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Serial N-Terminal Pro Brain Natriuretic Peptide Assessments in Predicting New-Onset Atrial Fibrillation in ST Elevation Myocardial Infarction Patients who Undergo Primary Percutaneous Coronary Intervention

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Abstract

Background: N-terminal pro-Brain Natriuretic Peptide(NT-proBNP)is associated with atrial fibrillation(AF) in the setting of acute ST-elevation myocardial infarction (STEMI), and the present study was aimed at assessing the temporal association between NT-proBNP and incident AF.

Methods: 830 patients enrolled in On-TIME II were included. NT-proBNP was assessed at baseline, 24 h and 72 h after admission for STEMI. Patients with new-onset AF <30 days after STEMI were divided among 3 subgroups: AF on admission, AF 24-72 h after admission and AF >72 h after admission. NT-proBNP serum levels at the three assessment intervals was used to predict the timing of AF with a receiver-operator characteristic, and a binary logistic model was created to predict the AF at the various timings.

Results: Mean age was 62 ±12 years and 76% were male. 73 patients developed incident AF, 41 developed AF on admission, 14 patients developed AF 24-72 h after admission and 18 patients developed AF >72 h after admission. NT-proBNP at baseline (area under curve (AUC) 0.657, P<0.001), after 24 h (AUC 0.829, P<0.001) and after 72 h (AUC 0.891, P<0.001) predicted AF. However, NT-proBNP at baseline did not predict AF on admission (AUC 0.591, P=0.058). NT-proBNP after 24 h and 72 h were stronger predictors of AF compared to NT-proBNP at baseline. In regression analysis, NT-proBNP after 24 h (OR:1.220, P<0.001) and 72 h (OR:1.290, P<0.002) showed a significant association with postinfarction AF.

Conclusion: This study shows serial NT-proBNP plasma level assessments enhance risk stratification for incident AF in STEMI patients.

Keywords: Atrial fibrillation; Myocardial infarction; Biomarkers NT-proBNP

Introduction

New-onset atrial fibrillation (AF) occurs in 5-23% of patients admitted with an acute ST elevation myocardial infarction (STEMI) [1-4] and is associated with an impaired long-term cardiovascular outcome, including a 40% increase in mortality [5-7]. Therefore, predicting AF in STEMI patients can impact clinical practice by identifying patients at increased risk after STEMI. Several biomarkers have been associated with new-onset AF, [8,9] A recent study showed that incident AF after STEMI can be predicted by N-terminal pro-brain natriuretic peptide (NT-proBNP) plasma level assessment [9]. However, in this study, NT-proBNP was assessed somewhere during the first 72 hours after admission and thus there are no data on the temporal relationship between serial NT-proBNP plasma level assessments and mode of onset AF in STEMI patients. The aim of this study was to investigate if assessment of NT-proBNP plasma levels at 3 distinct timings enhances the risk stratification for the development of AF in STEMI patients treated with primary percutaneous coronary intervention (PPCI).

Methods

Our population consisted of patients with a STEMI, who were admitted for PPCI and included in the Ongoing Tirofiban in Myocardial Infarction Evaluation (On-TIME) II study [10,11] a prospective, multi-center, placebo controlled, randomized, clinical trial. The rationale, design and primary results of On-TIME II have been previously described [11]. Briefly, enrollment was from June 2006 to November 2007. Eligible patients were aged 21-85 years with symptoms of acute myocardial infarction of more than 30 minutes but less than 24 hours and ST-segment elevation of more than 1 mV in two adjacent electrocardiograph (ECG) leads. Exclusion criteria were severe renal dysfunction (glomerular filtration rate <30 mL/min or serum creatinine >200 mmol/L (>2.5 mg/dL), therapy resistant cardiogenic shock (systolic blood pressure ≤80 mmHg for >30 minutes), persistent severe hypertension (systolic pressure >180 mmHg or diastolic pressure >110 mmHg), or a contraindication to anticoagulation or increased risk of bleeding. Also, patients with a left bundle branch block, pregnant and/or Breast feeding women, and patients with a life expectancy of less than one year were excluded. For the present study, patients with a history of AF were excluded. From each patient, a written informed consent for participation in the On-TIME II study was obtained. The local ethics committees approved the study protocol.

