

# Apelin in ST segment elevation and non-ST segment elevation acute coronary syndromes: a novel finding

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## Abstract

**Background:** Apelin is a novel endogenous peptide with inotropic and vasodilatory properties.

**Aim:** To investigate the role of apelin in the prognosis of acute coronary syndromes (ACS) and to assess the relationship between apelin and other diagnostic and prognostic markers.

**Methods:** Seventy-six patients with ACS (mean age  $62.1 \pm 10$  years) were evaluated in terms of their plasma apelin-36 concentrations, ejection fraction (EF), high sensitivity C-reactive protein (hsCRP), creatine kinase (CK), CK-MB and troponin I levels. The study group consisted of 35 ST elevation myocardial infarction (STEMI) and 41 non-ST elevation (NSTEMI) ACS patients. Patients were followed up for one year for cardiovascular outcomes.

**Results:** There was no significant relationship between apelin and TIMI, GRACE, GENSINI scores, hsCRP and EF in STEMI and NSTEMI-ACS groups ( $p > 0.05$ ). Apelin showed positive correlations with CK, CK-MB and troponin I in patients with NSTEMI-ACS, but a negative correlation in patients with STEMI ( $p < 0.05$ ). There were no statistically significant differences between patients reaching the composite end point at one year with regard to apelin levels.

**Conclusions:** Apelin was positively correlated with cardiac biomarkers in patients with NSTEMI-ACS but negatively correlated in patients with STEMI. In STEMI, generally larger amounts of myocardial cells are subjected to infarction compared to NSTEMI-ACS, which may explain why apelin levels decrease with increasing CK, CK-MB and troponin levels in STEMI patients.

**Key words:** acute coronary syndrome, apelin, prognosis, troponin

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## INTRODUCTION

Apelin is the only known ligand for human orphan G-protein-coupled (APJ) receptor and is synthesised as a pre-pro-peptide consisting of 77 amino acids. Its shorter forms, including the one with 36 amino acids encoded in the COOH-terminal region (apelin-36), are known to be biologically active [1–3]. Apelin mRNA expression has been found in the gastrointestinal tract, adipose tissue, brain, lung, kidney, liver, skeletal muscle, and cardiovascular system. In the cardiovascular system, it has been detected in endothelial cells of large conduit arteries, coronary vessels, and endocardium of

the right atrium [4]. Apelin has been shown to be a powerful inotrope [2] and a vasodilator, dilating intact vessels using an endothelial nitric oxide-dependent pathway [3–6]. Since its discovery, the apelin–APJ system has emerged as an important regulator of cardiovascular homeostasis that may play a role in the pathophysiology of various cardiac diseases and represents an exciting target for the development of new therapies.

Apelin is largely produced and released from intact coronary endothelium and myocardial cells of the heart. Current studies suggest that apelin expression is at least maintained and possibly augmented in mild, compensated chronic heart

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failure but declines in severe disease [7]. To date, *in vivo* studies have demonstrated an up-regulation of APJ gene expression in response to ischaemia [8]. The apelin-APJ system may be involved in myocardial protection during acute myocardial ischaemia. It is not yet known if apelin may be useful as a marker of prognosis in acute myocardial infarction. The aims of this study were to investigate the role of apelin in the prognosis of acute coronary syndromes (ACS) and to assess the relationship between apelin and other prognostic and diagnostic markers.

## METHODS

### Study population

Seventy-six patients (54 men, mean age  $61.5 \pm 10.3$  years and 22 women, mean age  $63.6 \pm 10.9$  years), who had been admitted to the coronary care unit with a first time diagnosis of ACS ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction, and unstable angina pectoris (NSTEMI-ACS), were included in the study. The definition of ACS was made according to the 2012 'Third universal definition of myocardial infarction' expert consensus document and all patients with myocardial necrosis had type I myocardial infarction [9]. The exclusion criteria were: rheumatic heart disease, valvular heart disease, thyroid dysfunction, atrial fibrillation, malignancy and age  $\geq 80$ . Eligible patients were between 18 and 80 years of age and able to provide written informed consent, which was a prerequisite for enrollment. The study complied with the Declaration of Helsinki and the trial protocol was approved by the local Ethics Committee of Istanbul University (12/01/2010-C-004).

