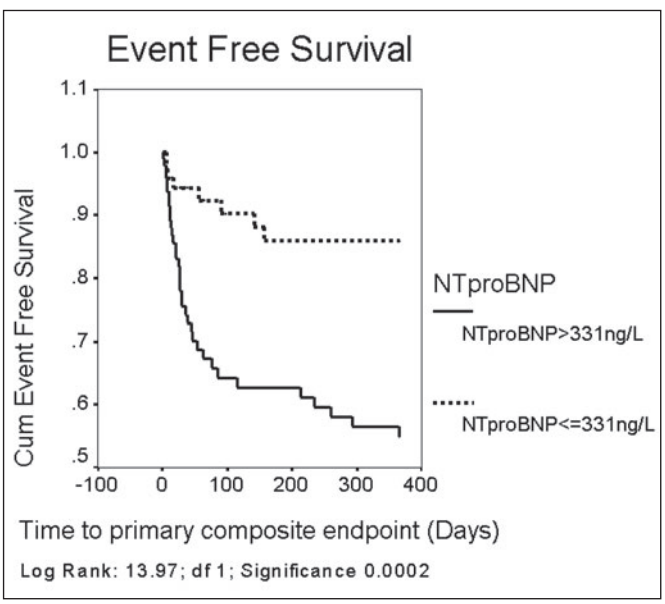

Figure 2. *Kaplan-Meier survival analysis.*

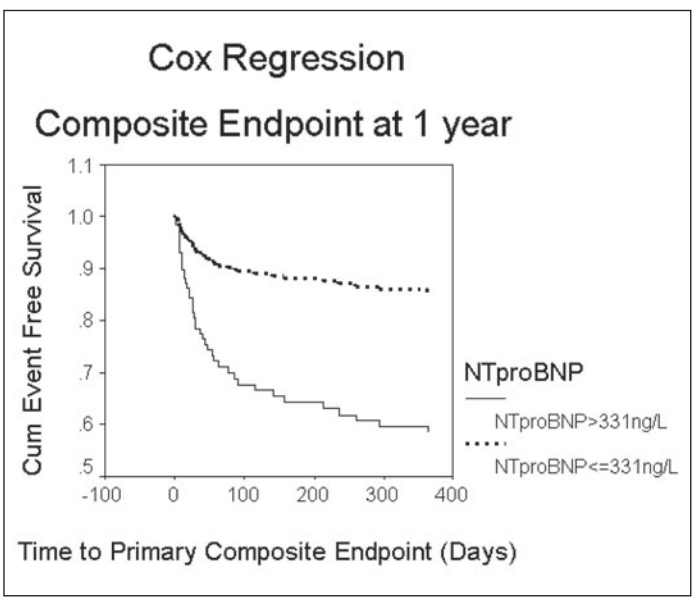

Figure 3. *Cox Regression – Primary composite endpoint at 1 year. NTproBNP>331 ng/L predicted primary composite endpoint with a HR of 3.4 (CI 1.6-7.5; p=0.002)*

Prognostic Power of NTproBNP Compared with Traditional Prognostic Indicators

Decompensated CHF alone could cause NTproBNP elevation.[4] In our study, 32 (18%) patients had decompensated CHF during index admission. CHF during index admission was a significant predictor of outcome in univariate analysis (OR 2.6; CI 1.2-5.9; p=0.017). However, the prognostic power of CHF during index admission was lost after addition of NTproBNP into Cox Regression analysis. Clinical diagnosis of decompensated CHF during index admission predicted primary composite endpoints with sensitivity of 30.2%, specificity of 85.8%, positive predictive value (PPV) of 40.6% and negative predictive value (NPV) of 79% (OR 2.623; CI: 1.165-5.91; p=0.017). TIMI risk score cutoff >4 predicted primary composite endpoint with sensitivity of 46.5%, specificity of 82.1% (OR 3.99; CI 1.89-8.4, p<0.001), PPV of 45.5% and NPV of 82.7%. LVEF<40% predicted primary composite endpoint with sensitivity of 72.1%, specificity of 14.2%, PPV of 21.2% and NPV of 61.3% (OR 0.427; CI 0.187-0.973; p=0.039). NTproBNP cutoff of >331 ng/L predicted primary composite endpoint with sensitivity of 81.4%, specificity of 52.2%; (OR of 4.79; CI2.07-11.1; p<0.001), PPV of 35.4% and NPV of 90%.