Measurements

NT-proBNP plasma levels were measured in each patient at

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baseline after sheath insertion before PPCI was performed, 24 hours after admission and 72 hours after admission. All plasma samples were analysed using an electrochemiluminiscence immunoassay "ECLIA" (proBNP kit, Roche Diagnostics, Mannheim, Germany) on an Elecsys 2010 analyser. The assay had a measuring range from 0.6 to 4130 pg/ml and a functional sensitivity of <50 pg/ml. Creatine kinase-MB isoenzyme (CK-MB) plasma levels were assessed every 6 hours, until the peak CK-MB was identified.

Treatment

All patients were planned to undergo PPCI and were treated according to the On-TIME II study protocol, randomly assigned to (prehospital) treatment with tirofiban (25 μg/kg bolus and 0.15 μg/kg/min maintenance infusion for 18 hours) or placebo. PPCI was performed with standard techniques if the coronary anatomy was suitable for angioplasty. Additional treatment with stents and devices was to the discretion of the treating cardiologist. All patients were treated with optimal drug-therapy including angiotensin-converting enzyme inhibitors, β-blockers, aspirin and a statin. Final discharge and admission duration was to the discretion of the treating cardiologist, irrespective of NT-proBNP values.

Endpoints

The primary endpoint was the occurrence of AF/atrial flutter/atrial tachycardia >30 seconds, either on a telemetry strip or on a 12-lead ECG, in accordance with European guidelines [12] within 30 days after admission. Patients were on telemetry during the first 48 hours after admission, and an ECG was performed once every 24 hours, or whenever deemed necessary. Whenever a patient experienced symptoms and was not on telemetry, an ECG was performed immediately.

Statistical analysis

Continuous variables were expressed as mean with standard deviation (SD). NT-proBNP plasma values were expressed as mean with SD, range and median value. STEMI patients who developed AF <30 days after admission for PPCI were categorized to the "incident AF" group.: These patients with incident AF were divided among 3 subgroups depending on the timing of the first AF episode. Patients who developed AF <24 hours after admission were categorized to the "AF on admission" subgroup. Patients who developed AF <30 days after admission, but 24-72 hours after admission were additionally categorized to the "AF 24-72 hours after admission" subgroup. Patients who developed AF <30 days after admission but >72 hours after admission were categorized to the "AF >72 hours after admission" subgroup, as displayed in Figure 1. Baseline characteristics were compared with a Mann Whitney U test in case of continuous variables and Chi-squared test in case of dichotomous or categorical data, except for previous CABG and stroke, in which case a Fisher's exact test was used due to the number of cells with a value <5. Mean NT-proBNP values were compared between AF and AF free patients with a Mann Whitney U test. Receiver-operator characteristic (ROC) analysis was performed to determine the area under the curve (AUC) of the 3 NT-proBNP plasma level assessment timings in predicting AF in the 4 groups. ROC curves were compared as described by Hanley and McNeill [13] using Medcalc v13.3.1 (Medcalc Software bvba, Ostend, Belgium). The association between patient characteristics, biomarkers and incident AF was assessed with a binary logistic model, with variables being entered in the model. A multivariate model was created for incident AF and the AF on admission subgroup, with variables with a P-value <0.05 in univariate analysis being eligible to be entered into the model. No multivariate analysis was performed in the AF 24-72 hours after admission and AF >72 hours after admission subgroups due to the limited number of endpoints in these subgroups. Whenever a multivariate model was created, use of study medication was also included in the multivariate model. The difference between patient age in smoking vs. non-smoking patients was assessed with a Mann Whitney U test. Statistical analysis was performed using IBM SPSS statistics version 20 (IBM inc., Armonk, NY, USA). A P-value of ≤0.05 was considered statistically significant.

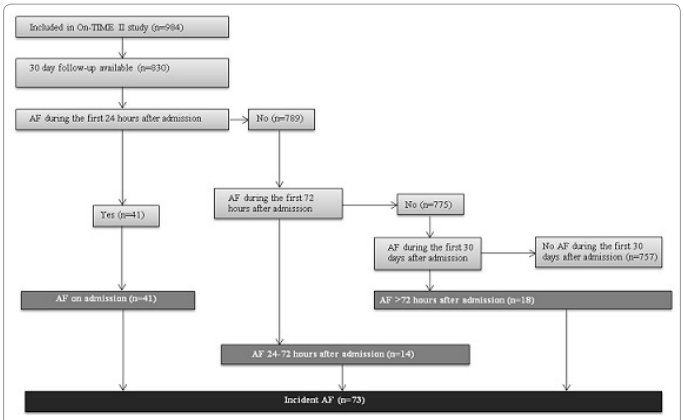

Figure 1: Flow chart of patient categorization into AF subgroups. Patient categorization flow chart. AF: atrial fibrillation; NT-proBNP: N-terminal pro-brain natriuretic peptide.