### Study protocol

Patients were divided into two sub-groups, STEMI and NSTEMI-ACS, and they were followed up for one year for cardiovascular outcomes including a composite end point (CEP) consisting of life threatening arrhythmias, re-hospitalisation for ACS, re-infarction, need for revascularisation, stroke, acute heart failure and all-cause and cardiovascular mortality. The patients were further divided into sub-groups depending on left ventricular ejection fraction (LVEF) as preserved (LVEF  $\geq 40\%$ ) and low LVEF ( $< 40\%$ ) for the comparison of apelin levels.

All patients were given standard therapy for ACS on admission which consisted of 300 mg acetylsalicylic acid, 300 mg (600 mg in STEMI patients undergoing primary percutaneous coronary intervention [PCI]) clopidogrel, an angiotensin converting enzyme inhibitor, a beta-blocker, a statin and low molecular weight heparin (enoxaparin). Patients with STEMI also were treated with either fibrinolytic agent alteplase or PCI. Patients with NSTEMI-ACS underwent coronary angiography as clinically indicated and PCI was performed in eligible cases. Glycoprotein IIb/IIIa inhibitors (tirofiban), unfractionated heparin, and nitrates were used according to attending physicians' discretion.

All patients underwent trans-thoracic echocardiographic examination (Vivid 3; General Electric, Milwaukee, WI, USA) to evaluate LVEF. Patients with ACS were hospitalised in the coronary care unit and underwent coronary angiography in the absence of any contra-indications. Coronary artery disease severity was assessed with the number of significantly narrowed vessels (left main coronary artery  $\geq 50\%$ ; other coronary arteries  $\geq 70\%$ ) and the Gensini score.

### Blood analyses

Apelin levels were studied using sera collected within 48 h ( $35 \pm 10$ ) of admission. Lipid parameters and fasting plasma glucose were assessed after an overnight fast. Creatinine and high sensitivity C-reactive protein (hsCRP) levels were also studied in the same samples. Cardiac biomarkers including creatinine kinase (CK), creatinine kinase-MB (CK-MB) and troponin I were assessed at admission, and six, 12, 24 and 48 h after hospitalisation and peak values were recorded. Apelin-36 levels were measured using an enzyme immunoassay (ELISA) (Phoenix Pharmaceuticals, Inc., Burlingame, CA, USA) according to the manufacturer's instructions. To measure apelin, serum was separated from the blood by centrifugation at 3,000 rpm for 10 min and kept frozen at  $-80^\circ\text{C}$  until analysis. Inter and intra-assay coefficients of variance were 5–10% and  $< 15\%$ , respectively. Minimal detectable limit of apelin was 0.09 ng/mL. Glomerular filtration rate (GFR) for each patient was calculated using the measured plasma creatinine levels and the Cockcroft-Gault formula for the estimation of renal function.

### Statistical analysis

The values were expressed as mean  $\pm$  standard deviation. We used Pearson's test in order to investigate the correlations between apelin levels and clinical and biochemical parameters. Differences of continuous variables and categorical variables between STEMI and NSTEMI groups were assessed using the independent samples Student t or Mann Whitney U test. Associations between categorical variables were evaluated using the  $\chi^2$  or Fisher's Exact tests. In order to compare quartiles of plasma apelin and hsCRP levels with other parameters, we used the ANOVA or Kruskal-Wallis tests. Multivariate Cox regression models were used to examine the relationships between apelin levels and the CEP at one year. A p value  $< 0.05$  was considered to be statistically significant. All statistical analyses were performed using SPSS version 16 (SPSS for Windows, Version 16.0., SPSS Inc., Chicago, IL, USA).

