Baseline NT-proBNP and biomarkers of inflammation and necrosis in patients with ST-segment elevation myocardial infarction: insights from the APEX-AMI trial

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Abstract Coronary plaque rupture is associated with a systemic inflammatory response. The relationship between baseline N-terminal pro B-type natriuretic peptide (NT-proBNP), a prognostic marker in patients with acute coronary syndromes, and systemic inflammatory mediators in patients with ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI) is not well described. Of 5,745 STEMI patients treated with primary PCI in the APEX-AMI trial, we evaluated the relationship between baseline NT-proBNP levels and baseline levels of inflammatory markers and markers of myonecrosis in a subset of 772 who were enrolled in a biomarker substudy. Spearman correlations (r_s) were calculated between baseline NT-proBNP levels and a panel of ten systemic inflammatory biomarkers. Interleukin (IL)-6, a pro-inflammatory cytokine, was significantly positively correlated with NT-proBNP ($r_s = 0.317$, $P < 0.001$). In a sensitivity analysis excluding all heart failure patients, the correlation between baseline IL-6 and NT-proBNP remained significant ($n = 651$, $r_s = 0.296$, $P < 0.001$). A positive association was also observed with high sensitivity C-reactive protein ($r_s = 0.377$, $P < 0.001$) and there was a weak negative correlation with the anti-inflammatory cytokine IL-10 ($r_s = -0.109$, $P = 0.003$). No other significant correlations were observed among the other testes inflammatory cytokines and chemokines. In STEMI patients undergoing primary PCI, the pro-inflammatory cytokine IL-6 was modestly correlated with baseline NT-proBNP levels. This relationship remained significant in patients without heart failure. This finding is consistent with pre-clinical and clinical research suggesting that systemic inflammation may influence NT-proBNP expression independently of myocardial stretch.

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Introduction

B-type natriuretic peptide (BNP) is an important prognostic biomarker in patients with acute coronary syndrome (ACS) [1–4]. N-terminal pro B-type natriuretic peptide (NT-proBNP) and markers of myocardial cell necrosis add prognostic value to established risk prediction scores [5, 6]. In non ST-segment elevation myocardial infarction (NSTEMI) baseline NT-proBNP values have been shown to correlate with troponin T; however, little is known about its relationship with markers of myocardial necrosis in the ST-elevation myocardial infarction (STEMI) population treated with primary percutaneous coronary intervention (PCI) [7].

There is emerging evidence that coronary plaque rupture triggers both a pro- and anti-inflammatory cytokine response [8–13]. BNP expression is commonly thought to result from myocardial stretch; however, it may also be regulated by systemic inflammatory mediators [14]. In preclinical studies, the pro-inflammatory cytokines interleukin (IL)-1β, IL-6, and tumor necrosis factor alpha (TNFα) all stimulated cardiocyte BNP expression [15–17]. Further, BNP can be elevated in the presence of normal cardiac function in inflammatory conditions, such as sepsis and burns [18, 19]. IL-10, an anti-inflammatory cytokine, can transiently rise in ACS [20]. BNP has been shown to increase IL-10 release in vitro, suggesting that BNP can stimulate an anti-inflammatory response; however, this relationship has not been established in vivo [21]. Although, BNP and both pro- and anti-inflammatory mediators can be elevated after plaque rupture, the relationship between baseline N-terminal pro-brain natriuretic peptide (NT-proBNP) and baseline inflammatory biomarkers in STEMI patients treated with primary PCI is not well described.

The purpose of this study was to describe the relationship between baseline NT-proBNP and inflammatory serum biomarkers in STEMI patients treated with primary PCI. Additionally, the relationship between NT-proBNP with markers of cell necrosis, time to revascularization, and sum ST-segment deviation were also explored.

Methods

The assessment of pexelizumab in acute myocardial infarction (APEX-AMI) trial was a multicenter, double blind, placebo-controlled, randomized clinical trial comparing pexelizumab versus placebo in 5,745 STEMI patients undergoing primary (PCI) [22, 23]. Patients over the age of 18 were eligible if they presented for primary PCI within 6 h of symptom onset with high-risk electrocardiographic features. Treatment groups were pooled for this analysis since no treatment effect on outcomes was observed.