Results

984 patients were admitted with the diagnosis of STEMI. A total of 861 patients underwent PPCI. Baseline characteristics of the whole study population have been previously reported [11]. 30 day follow-up was present in 830 patients, who were included in the analysis. Baseline characteristics of the study population are displayed in Table 1.

Atrial Fibrillation

73 patients (8.8%) developed AF <30 days after STEMI, of whom 41 developed AF during the first 24 hours after admission, 14 patients developed AF 24-72 hours after admission and 18 patients developed AF >72 hours after admission, as displayed in Figure 1. Patients who developed AF were older (61.5 vs. 68.4 years, P<0.001), less often smokers (49.7% vs. 37.5%), with more often a Killip Class >1 (10.4% vs. 25.0%, P<0.001) and a Thrombolysis In Myocardial Infarction (TIMI) grade flow <3 after PCI (8.3% vs 16.4%, P=0.020), with a higher mean NT-proBNP plasma level at baseline (517 vs. 1339 pg/ml, P<0.001), a higher high sensitive cardiac troponin T (HScTnT) level (0.358 vs. 0.610 pg/ml, P=0.007) and a higher peak CK-MB plasma (207 vs. 303 U/l, P=0.001), as displayed in Table 1. Table 2 displays the NT-proBNP plasma levels at all 3 timings.

Association between NT-Probnp and incident AF

NT-proBNP at baseline was a significant predictor of incident AF (AUC 0.657, P<0.001), as displayed in Table 3. In univariate analysis, age (odds ratio (OR) 1.056, P<0.001), smoking (OR 0.608, P=0.050), Killip class >1 (OR 2.868, P<0.001), TIMI flow post PCI <3 (OR 2.183, P=0.023) and NT-proBNP at baseline (OR 1.128, P=0.010) were associated with incident AF. Of note, current smokers were significantly younger compared to non-smokers (57.2 vs. 66.7 years, P<0.001). Table 4 displays the univariate and multivariate analyses for incident AF. In multivariate analysis, age (adjusted OR 1.058, P<0.001) and Killip class

	Total (n=830)	AF free (n=757)	Incident AF (n=73)	P-value
Age (years)	62.1 (SD 11.6)	61.5 (SD 11.5)	68.4 (SD 10.9)	<0.001
Male gender	631/830 (76.0%)	580/757 (76.6%)	51/73 (69.9%)	0.197
BMI (kg/m²)	26.9 (SD 3.7)	26.9 (SD 3.7)	26.4 (SD 3.5)	0.126
Current smoker	402/827 (48.6%)	375/755 (49.7%)	27/72 (37.5%)	0.048
Diabetes	89/829 (10.2%)	77/756 (10.2%)	12/73 (16.4%)	0.099
Hypertension	276/830 (33.3%)	251/757 (33.2%)	25/73 (34.2%)	0.850
Hypercholesterolaemia	214/829 (25.8%)	195/756 (25.8%)	19/73 (26.0%)	0.965
Killip Class >1	96/821 (11.7%)	78/749 (10.4%)	18/72 (25.0%)	<0.001
Previous MI	68/828 (8.2%)	62/755 (8.2%)	6/73 (8.2%)	0.998
Previous PCI	68/830 (8.2%)	65/757 (8.3%)	5/73 (6.8%)	0.661
Previous CABG	12/830 (1.4%)	11/757 (1.5%)	1/73 (1.4%)	>0.99*
Previous stroke	15/830 (1.8%)	151/757 (2.0%)	0/73 (0%)	0.634*
Systolic BP (mm Hg)	130.9 (SD 24.1)	131.3 (SD 23.8)	126.2 (SD 24.6)	0.143
Diastolic BP (mm Hg)	76.6 (SD 15.0)	76.8 (SD 14.8)	74.3 (SD 16.1)	0.306
Tirofiban study medication	406/830 (48.9%)	369/757 (48.7%)	37/73 (50.7%)	0.752
Culprit Vessl				0.997
Culprit Vessel RCA	390/821 (47.5%)	355/748 (47.5%)	35/73 (47.9%)	
Culprit Vessel LAD	340/821 (41.4%)	310/748 (41.4%)	30/73 (41.1%)	
Culprit Vessel LCx	91/821 (11.1%)	83/748 (11.1%)	8/73 (11.0%)	
TIMI grade flow post PCI <3	74/823 (9.0%)	62/750 (8.3%)	12/73 (16.4%)	0.020
NT-proBNP baseline (pg/ml)	589 (SD 1896)	517 (SD 1490)	1339 (SD 4178)	<0.001
HScTnT (pg/ml)	0.380 (SD 1.27)	0.358 (SD 1.12)	0.610 (SD 2.32)	0.008
Peak CK-MB (U/l)	216 (SD 197)	207 (SD 189)	303 (SD 245)	0.001