## RESULTS

Seventy-six patients with ACS were enrolled. There were 35 (46%) patients with STEMI and 41 (54%) patients with NSTEMI-ACS (39 non STEMI and two unstable angina patients). Baseline characteristics and cardiovascular risk factors of the

patients are given in Table 1. Body mass index (BMI) was significantly higher in the NSTEMI-ACS group compared to STEMI ( $p < 0.05$ ) patients. There were more hypertensive and diabetic patients in the NSTEMI-ACS group ( $p < 0.05$ ). All the patients had CCS III–IV angina. In the patient group, there were no cases with liver and lung disease but 13.2% of patients had chronic renal disease in our study.

When the STEMI and NSTEMI-ACS groups were compared in terms of medications used during hospitalisation, no significant difference was found. Thrombolytic therapy was given to 12 (34%) patients in the STEMI group, who also underwent coronary angiography 3–24 h after administration of tissue plasminogen activator. Coronary angiography was performed in 30 patients (86%) in the STEMI group and 32 (78%) patients in the NSTEMI-ACS group. When the PCI rate in the STEMI group was compared to that of the NSTEMI-ACS group, more

patients in the STEMI group were found to have undergone PCI [21 (70%) patients vs. eight (25%) patients, respectively;  $p < 0.0001$ ]. When coronary artery by-pass grafting rates between STEMI and NSTEMI-ACS patients were compared, no significant difference was found [eight (27%) patients vs. eight (25%) patients, respectively].

We compared STEMI and NSTEMI-ACS groups according to the presence of various risk predictors. In the STEMI group, cardiac markers ( $p < 0.001$ ), Gensini score ( $p = 0.026$ ), and hsCRP ( $p = 0.04$ ) were significantly higher compared to the NSTEMI-ACS group. LVEF was significantly lower ( $p = 0.001$ ) in the STEMI group compared to the NSTEMI-ACS group. There were no statistically significant differences between groups with respect to the TIMI scores and mean apelin ( $p = 0.54$ ) levels, but apelin tended to be lower in the STEMI group.

We also divided STEMI and NSTEMI-ACS patients into two groups according to their LVEF as preserved LVEF ( $\geq 40\%$ ) and low LVEF ( $< 40\%$ ) groups. There was no significant difference between preserved and reduced LVEF patients in the STEMI group with respect to mean apelin levels. There was also no significant difference between preserved and reduced LVEF patients in the NSTEMI-ACS group with regard to mean apelin levels.

We found statistically significant correlations between apelin levels and all cardiac markers (CK, CK-MB, troponin I) in both STEMI and NSTEMI-ACS groups (Table 2). Interestingly, in the NSTEMI-ACS group this correlation was positive, but in the STEMI group it was vice versa (Fig. 1A–C). We could not demonstrate any significant correlations between serum apelin levels and risk predictors such as TIMI, GRACE, hsCRP, and GENSINI scores. The patients were divided into quartiles according to their apelin levels. The groups were compared in terms of TIMI, GRACE scores and hsCRP levels, but no significant differences were found. The patients were also divided into quartiles according to their hsCRP levels. When the groups were compared in terms of TIMI, GRACE scores and apelin levels, no significant differences were found.

We did not find any significant correlations between apelin levels and age and BMI. Also, no significant correlations between apelin levels and clinical variables such as heart rate, systolic and diastolic blood pressure, as well as between apelin and biochemical measurements such as