The study population for our analyzes comprised of a subset of patients presenting to an APEX-AMI biomarker study center and consented to provide blood samples for future biomarker research. Blood samples were drawn in participating patients after randomization, but prior study drug administration and PCI [24]. Samples were allowed to clot, then centrifuged and the resultant serum frozen to −20°C then to −70°C the following day (if available). Samples were bulk shipped on dry ice to a central collection facility (Duke Center for Human Genetics, Durham, NC, USA) then to a central laboratory (Montreal Heart Institute, Montreal, Quebec, Canada) for batched biomarker analysis.

N-terminal pro B-type natriuretic peptide was measured using electrochemiluminescence immunoassay with Elecsys instrument and reagent kit (Roche Diagnostics, Indianapolis, IN). The analytical range was 5–35,000 pg/ml with an inter and intra-assay variability of 4–8%, respectively [25]. The remaining ten biomarkers measured in up to 772 patients were: the acute phase reactant high sensitivity C-reactive protein (hsCRP), pro-inflammatory cytokines (IL-1β, Il-6, IL-12), anti-inflammatory cytokines [IL-1 receptor antagonist (IL-1ra), IL-4, and IL-10], chemokines interferon gamma (IFNγ) and interferon inducible protein 10 (IP-10). These were measured using phase sandwich ELISA tests, cytometric beads assays, multiple fluorescent beads assays, and immunonephelometry.

Baseline markers of myocardial cell necrosis [creatinine kinase (CK), CK-MB, troponin I] were drawn after prior to study drug administration and analyzed at APEX-AMI study centers. The method for measuring sum ST-segment deviation (Σ STD) has been previously described [26]. Briefly, blinded central electrocardiogram evaluation took place at two core laboratories (Canadian VIGOUR Centre, Edmonton, Canada; Duke Clinical Research Institute, Durham, NC). Σ STD was calculated by adding the sums of ST-segment elevation and reciprocal depression.

Statistical analysis

Categorical variables are reported using frequencies and counts and continuous variables are represented as medians (25th, 75th percentiles). Testing of differences between those in the biomarker substudy and those who were not, used the Wilcoxon rank-sum test for continuous variables and the χ^2 test for categorical variables.

Statistical dependence between variables was tested with the Spearman rank correlation test (r_s). Since NT-proBNP is

elevated in heart failure, a clinical and a hemodynamic sensitivity analysis were performed on the correlation between NT-proBNP and IL-6 [27]. In the first analysis, patients with either a history of heart failure and those who developed clinical heart failure within 90 days of the index STEMI presentation were excluded. In the second, the correlation was controlled for patients with a left ventricular end diastolic pressure or pulmonary capillary wedge pressure >16 mmHg at the time of PCI [28]. Analyzes were performed with SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

Study population

Baseline patient characteristics of the 772 patient included in this analysis are presented in Table 1. Compared with the overall trial population, the substudy population had a higher percentage of female patients, were more likely to be older, hypertensive, have prior coronary artery disease, stroke, a chronic inflammatory condition, and have a smoking history. Patients enrolled in the biomarker substudy tended to be sicker with more anterior infarctions, higher Killip class, lower blood pressure at hospital presentation, and higher baseline creatinine.

NT-proBNP and inflammatory biomarkers

Table 2 shows the correlations between baseline inflammatory marker levels and quartiles of baseline NT-proBNP. There was significant positive correlation between hsCRP and NT-proBNP [Spearman correlation $(r_s) = 0.377, P < 0.001$]. Among all pro-inflammatory cytokines and chemokines, only IL-6 had a moderate significant positive correlation with NT-proBNP $(r_s = 0.317, P < 0.001)$. No significant correlations were observed with either IL-1β or TNFα. There was a weak negative correlation between NT-proBNP and the anti-inflammatory cytokine IL-10 $(r_s = -0.109, P = 0.003)$. The relationship between NT-proBNP quartiles and IL-6, IL-10, and hsCRP is shown in Fig. 1.

In a sensitivity analysis excluding all patients with a history of heart failure $(n = 29)$ and those who developed heart failure within 90 days of study enrolment $(n = 92)$, the correlation between baseline IL-6 and NT-proBNP remained significant $(r_s = 0.296, P < 0.001)$. In a second sensitivity analysis controlling for left ventricular end diastolic pressure or pulmonary capillary wedge pressures recorded at the time of PCI, the relationship remained significant $(r_s = 0.184, P < 0.001)$ in the subset of patients in whom data was available $(n = 315)$.