Data are presented as mean with their SD between parentheses or fraction with percentages where appropriate. AF: Atrial Fibrillation; BMI: Body Mass Index; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Grafting; BP: Blood Pressure; RCA: Right Coronary Artery; LAD: Left Anterior Descending Artery; LCx: Left Circumflex Artery; TIMI: Thrombolysis in Myocardial Infarction; TIMI: Thrombolysis in Myocardial Infarction; NT-proBNP: N-terminal pro Brain Natriuretic Peptide; HScTnT: High Sensitive Cardiac Troponin T; CK-MB; Creatine Kinase, MB Isoenzyme. P-value between AF free and incident AF patient groups.

Table 1: Baseline characteristics.

		Total	AF free	Not AF free	P-value
NT-proBNP at baseline (n=810)	Mean ± SD	589 (SD 1896) pg/ml	517 (SD 1490) pg/ml	1339 (SD 4178) pg/ml	<0.001
	Range	9-33927 pg/ml	9-19095 pg/ml	27-33927 pg/ml	
	Median	134 pg/ml	124 pg/ml	270 pg/ml	
NT-proBNP after 24 hours (n=652)	Mean ± SD	2150 (SD 2810) pg/ml	1943 (SD 2452) pg/ml	4240 (SD 4735) pg/ml	<0.001
	Range	45-20653 pg/ml	45-20653 pg/ml	312-19497 pg/ml	
	Median	1318 pg/ml	1244 pg/ml	2256 pg/ml	
NT-proBNP after 72 hours (n=544)	Mean ± SD	1797 (SD 4289) pg/ml	1377 (SD 2057) pg/ml	7675 (SD 13568) pg/ml	<0.001
	Range	17-25507 (of 81810) pg/ml	17-25507 pg/ml	214-24119 (of 81810) pg/ml	
	Median	885 pg/ml	809 pg/ml	3224 pg/ml	

Data are presented as mean with their SD between parentheses, range or median. AF: Atrial Fibrillation. NT-proBNP: N-terminal pro-Brain Natriuretic Peptide. P-value between mean NT-proBNP values of AF free and not AF free patients. P-value between mean NT-proBNP values.

Table 2: NT-proBNP levels.

	NT-proBNP at baseline	P-value	NT-proBNP after 24 hours	P-value	NT-proBNP after 72 hours	P-value
Incident AF	0.657 (SE 0.034)	<0.001	N/A		N/A	
AF on admission	0.591 (SE 0.049)	0.058	N/A		N/A	
AF 24-72 hours after admission	0.747 (SE 0.060)	0.002	0.829 (SE 0.045)	<0.001	N/A	
AF >72 hours after admission	0.705 (SE 0.053)	0.003	0.736 (SE 0.061)	0.001	0.891 (SE 0.057)	<0.001

Data are presented as AUC (SE). AF: atrial fibrillation; NT-proBNP: N-terminal pro-brain natriuretic peptide. P-values of AUC.
P-values between AUCs:

AF >24 hours after admission	NT-proBNP at baseline	vs. NT-proBNP after 24 hours:	z-statistic 1.177,	P=0.239
AF >72 hours after admission	NT-proBNP at baseline	vs. NT-proBNP after 24 hours:	z-statistic 3.111,	P=0.002
AF >72 hours after admission	NT-proBNP at baseline	vs. NT-proBNP after 72 hours:	z-statistic 2.779,	P=0.006
AF >72 hours after admission	NT-proBNP after 24 hours	vs. NT-proBNP after 72 hours:	z-statistic 0.495,	P=0.621

Table 3: Receiver-operator characteristic of NT-proBNP in the prediction of atrial fibrillation.