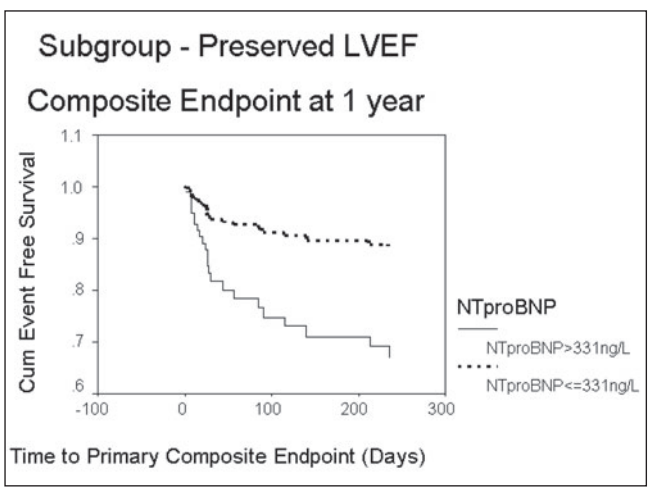

Figure 4. *Subgroup analysis (LVEF ≥55%). NTproBNP >331 ng/L predicted primary composite endpoint with a HR of 3.1 (CI 1.2-8.3; p=0.02).*

Subgroup Analysis

In subgroup analysis, NTproBNP>331 ng/L demonstrated its independent prognostic value in predicting primary endpoint at 1 year even in patients with preserved left ventricular systolic function (LVEF ≥55%) (HR 3.1, CI 1.2-8.3; p=0.02), normal troponin (HR 5.6, CI 1.9-16.7; p=0.02) and TIMI score ≤4 (HR 2.6, CI 1.1-6.3; p=0.036) (Figures 4-6).

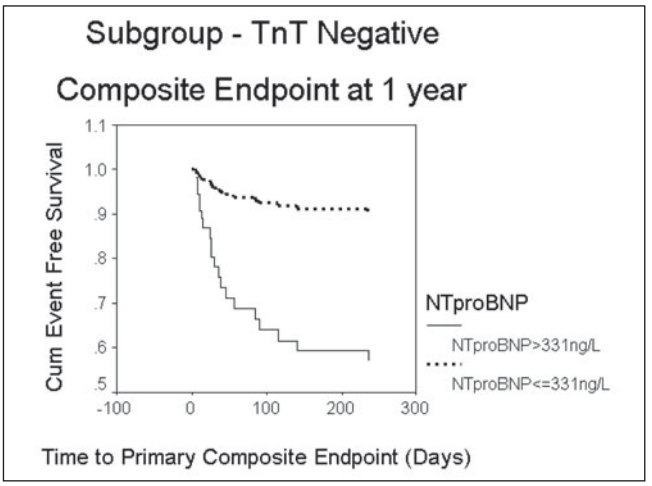

Figure 5. *Subgroup analysis (Troponin negative). NTproBNP >331 ng/L predicted primary composite endpoint at 1 year with HR 5.6 (CI 1.9-16.7; p=0.02).*

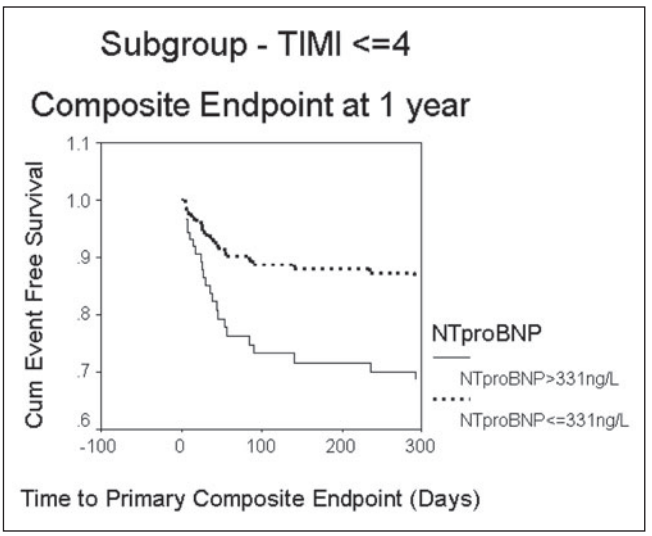

Figure 6. *Subgroup analysis (TIMI risk score ≤4). NTproBNP >331 ng/L predicted 1 year composite endpoint with HR of 2.6 (CI 1.1-6.3; p=0.036).*

Discussion

An ideal prognostic biomarker should have high sensitivity, negative predictive value and cost-effectiveness, compared with traditional prognostic markers and clinical scoring systems. Traditional prognostic markers in NSTEMI/UA include clinical vascular risk factors e.g. DM, HT, smoking status, family history of coronary artery disease (CAD), angina symptom, ECG changes, cardiac enzyme elevation, stress test, LVEF, and clinical scoring systems (e.g. TIMI Score). However, these risk stratification systems have their own limitations in terms of sensitivity, negative predictive value and cost-effectiveness.