NT-proBNP correlation with markers of myocardial necrosis and time from symptom onset

The relationship between baseline markers of myocardial cell necrosis and baseline NT-proBNP are presented in Table 3. Total CK $(r_s = 0.113, P = 0.011)$ was weakly positively correlated with baseline NT-proBNP levels, while moderate positive correlations were observed with CK-MB $(r_s = 0.338, P < 0.001)$ and troponin I $(r_s = 0.420, P < 0.001)$.

Weak positive correlations with symptom onset to randomization time $(r_s = 0.275, P < 0.001)$ and symptom onset to presentation time $(r_s = 0.197, P < 0.001)$ were observed. There was no significant correlation with Σ STD $(r_s = -0.071, P = 0.051)$.

Discussion

This analysis from a contemporary international trial of STEMI patients undergoing primary PCI has three main findings that build upon pre-existing biomarker knowledge. First, although pre-clinical studies have reported that lL-1β, IL-6, and TNFα can stimulate BNP expression, IL-6 was the only cytokine with a modest positive correlation with baseline NT-proBNP levels [15–17]. Importantly, the relationship remained significant after excluding patients with clinical heart failure and after controlling for elevated filling pressures. Secondly, the small inverse relationship between NT-proBNP and IL-10 suggests there is not a clinically meaningful correlation between NT-proBNP and anti-inflammatory cytokine activation in ACSs. Finally, baseline NT-proBNP levels were only moderately correlated with baseline CK-MB and troponin I levels.

Coronary plaque rupture triggers an inflammatory cascade [8–12]. Three pro-inflammatory cytokines have been reported to stimulate BNP release. In separate studies using rat myocytes, Tanaka et al. [16] and Kuwahara et al. [17] showed that IL-6 stimulates BNP expression, while a study by Ma et al. [15] showed that IL-1β and TNFα stimulate BNP mRNA expression. In the present analysis, IL-6 was the only pro-inflammatory cytokine IL-6 with a significant positive correlation with NT-proBNP, though the association was only of modest strength. Importantly, this relationship remained significant after excluding patients with a history of heart failure and those who developed clinical heart failure. This is notable given the established relationship between NT-proBNP and clinical heart failure and elevated filling pressures [27]. This latter sensitivity analysis should be interpreted with caution given that less than half of the study patients had filling pressures measured. This observation supports the hypothesis that, in addition to release in response to myocardial stretch, BNP expression

Table 1 Selected baseline characteristics in overall trial and biomarker substudy populations