Univariate	P-value	OR	95% CI	Multivariate	P-value	Adjusted OR	95% CI
Age (per year)	<0.001	1.056	1.033-1.081	**Age (per year)**	<0.001	1.058	1.033-1.084
Gender male	0.198	0.707	0.417-1.199	**Killip Class >1**	<0.001	3.253	1.7438-6.089
BMI	0.165	0.950	0.884-1.021	**TIMI flow post PCI <3**	0.2343	1.556	0.741-3.268

Current smoker	0.050	0.608	0.370-1.000	**Tirofiban study medication**	0.768	1.080	0.646-1.807
Diabetes	0.103	1.735	0.895-3.364	**NT-proBNP baseline (per 1000 increase)**	0.162	1.065	0.975-1.164
Hypertension	0.850	1.050	0.633-1.742				
Hypercholesterolaemia	0.965	1.012	0.585-1.750				
Killip Class >1	<0.001	2.868	1.601-5.135				
Previous MI	0.998	1.001	0.417-2.400				
Previous PCI	0.662	0.810	0.315-2.082				
Previous CABG	0.955	0.942	0.120-7.400				
Systolic BP (per 10 mm Hg)	0.111	0.920	0.831-1.019				
Diastolic BP (per 10 mm Hg)	0.202	0.900	0.765-1.058				
Tirofiban study medication	0.752	1.081	0.668-1.747				
Culprit Vessel RCA*	0.956	1.023	0.458-2.286				
Culprit Vessel LAD*	0.992	1.004	0.444-2.272				
TIMI grade flow post PCI <3	0.023	2.183	1.116-4.272				
NT-proBNP baseline (per 1000 increase)	0.010	1.128	1.029-1.236				
HScTnT (per 0.1 increase)	0.135	1.010	0.997-1.024				

AF: atrial fibrillation; BMI: body mass index; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; BP: blood pressure; TIMI: thrombolysis in myocardial infarction; RCA: right coronary artery; LAD: left anterior descending artery; NT-proBNP: N-terminal pro Brain Natriuretic peptide; HScTnT: High sensitive cardiac troponin T; OR: odds ratio; CI: confidence interval. *: as compared to culprit vessel left circumflex artery.

Table 4: Odds ratio and adjusted odds ratio analysis for incident AF.

>1 (adjusted OR 3.253, P<0.001) were significantly associated with incident AF. Of note, in multivariate analysis, NT-proBNP at baseline was not associated with incident AF (OR 1.065, P=0.162).

Association between NT-Probnp and AF on admission

NT-proBNP at baseline did not significantly predict AF on admission (AUC 0.591, P=0.058), as displayed in Table 3. In univariate analysis, only Killip class >1 was significantly associated with AF on admission (OR 2.694, P=0.010). NT-proBNP at baseline was not associated with AF on admission (OR 1.044, P=0.473). In multivariate analysis, only Killip class >1 was significantly associated with AF on admission (adjusted OR 2.784, P=0.008). Table 5 displays the univariate and multivariate analyses for AF on admission.

Association between NT-Probnp and AF 24-72 hours after admission

NT-proBNP at baseline was a significant predictor of AF 24-72 hours after admission (AUC 0.747, P=0.002). NT-proBNP after 24 hours also significantly predicted AF 24-72 hours after admission (AUC 0.829, P<0.001). There was no significant difference in AUC between NT-proBNP at baseline and NT-proBNP after 24 hours (z-statistic 1.177, P=0.239), as displayed in Table 3. In univariate analysis, age (OR 1.117, P<0.001), Killip class >1 (OR 3.341, P=0.045), TIMI grade flow < 3 (OR 4.476, P=0.013), NT-proBNP plasma level at baseline (OR 1.186, P=0.002) and after 24 hours (OR 1.220, P<0.001), HScTnT plasma level (OR 1.027, P=0.001) and peak CK-MB plasma level (OR 1.213, P=0.047) were significantly associated with AF 24-72 hours after admission. Table 6 displays the univariate analysis for AF 24-72 hours after admission.