Cardiac enzyme has limited role in further risk stratifying patients with UA without enzyme leak. In our study, the 1 year rate of primary composite endpoint was up to 21% (19 out of 92) among the subgroup of patients with unstable angina. This means 1 out of 5 patients classified as low risk by negative cardiac enzyme alone could potentially develop adverse cardiac events at 1 year.

TIMI score is limited by its low negative predictive value. In our study, the 1 year rate of primary composite endpoint was up to 17% in the unstable angina subgroup. In the subanalysis study of TIMI 11B and ESSENCE, NSTEMI/UA patients with TIMI score =3 still had a 13.2% risk of all-cause mortality, MI, or recurrent ischemia requiring urgent revascularization at 14 days.[5] In the CURE substudy, the risk of cardiovascular death, myocardial infarction and stroke at 9 months for NSTEMI/UA patients with TIMI score ≤4 was still ~14% in the clopidogrel arm.[6]

Similarly, echocardiogram is limited by its lack of sensitivity in further risk stratifying patients with preserved LVEF (left ventricular ejection fraction >55%). In our study, patients with preserved LVEF still had 1 year rate of primary composite endpoint of 21%.

NTproBNP surpasses traditional prognostic factors by its distinctive characteristics. In the setting of acute coronary syndrome (ACS), it is cardiac specific, has more rapid release (as early as 3 hours) and higher sensitivity than cardiac enzymes.[7] It could be elevated even before the occurrence or in the absence of myocardial necrosis.[8] In ACS patients with normal LVEF, myocardial wall stress and neurohormonal activation can cause NTproBNP elevation, even in the absence of myocardial necrosis.[9,10] This could account for the high sensitivity of NTproBNP in predicting adverse outcome in ACS patients without cardiac enzyme elevation.

As a result, measurement of BNP or NTproBNP is recommended for assessment of global risk in patients with suspected ACS.[2] Major studies yielded conflicting results on the role of natriuretic peptides in risk stratification intervention strategy.[11,12] According to current guideline,[2] measurement of BNP or NT-pro-BNP is a class II b recommendation, in risk stratification of ACS patients. At the moment, there is no international consensus on the cutoff value of NTproBNP in risk stratification of NSTEMI/UA patients and guidance on intervention strategy. NTproBNP level was found to be lower among healthy Chinese population compared with their Western counterparts.[13] The prognostic value and cutoff level of NTproBNP among Chinese ACS population has remained undefined.

In acute myocardial infarction, plasma NTproBNP level rises rapidly, starting from 3 hours,[7] to a maximum at 20-30 hours from onset of symptoms.[7,9,14,15] The profile of plasma NTproBNP release after MI depends on the extent of infarct. In small or moderate myocardial infarction (MI), NTproBNP peaks at 24-48 hours.[16] In major MI, it demonstrates biphasic peaks - with the first peak on first 1-2 days, and the second peak on days 5-7 (indicative of adverse ventricular remodeling).[9] Therefore, the NTproBNP sampling timeframe is of paramount importance in prognostication of ACS patients. In our study, the mean and median time between symptom onset and NTproBNP sampling was 62.9±138.1 hours and 36 hours (interquartile range 23-54 hours) respectively, which coincided with the initial peak of NTproBNP after myocardial infarction.

The cutoff level of NTproBNP in our study population was 331 ng/L (interquartile range 95.6-1758 ng/L). NTproBNP cutoff of >331 ng/L predicted 1 year all cause mortality (11.1% vs 1.3% for those above and below the cutoff respectively, p=0.01) and composite endpoint of all-cause mortality, MI/UA and CHF requiring hospitalization (35.4% vs 10.3%

for those above and below the cutoff respectively, p<0.001).

NTproBNP also predicted a trend towards higher future risk of myocardial infarction (MI) and cardiovascular (CVS) death at 1 year (6.1% vs 1.3% for those above and below the cutoff, p=0.136), although it did not reach statistical significance. The use of single cutoff level of NTproBNP might limit its sensitivity in predicting future MI and CVS death, as it is not a specific marker in reflecting myocardial necrosis. Adoption of interquartile range might overcome this potential limitation, but a larger sample size would be required.