**Table 1.** Baseline characteristics and cardiovascular risk factors of the patient groups

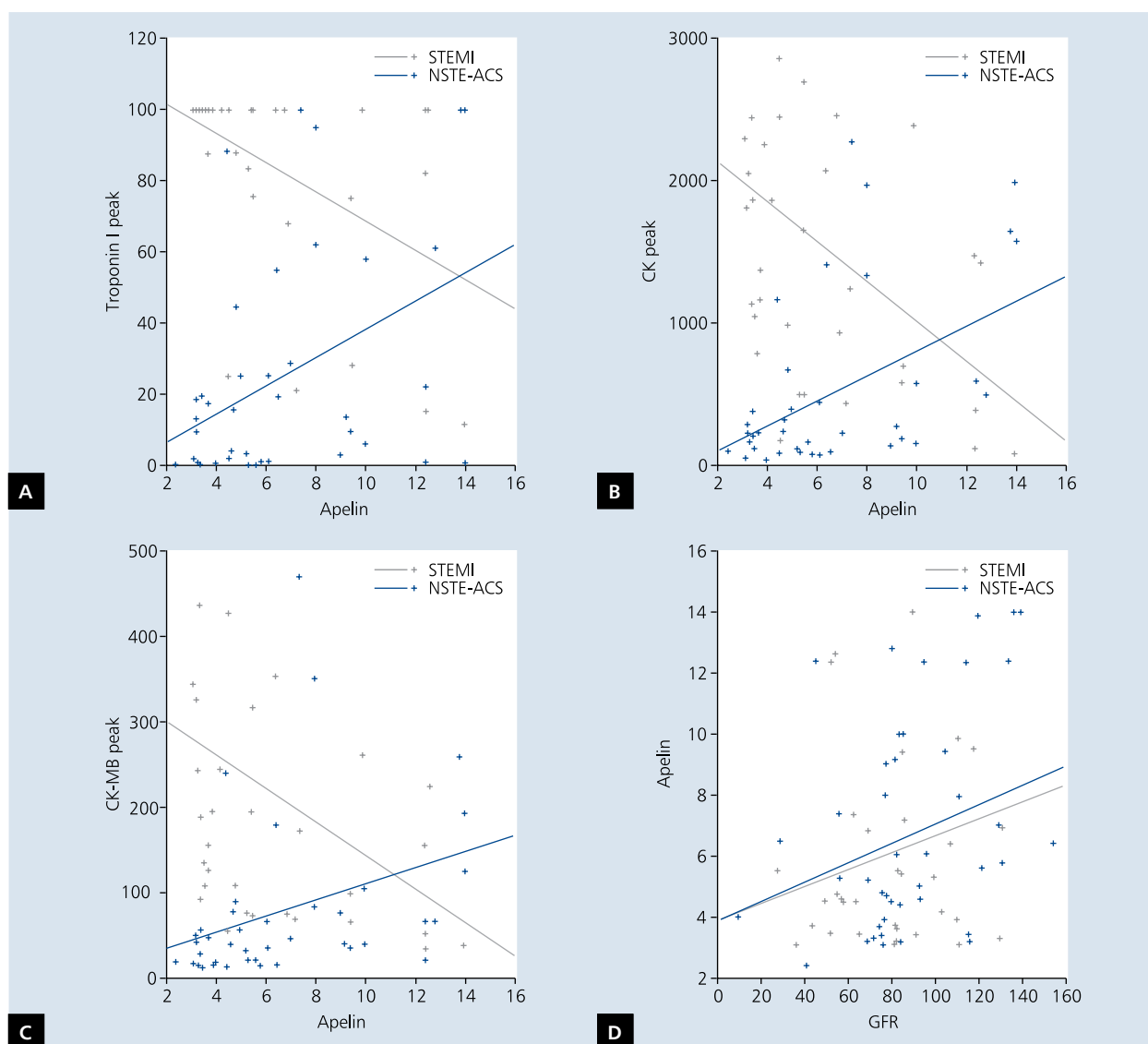
	STEMI	NSTEMI-ACS	P
Number of patients	35 (46%)	41 (54%)	
Age [years]	63 ± 11	62 ± 10	> 0.05
Body mass index [kg/m <sup>2</sup> ]	26 ± 3	28 ± 5	< 0.05*
Pulse [bpm]	83 ± 15	80 ± 26	0.05
Pulse pressure [mm Hg]	51 ± 16	60 ± 21	> 0.05
LDL-C [mg/dL]	117 ± 39	113 ± 38	> 0.05
Triglycerides [mg/dL]	138 ± 58	166 ± 87	> 0.05
HDL-C [mg/dL]	36 ± 9	36 ± 10	> 0.05
Fasting glucose [mg/dL]	134 ± 57	133 ± 47	0.892
Hypertension	17 (49%)	29 (71%)	< 0.05*
Diabetes mellitus	9 (26%)	21 (51%)	< 0.05*
Hyperlipidaemia	10 (29%)	14 (34%)	> 0.05
Smoking	20 (57%)	28 (68%)	> 0.05
Family history	14 (40%)	17 (41%)	> 0.05
Chronic renal failure	6 (17%)	4 (9.8%)	> 0.05
LVEF [%]	41 ± 10	49 ± 11	0.001*