Association between NT-Probnp and AF >72 hours after admission

NT-proBNP at baseline (AUC 0.705, P=0.003), after 24 hours (AUC 0.736, P=0.001) and after 72 hours (AUC 0.891, P<0.001) significantly predicted AF >72 hours after admission, as displayed in Table 3. NT-proBNP after 24 hours was a significantly stronger predictor of AF >72 hours after admission compared to NT-proBNP at baseline (z-statistic 3.111, P=0.002). Furthermore, NT-proBNP after 72 hours was a significantly stronger predictor of AF >72 hours after admission compared to NT-proBNP at baseline (z-statistic 2.779, P=0.006). There was no significant difference in AUC between NT-proBNP after 24 hours and NT-proBNP after 72 hours in the prediction of AF (z-statistic 0.495, P=0.621), as displayed in Table 3. In univariate analysis, age (OR 1.094, P<0.001), current smoking (OR 0.203, P=0.012), history of diabetes (OR 3.392, P=0.024), previous percutaneous coronary intervention (OR 3.147, P=0.049) NT-proBNP after 24 hours (OR 1.193, P<0.001) and after 72 hours (OR 1.290, P<0.001) and peak CK-MB plasma level (OR 1.230, P=0.014) were significantly associated with AF >72 hours after admission. In univariate analysis, NT-proBNP at baseline was not associated with AF >72 hours after admission (OR 1.070, P=0.539). Of note, current smokers were significantly younger compared to non-smokers (57.0 vs. 66.2 years, P<0.001). Table 7 displays the univariate analysis for AF >72 hours after admission.

Discussion

This study reports the temporal association between serial NT-proBNP plasma level assessments at different timings after admission and the development of AF in the setting of STEMI. Of note, NT-proBNP plasma level at baseline was not associated with incident AF in multivariate analysis and did not predict AF on admission. NT-proBNP at baseline did predict AF 24-72 and >72 hours after admission. However, NT-proBNP plasma level assessment 24 and 72 hours after admission were stronger predictors of AF >72 hours after admission compared to NT-proBNP at baseline.

NT-Probnp and incident AF

The association between NT-proBNP and AF has been previously reported in the general population [14] and previous studies have reported an association between NT-proBNP and incident AF [9,15]. Presumably, the increased LV diastolic pressure that results in an increase of NT-proBNP plasma level also results in an increased atrial stretch, inflammation and myocardial ischemia, which play a key role in the development of AF [16,17]. This study is in accordance with these studies. However, in this study, NT-proBNP assessments were performed at 3 distinct timings.

NT-Probnp at baseline

This study indicates that although NT-proBNP plasma level

Univariate	P-value	OR	95% CI	Multivariate	P-value	Adjusted OR	95% CI
Age (per year)	0.099	1.024	0.996-1.052	**Age (per year)**	0.064	1.027	0.998-1.057
Gender male	0.237	0.664	0.337-1.309	**Killip Class >1**	0.008	2.784	1.310-5.919
BMI	0.182	0.936	0.849-1.032	**Tirofiban study medication**	0.818	1.078	0.568-2.044
Current smoker	0.614	1.178	0.623-2.225				
Diabetes	0.835	0.894	0.311-2.570				
Hypertension	0.120	0.550	0.259-1.169				
Hypercholesterolaemia	0.347	0.685	0.311-1.507				
Killip Class >1	0.010	2.694	1.273-5.702				
Previous MI	0.830	0.877	0.263-2.919				
Previous PCI	0.199	0.269	0.036-1.991				
Previous CABG	0.590	1.768	0.223-14.035				
Systolic BP (per 10 mm Hg)	0.106	0.895	0.782-1.024				
Diastolic BP (per 10 mm Hg)	0.723	0.963	0.780-1.187				
Tirofiban study medication	0.986	0.994	0.531-1.863				
Culprit Vessel RCA*	0.887	0.930	0.339-2.547				
Culprit Vessel LAD*	0.757	0.849	0.303-2.384				
TIMI grade flow post PCI <3	0.070	2.197	0.938-5.146				
NT-proBNP baseline (per 1000 increase)	0.473	1.044	0.928-1.174				
HScTnT (per 0.1 increase)	0.556	0.988	0.949-1.029				