	Entire APEX population (n = 5743)	Not in substudy (n = 4971)	Biomarker substudy (n = 772)[a]	P value[b]
Age, median (25th, 75th %tile), years	61 (52, 71)	61 (52, 97)	65 (56, 76)	<0.01
Women, n (%)	1,325 (23.1)	1,116 (22.5)	209 (27.1)	<0.01
Body mass index, median (25th, 75th %tile), kg/m²	27.1 (24.5, 30.1)	27.0 (24.5, 30.1)	27.2 (24.2, 30.1)	0.97
Clinical history				
Hypertension, n (%)	2,838 (49.4)	2,429 (48.9)	409 (53.0)	0.03
Diabetes mellitus, n (%)	912 (15.9)	785 (15.8)	127 (16.5)	0.64
Dyslipidemia, n (%)	2,180 (49.7)	1,859 (49.7)	321 (49.7)	1.00
Prior coronary artery disease, n (%)	942 (16.4)	790 (15.9)	152 (19.7)	0.01
Prior MI, n (%)	694 (12.1)	574 (11.6)	120 (15.5)	<0.01
Prior PCI, n (%)	562 (9.8)	460 (9.3)	102 (13.2)	<0.01
Prior CABG, n (%)	128 (2.2)	107 (2.2)	21 (2.7)	0.32
Prior CHF, n (%)	207 (3.6)	178 (3.6)	29 (3.8)	0.81
Prior AF, n (%)	238 (4.1)	196 (3.9)	42 (5.4)	0.05
Prior stroke, n (%)	216 (3.8)	177 (3.6)	39 (5.1)	0.04
COPD, n (%)	282 (4.9)	233 (4.7)	49 (6.3)	0.05
Past or current smoker, n (%)	3,822 (66.6)	3,345 (67.5)	477 (61.9)	<0.01
Peripheral vascular disease, n (%)	246 (4.3)	205 (4.1)	41 (5.3)	0.13
Chronic inflammatory condition, n (%)	103 (1.8)	5 (3.6)	30 (3.9)	<0.01
Presenting characteristics				
Heart rate, median (25th, 75th %tile), beats/min	75 (65, 86)	75 (65, 86)	76 (65, 88)	0.06
Systolic blood pressure, median (25th, 75th %tile), mm Hg	133 (117, 150)	133 (118, 150)	130 (114, 148)	<0.01
Diastolic blood pressure, median (25th, 75th %tile), mmHg	80 (70, 90)	80 (70, 90)	78 (66, 89)	<0.01
Killip class > I, n (%)	610 (10.6)	479 (9.6)	131 (17.0)	<0.01
High-risk inferior (ECG), n (%)	2346 (40.8)	2094 (42.1)	252 (32.6)	<0.01
Sum ST-segment deviation, median (25th, 75th %tile), mm	13.0 (9.0, 18.5)	13.0 (9.0, 18.5)	12.5 (9.0, 19.0)	0.68
Symptom onset to randomization, median (25th, 75th %tile), h	2.8 (2.0, 4.0)	2.8 (2.0, 4.0)	2.7 (1.9, 3.7)	0.01
Baseline CK-MB median (25th, 75th %tile), µg/l	4.7 (2.2, 15.0)	6.7 (2.9, 21.9)	2.3 (5.3, 18.0)	0.039
Baseline CK median (25th, 75th %tile), µg/l	143 (90, 278)	144 (91, 278)	137 (83, 283)	0.43
Baseline troponin I median (25th, 75th %tile), µg/l	0.20 (0.07, 1.0)	0.2 (0.1, 1.0)	0.17 (0.08, 0.88)	0.64
Creatinine, median (25th, 75th %tile), µmol/l	89 (80, 106)	88 (79, 106)	97 (80, 115)	<0.01
Region, n (%)				<0.01
Australia and New Zealand	558 (9.7)	496 (9.6)	82 (10.6)	
Eastern Europe	1,336 (23.3)	1,312 (26.4)	24 (3.1)	
Western Europe	1,764 (30.7)	1,668 (33.6)	96 (12.4)	
North America	2,085 (36.3)	1,515 (30.5)	570 (73.8)	

AF atrial fibrillation, bpm beats per minute, CABG coronary artery bypass grafting, CHF congestive heart failure, COPD chronic obstructive pulmonary disease, ECG electrocardiogram, CK creatine kinase, min minute, n number, MI myocardial infarction, PCI percutaneous coronary intervention, ULN upper limit of normal

[a] Due to missing data, not all rows represent 100% of the substudy population

[b] P value for comparison between excluded patients and those in the biomarker substudy

may, in part, also be regulated by systemic inflammatory mediators [14].

The hypothesis that cytokines can stimulate BNP release has not been well studied in humans with ACS, but evidence supporting this postulate exists. BNP rises have been reported during temporary coronary artery occlusion when cardiac filling pressures have remained unchanged [29]. Studies of critically ill septic and burn patients with normal echocardiograms have reported elevated BNP levels [18, 19]. These studies did not include measurements of inflammatory cytokines, but the results are supportive of the hypothesis given that the study patients' had conditions

Table 2 Correlation between baseline NT-proBNP quartiles and baseline inflammatory biomarkers levels