\*Statistically significant; HDL-C — high density lipoprotein cholesterol; LDL-C — low density lipoprotein cholesterol; LVEF — left ventricular ejection fraction; NSTEMI-ACS — non ST segment elevation acute coronary syndrome; STEMI — ST segment elevation myocardial infarction

**Table 2.** Correlation of apelin and cardiac biomarkers

	NSTEMI-ACS group		STEMI group	
	r	p	r	p
Creatinine kinase peak	0.484	0.001*	-0.460	0.005*
Creatinine kinase-MB peak	0.333	0.033*	-0.395	0.019*
Troponin peak	0.421	0.006*	-0.491	0.003*

\*Statistically significant; NSTEMI-ACS — non ST segment elevation acute coronary syndrome; STEMI — ST segment elevation myocardial infarction



**Figure 1.** **A.** Correlation between apelin and troponin I peak in ST segment elevation myocardial infarction (STEMI) and non ST segment elevation acute coronary syndrome (NSTEMI-ACS) groups; **B.** Correlation between apelin and creatine kinase (CK) peak in STEMI and NSTEMI-ACS groups; **C.** Correlation between apelin and CK-MB peak in STEMI and NSTEMI-ACS groups; **D.** Correlation between apelin levels and glomerular filtration rate (GFR) in STEMI and NSTEMI-ACS groups

total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, or triglycerides could be demonstrated. When the relation between estimated GFR values and apelin levels was studied, a significant correlation was found in patients with NSTEMI-ACS ( $r = 0.33$ ,  $p = 0.037$ ), but not in the STEMI group ( $r = 0.23$ ,  $p = 0.185$ ) (Fig. 1D). Out of 16 patients with chronic renal failure, 13 (81.25%) patients were hypertensive. Among ten cases with chronic renal failure in the STEMI group, seven patients were hypertensive, whereas all six patients with chronic renal failure in the NSTEMI-ACS group had hypertension.

Mean apelin levels were investigated with respect to the presence of hypertension and diabetes in both the pa-

tient groups. There was no significant difference in apelin levels in hypertensive patients compared to patients without hypertension, although there was a trend for lower apelin levels in hypertensives ( $p = 0.065$ ). There was no significant difference in apelin levels in diabetic patients compared to non-diabetics. When the same analyses were carried out in STEMI and NSTEMI-ACS groups, again no significant difference was found in mean apelin levels with respect to the presence of hypertension or diabetes.

When clinical end points were investigated, there were four cardiovascular deaths, 13 cases with life threatening arrhythmias, 14 cases with re-infarction, 14 cases with acute heart failure, 22 cases with re-hospitalisation for heart failure,

12 cases with the need for revascularisation, and four cases with stroke. Multivariate Cox regression models were used to examine the relationships between apelin levels and the clinical end points. When adjusted for age and sex, apelin level determined during initial hospitalisation for myocardial infarction could not predict CEP at one year.

When investigated clinical end points were considered, no significant differences in mean apelin levels were observed between patients reaching CEP and the rest of the cases. Furthermore, when each end point was individually investigated in terms of mean apelin levels, we did not find any significant differences.

In summary, apelin levels were positively correlated with markers of cardiac injury in NSTEMI-ACS patients and negatively correlated in STEMI patients. Mean apelin levels were similar between the STEMI and NSTEMI-ACS groups. Apelin levels were not correlated with traditional risk predictors in ACS, and apelin could not independently predict CEP at one year.