AF: Atrial Fibrillation; BMI: Body Mass Index; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Grafting; BP: Blood Pressure; TIMI: Thrombolysis in Myocardial Infarction; RCA: Right Coronary Artery; LAD: Left Anterior Descending Artery; NT-proBNP: N-terminal pro Brain Natriuretic Peptide; HScTnT: High Sensitive Cardiac Troponin T; OR: Odds Ratio; CI: Confidence Interval. *: as compared to culprit vessel left circumflex artery.

Table 5: Odds ratio and adjusted odds ratio analysis for AF on admission.

Univariate	P-value	OR	95% CI
Age (per year)	<0.001	1.117	1.050-1.188
Gender male	0.287	0.548	0.182-1.657
BMI	0.287	0.916	0.778-1.077
Current smoker	0.055	0.285	0.079-1.030
Diabetes	0.208	2.302	0.629-8.419
Hypertension	0.206	1.981	0.687– 5.707
Hypercholesterolaemia	0.686	0.767	0.212-2.777
Killip Class >1	0.045	3.341	1.025– 10.895
Previous MI	0.878	0.852	0.110-6.619
Systolic BP (per 10 mm Hg)	0.702	1.044	0.839-1.298
Diastolic BP (per 10 mm Hg)	0.317	0.827	0.570-1.199
Tirofiban study medication	0.324	0.575	0.191-1.730
Culprit Vessel RCA*	0.756	1.401	0.166-11.792
Culprit Vessel LAD*	0.558	1.877	0.228-15.465
TIMI grade flow post PCI <3	0.013	4.476	1.365-14.682
NT-proBNP baseline (per 1000 increase)	0.002	1.186	1.063-1.324
NT-proBNP 24 hr (per 1000 increase)	<0.001	1.220	1.112-1.340
HScTnT (per 0.1 increase)	0.001	1.027	1.011-1.043
Peak CK-MB (per 100 increase)	0.047	1.213	1.003-1.467

AF: Atrial Fibrillation; BMI: Body Mass Index; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Grafting; BP: Blood Pressure; TIMI: Thrombolysis in Myocardial Infarction; RCA: Right Coronary Artery; LAD: Left Anterior Descending Artery; NT-proBNP: N-terminal pro Brain Natriuretic Peptide; HScTnT: High Sensitive Cardiac Troponin T; OR: Odds Ratio; CI: Confidence Interval. *: as compared to culprit vessel left circumflex artery.

Table 6: Odds ratio analysis for AF 24-72 hr after admission.

Univariate	P-value	OR	95% CI
Age (per year)	<0.001	1.094	1.041-1.150
Gender male	0.909	1.068	0.347-3.286
BMI	0.941	1.005	0.885-1.141
Current smoker	0.012	0.203	0.058-0.706
Diabetes	0.024	3.392	1.177-9.770
Hypertension	0.142	2.016	0.790-5.141
Hypercholesterolaemia	0.083	2.302	0.896-5.915
Killip Class >1	0.121	2.458	0.789-7.652
Previous MI	0.661	1.397	0.314-6.217
Previous PCI	0.049	3.147	1.006-9.848
Systolic BP (per 10 mm Hg)	0.262	0.891	0.728-1.090
Diastolic BP (per 10 mm Hg)	0.256	0.832	0.606-1.143
Tirofiban study medication	0.141	2.103	0.781-5.661
Culprit Vessel RCA*	0.949	1.052	0.223-4.960
Culprit Vessel LAD*	0.936	0.937	0.191-4.595
TIMI grade flow post PCI <3	0.681	0.653	0.085-4.987
NT-proBNP baseline (per 1000 increase)	0.539	1.070	0.862-1.329
NT-proBNP 24 hr (per 1000 increase)	<0.001	1.193	1.088-1.308
NT-proBNP 72 hr (per 1000 increase)	<0.001	1.290	1.151-1.447
HScTnT (per 0.1 increase)	0.513	0.970	0.884-1.063
Peak CK-MB (per 100 increase)	0.014	1.230	1.044-1.450

AF: Atrial Fibrillation; BMI: Body Mass Index; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Grafting; BP: Blood Pressure; TIMI: Thrombolysis in Myocardial Infarction; RCA: Right Coronary Artery; LAD: Left Anterior Descending Artery; NT-proBNP: N-terminal Pro Brain Natriuretic Peptide; HScTnT: High Sensitive Cardiac Troponin T; OR: Odds Ratio; CI: Confidence Interval. *: as compared to culprit vessel left circumflex artery.