	NT-proBNP quartile (ng/ml)				P value	Spearman correlation
	1 (<66)	2 (66–207)	3 (208–796)	4 (>796)		
hsCRP, median (25th, 75th %tile), mg/l	2.3 (1.1, 5.6)	2.4 (1.3, 6.2)	4.0 (1.7, 8.4)	8.6 (3.8, 26.2)	<0.001	0.377
IL-1β, median (25th, 75th %tile), pg/ml	8.5 (7.0, 9.9)	8.4 (7.0, 9.5)	8.3 (7.0, 9.5)	8.0 (6.2, 9.3)	0.084	0.062
Il-4, median (25th, 75th %tile), pg/ml	6.8 (6.0, 7.7)	6.7 (5.9, 7.9)	6.8 (5.6, 7.8)	6.7 (5.5, 7.6)	0.206	0.046
Il-6, median (25th, 75th %tile), pg/ml	12.3 (10.1, 15.5)	13.3 (10.9, 17.8)	14.3 (11.1, 19.7)	18.8 (11.1, 19.7)	<0.001	0.317
Il-10, median (25th, 75th %tile), pg/ml	8.3 (4.7, 14.5)	8.1 (4.5, 15.7)	6.8 (3.7, 14.4)	5.4 (3.2, 13.4)	0.003	−0.109
IL-12, median (25th, 75th %tile), pg/ml	8.1 (6.4, 10.6)	8.1 (6.1, 10.6)	7.7 (5.9, 11.0)	7.3 (5.7, 10.0)	0.052	−0.070
IL-1ra, median (25th, 75th %tile), pg/ml	218 (147, 348)	216 (142, 347)	206 (140, 350)	217 (158, 456)	0.116	0.057
IFNγ, median (25th, 75th %tile), pg/ml	124 (98, 143)	123 (102, 146)	126 (99, 151)	122 (93, 147)	0.436	0.028
IP-10, median (25th, 75th %tile), pg/ml	818 (503, 1,234)	841 (520, 1,286)	802 (525, 1,238)	873 (513, 1,290)	0.484	0.025
TNFα, median (25th, 75th %tile), pg/ml	66.5 (54.5, 74.4)	65.5 (55.9, 73.7)	64.9 (54.3, 74.1)	64.5 (52.2, 74.2)	0.689	−0.014
WBC, median (25th, 75th %tile), ×10^9/l	10.9 (8.6, 14.4)	10.4 (8.4, 13.4)	10.4 (8.6, 13.5)	10.6 (8.6, 13.1)	0.820	0.008

hsCRP high sensitivity C-reactive protein, *IFNδ*, interferon gamma, *IL* interleukin, *IL-1ra* IL-1 receptor antagonist, *IP-10* interferon inducible protein 10, *TNFα* tumor necrosis factor alpha, *WBC* white blood cell count

Fig. 1 Interleukin-6, interleukin-10, and C-reactive protein levels stratified by NT-pro-brain natriuretic peptide quartiles
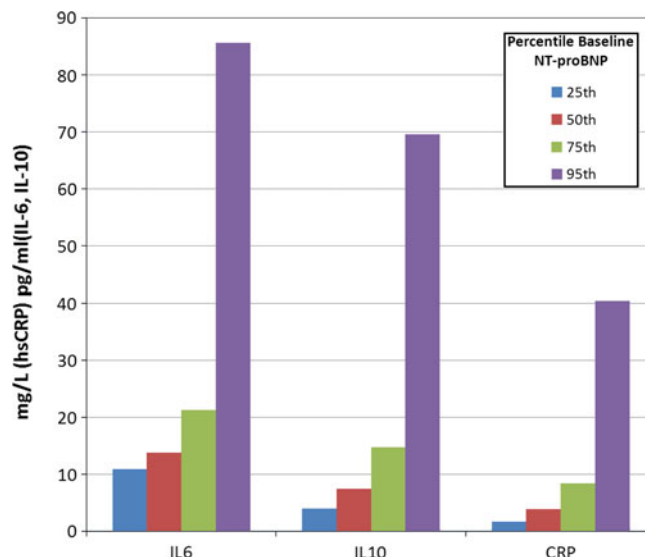
Table 3 Correlation between NT-proBNP quartiles and markers of myocardial necrosis

Baseline biomarkers	NT-proBNP quartile (ng/ml)				P value	Spearman correlation
	1 (<66)	2 (66–207)	3 (208–796)	4 (>796)		
CK, median (25th, 75th %tile), μg/l	137 (80, 215)	141 (92, 276)	141 (92, 276)	121 (75, 249)	0.011	0.113
CK-MB, median (25th, 75th %tile), ug/l	3.3 (1.8, 6.2)	5.0 (2.0, 16.0)	5.3 (2.5, 11.3)	16.8 (4.6, 49.0)	<0.001	0.338
TnI, median (25th, 75th %tile), μg/l	0.1 (0.0, 0.3)	0.1 (0.1, 0.4)	0.2 (0.1, 0.6)	1.2 (0.1, 7.9)	<0.001	0.420
Σ STD, median (25th, 75th %tile), mm	13.5 (9.5, 20.0)	12.5 (9.0, 17.5)	12.5 (8.0, 18.5)	12.5 (8.0, 18.5)	0.051	−0.071