Compared with traditional risk stratification strategy such as TIMI score, clinical diagnosis of CHF during index admission, and LVEF<40%, NTproBNP cutoff value of 331 ng/L provided superior sensitivity (81.4%) and NPV (90%) in prediction of composite endpoint. Its low PPV (35.4%) could be accounted by the use of single cutoff value at low level. The PPV could be improved by using inter-quartile ranges instead of a single cutoff value. However, a larger sample size would be needed to generate adequate prognostic power.

Brain-natriuretic peptide has been demonstrated to be independently associated with mortality in left ventricular dysfunction secondary to myocardial ischemia.[17] Level of brain natriuretic peptide also reflects the size of ischemia.[18] The ability to reflect myocardial stress even in the absence of myocardial necrosis and left ventricular systolic function impairment[9,10,19] explains its high sensitivity. In our study, we have demonstrated that NTproBNP was able to predict adverse outcome even in ACS patients with normal left ventricular systolic function and normal cardiac enzymes. These patients would be otherwise classified as low risk by conventional prognostic markers. NTproBNP predicted MACE (OR 4.8), CHF, mortality (OR 9.6) at 1 year independent of other confounding variables and conventional prognostic markers.

Impact of Revascularization Strategies

There was no major difference in the incidence of 3 vessels disease (23.3% vs 27.6%; p=0.729) and left main disease (7% vs 6%; p=0.73) between the two groups of patients with and without composite endpoint.

In our study, 84 (47.5%) patients received coronary angiogram, 72 (40.7%) patients received percutaneous coronary intervention (PCI), 2 (1.1%) patients received coronary artery bypass grafting (CABG). The mean time to coronary intervention was 12.4±33 days. The revascularization rate in our study population was 42% (74 out of 177). The early revascularization rate (within 7 days of admission) was 11.3% (20 out of 177). There was no statistically significant difference in the revascularisation rate among the two groups of patients categorized by NTproBNP cutoff of 331 ng/L or categorized by composite endpoint.

The mean time to PCI in patients who reached and who did not reach composite endpoints was 8±16 days and 14±37 days respectively (p=0.28) The mean time to PCI in patients with NTproBNP below and above cutoff level of 331 ng/L was 10±17 days and 14±41.5 days respectively (p=0.623)

Revascularisation strategy could potentially confound the prognostic value of NTproBNP. However, in our study population, there was no statistically significant difference in intervention strategy in the two groups of patients categorized by NTproBNP cutoff and composite endpoint at 1 year. The coronary intervention timing among the two groups of patients was also comparable.

Study Limitations

There are a number of limitations in our study. Firstly, we have not performed serial NTproBNP sampling. Studies have shown that serial monitoring of NTproBNP post MI revealed a biphasic profile of plasma concentration.[9] Serial NTproBNP sampling at baseline and 72 hours had been shown to predict adverse outcomes.[20] In our study, the median NTproBNP sampling time was 36 hours. A single sampling timeframe might limit its comprehensiveness in prognostication as compared with serial sampling. The effect of early medical therapy/coronary intervention for NSTEMI/UA might not be fully manifested at the time of NTproBNP sampling.

Secondly, the early revascularisation rate (within index admission) in our study was lower than that in

major clinical trials. The low early revascularisation rate (22.7%) in high risk patients (defined as TIMI score >4) would lead to heterogeneity of clinical outcomes due to the diversity of intervention timing. This reflected the limitation of resources and capacity of catheterization service. Revascularisation strategy could potentially confound the prognostic value of NTproBNP. However, in our study population, there was no statistically significant difference in intervention strategy in the two groups of patients categorized by NTproBNP cutoff and composite endpoint at 1 year. The coronary intervention timing, percentage of left main disease among the two groups of patients were also comparable.

Conclusion

In clinically high risk patients with NSTEMI/UA, NTproBNP provided incremental prognostic information over traditional prognostic markers. Among patients classified as low risk by conventional prognostic markers (patients with LVEF >55%, negative TnT, TIMI risk score ≤4), NTproBNP >331 ng/L also predicted a trend towards more adverse clinical outcomes. Whether NTproBNP could be used to guide intervention strategy in ACS patient should await future randomized trials. In patients with NSTEMI/UA, NTproBNP cutoff of 331 ng/L is an independent prognostic marker in prediction of all cause mortality, MI/UA, and CHF requiring hospitalization at 1 year. Measurement of NTproBNP in NSTEMI/UA patients should be considered for early risk stratification.

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