Table 7: Odds ratio analysis for AF >72 hr after admission.

assessment at baseline is a significant predictor of AF, the accuracy is only 0.657. However, in multivariate analysis, NT-proBNP at baseline was not associated with incident AF. Furthermore, NT-proBNP at baseline was not associated with AF on admission. The incidence of AF is thought to be influenced by atrial pressure, and thus heart failure. NT-proBNP levels substantially rise in a semi-acute fashion in acute heart failure. Possibly, the baseline assessment of NT-proBNP does not reflect the acutely elevated atrial pressure and clinical manifestations of heart failure at that moment. Furthermore, other factors such as the time to hospital admission and differences in the PPCI procedure may induce heterogeneity in patients, reducing the overall predictive value of NT-proBNP.

Incident AF after STEMI and HScTnT

In-hospital incident AF after STEMI has been associated with an increased left ventricular diastolic dysfunction, atrial oxidative

stress and end diastolic pressure, which may increase atrial stretch and atrial pressure [16,18,19]. Furthermore, atrial dysfunction, atrial ischemia, pericarditis, congestive heart failure due to ischemia, atrial reverse remodeling and enhanced sympathetic tone may also play an important role in AF in the setting of STEMI [20-24]. An increased sympathetic tone in STEMI patients is associated with worse outcome after 2 years [25]. Incident AF is associated with a higher rate of death, re-infarction, cardiogenic shock and ventricular arrhythmias, and therefore, identification of potentially high risk patients is important [5,6]. In accordance with previous studies in the healthy population [26] and in STEMI patients, [9] age has a strong association with the development of new-onset AF. Of note, previous studies did not report an association between HScTnT and AF [9]. Although incident AF was not associated with HScTnT in univariate analysis in our present analysis, AF >24 hours after admission was significantly associated with HScTnT plasma level. Since HScTnT was assessed during the first 72 hours after admission in the literature, perhaps an analysis with strict serial HScTnT assessment timings and peak HScTnT assessment may elucidate this association.

Implications on current clinical practice

This study changes the perspective on the association between NT-proBNP and AF in STEMI patients since NT-proBNP at baseline is a weak predictor of AF, and was not associated with AF in multivariate analysis. This suggests that the predictive characteristics of NT-proBNP plasma level assessment may alter in the days after admission, resulting in the observation that NT-proBNP 24 and 72 hours after admission were stronger predictors of AF. Therefore, NT-proBNP assessed 24 hours or 72 hours after admission, and not NT-proBNP at baseline, could serve as biomarker in assessing risk of incident AF in STEMI patients treated with PPCI.

Limitations

Current study is a substudy of the On-TIME II study and therefore, a predefined power assessment was not made for the relation of NT-proBNP and incident AF, and multivariate analysis in the AF 24-72 hours and >72 hours after admission subgroups could not be performed. Therefore, this study did not determine if the association between NT-proBNP and AF was independent for other variables, such as infarction size and Killip Class. Although all variables were prospectively registered, the present study is a post-hoc cross-sectional analysis. All patients were kept on telemetry for at least 48 hours, but thereafter, an ECG was performed once daily. This may have caused several AF episodes not to have been documented, and therefore have influenced the outcome of this study.Furthermore, analysis was limited to those having complete data sets.

Conclusion

This study shows that serial NT-proBNP plasma levels, especially determined 24 to 72 hours after admission, may help to enhance risk stratification of patients at risk of developing incident AF in the setting of STEMI. Baseline values of NT-proBNP did not predict AF on admission in the present study.

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Impact on Daily Practice

Biomarkers are used as predictors of low-risk patients. The present study shows that NT-proBNP at baseline has predictive value in assessing high-risk patients, but is surpassed by NT-proBNP plasma level assessments after 24 h and 72 h. These results suggest that serial assessment of NT-proBNP is indicated in STEMI patients to identify high-risk patients.

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