CK creatinine kinase, *Σ STD* sum ST-segment deviation, *TnI* troponin I

with a known systemic inflammatory response. Additionally, IL-6 and BNP levels were correlated in 15 unstable angina patients in a single center study; however, the study did not sample baseline values. Our study is the largest to report a significant positive correlation between baseline NT-proBNP and IL-6 in the STEMI population in the

contemporary era. The moderate correlation supports pre-clinical studies where IL-6 has been shown to stimulated NT-pro BNP expression although we cannot infer causation from this study as other possible pathophysiologic mechanisms exist. In addition to plaque rupture, myocardial stretch may also stimulate IL-6 expression [30]. This explanation would be consistent with the observation that both IL-6 and BNP are elevated in heart failure patients [31, 32]. Future studies should be directed at elucidating the potentially complex interaction between myocardial stretch, IL-6 and NT-proBNP synthesis.

IL-10 is an anti-inflammatory cytokine that promotes coronary plaque stability by inhibiting macrophage function, suppressing cytokines production, and inhibiting of metalloproteinases [33, 34]. Relatively low levels of IL-10 are thought to be a risk for coronary plaque rupture, yet levels can also transiently rise in some patients following an ACS [20, 35]. Pre-clinical studies showed that BNP stimulates macrophage IL-10 expression leading to the hypothesis that BNP may induce an anti-inflammatory cytokine response [21]. The small inverse relationship between NT-proBNP and IL-10 observed in this study suggests that the transient rise in IL-10 levels during the acute phase of ACS is not likely due to NT-proBNP. This result is consistent with animal and human studies showing that IL-10 is decreased in heart failure following acute myocardial infarction [36, 37]. Heeschen et al. [20] have shown that found elevated IL-10 levels at the time of hospital discharge were associated with lower mortality. Given the contrasting outcomes associated with elevated levels it of NT-proBNP and IL-10, it appears unlikely that there is a clinically significant correlation between these biomarkers.

Both BNP and markers of myocardial necrosis have been shown to improve baseline clinical prognostication in STEMI patients, but less is known about the relationship between these biomarkers in STEMI patients [6]. Moderate correlations between baseline BNP and troponin were reported in STEMI patients and in a single center series of 126 STEMI patients undergoing primary PCI [7, 38]. Additionally, correlations between peak CK-MB and BNP levels have been have been described previously, whereas similar correlations have not been reported for baseline levels [39]. The present study re-affirms the previously observed correlations former study's findings in an international population and to our knowledge, this is the first study show a modest correlation with between baseline NT-proBNP and CK-MB in STEMI patients treated with primary PCI.

Limitations

Limitations of this APEX-AMI biomarker analysis warrant consideration. First, measures of left ventricular end diastolic pressure (LVEDP) and left ventricular ejection fraction were not routinely collected. A sensitivity analysis using clinical heart failure as reflection of elevated LVEDP was performed; however, subclinical heart failure cannot be excluded. Second, BNP levels are inversely related to glomerular filtration rate and this study did not exclude patients with renal failure; however, the median creatinine in this study was within the normal range [40]. Lastly, these analyzes should be considered hypothesis-generating, and they have not been validated in an independent data set.

Conclusions

In cohort of contemporary STEMI patients treated with primary PCI, the pro-inflammatory cytokine IL-6 was modestly correlated with baseline NT-proBNP levels. This relationship remained significant after excluding patients with clinical heart failure and after controlling for elevated filling pressures. These findings support pre-clinical and clinical studies that suggest that BNP may be expressed in response to systemic inflammatory stimuli. Additionally, the small inverse relationship between NT-proBNP and IL-10 suggests that a clinically relevant correlation between NT-proBNP and anti-inflammatory cytokine activation in ACS is unlikely. Finally, moderate correlations were observed between baseline NT-proBNP and CK-MB and troponin I levels. Future research should be directed at elucidating the potentially complex relationships between pro-inflammatory cytokines and BNP expression while controlling for measures of myocardial stretch and exploring how these relationships impact clinical outcomes.

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