## DISCUSSION

Apelin, the endogenous ligand for the G-protein-coupled APJ receptor, is emerging as a key hormone in cardiovascular homeostasis. The biological roles of apelin in atherosclerotic diseases are recently being explored. Hypertension and diabetes are important risk factors for coronary artery disease and were present in a significant portion of our patient group. Apelin's physiological effect of lowering blood pressure after intravenous injection into rats had been demonstrated. In that study, Tatemoto et al. [3] suggested that apelin lowers blood pressure through a nitric oxide mechanism. Zhang et al. [10] suggested that the improving effect of exercise training on hypertension could be mediated by upregulating the cardiovascular apelin/APJ system. Apelin levels were found to be decreased in patients with masked hypertension, a finding suggested as carrying a potential for prognostic significance in terms of cardiovascular events [11]. Apelin levels were found to be lowered in cases with essential hypertension, too [12]. In our study, we did not find any significant relation between apelin level and admission systolic, diastolic and pulse pressure in patients with ACS. Although apelin levels tended to be lower in ACS patients with hypertension, this finding was not statistically significant.

The relationship between apelin levels and diabetes seems to be more complicated. Soriguer et al. [13] investigated apelin levels in morbidly obese patients and demonstrated that they were significantly elevated only in diabetic cases. In another study, apelin levels were demonstrated to be increased in type 2 diabetes patients along with increased mRNA expression for apelin in omentum and subcutaneous adipose tissue [14]. Apelin levels were also shown to be increased in obese patients with hyperinsulinaemia and in type 2 diabetes patients with long term therapy [15, 16]. On the other hand, apelin levels were demonstrated to be decreased

in newly diagnosed and untreated cases with type 2 diabetes [17]. We were unable to demonstrate any association between presence of diabetes, fasting plasma glucose levels and mean apelin levels in patients with ACS.

Apelin was investigated for its role in ischaemic heart disease in several studies. Simpkin et al. [18] were the first to provide evidence that apelin had a cardioprotective effect against reperfusion injury. When apelin was administered during reperfusion, reduction of the infarct size was observed.

In previous studies carried out in chronic renal failure patients on haemodialysis [19], and in renal transplant recipients [20], apelin was demonstrated to be lower in patients with concomitant stable coronary artery disease. In our study, a significant correlation was found between GFR and apelin levels in patients with NSTEMI-ACS but not in the STEMI group. The reasons behind the association of cardiac and renal function with apelin are not clear [20], however, our study, which is carried out in the setting of ACS, demonstrates for the first time the presence of such a relation beyond stable coronary artery disease patients. Since more than 80% of the cases with chronic renal failure had hypertension, we cannot rule out the impact of hypertension on the association between GFR and apelin levels.

The mean level of apelin in plasma was found to be significantly lower in subjects with stable angina compared to controls. In addition, plasma apelin correlated negatively with the Gensini score, which reflected the severity of coronary artery stenosis [21], an association which we could not demonstrate in patients with ACS. It is unclear whether apelin may be used as a marker of injury and prognosis in acute myocardial infarction. Weir et al. [22] showed that plasma apelin concentration is reduced early after acute myocardial infarction, increases significantly over time, but remains depressed at 24 weeks. In the KOZANI study, unstable angina and acute myocardial infarction groups had even lower apelin levels on admission compared to the asymptomatic coronary artery disease group. Apelin was shown to have an inverse relationship with the incidence of ACS and Gensini score independent of other cardiovascular risk factors [23]. Recently, significant reductions were found in apelin concentrations measured five days after primary PCI in STEMI patients. There were no significant differences found in apelin concentrations between patients with normal and low LVEF. In the same study, there was no difference in baseline apelin concentration in the group of patients who reached CEP compared to those without CEP [24]. In a similar study by Tycinska et al. [25], a significant decrease in apelin concentrations measured after five days of primary PCI for STEMI was found although apelin was not predictive of CEP.

The aim of this study was to investigate whether apelin was able to predict prognosis in patients with ACS. We did not find any significant relation between apelin levels and CEP at one year, just like the aforementioned studies

investigating the prognostic value of apelin in ACS [24, 25]. We could not find any relation between apelin levels with regard to gender and LVEF. There were also no relationships between apelin levels on admission and prognostic indicators like hsCRP, LVEF, GRACE and GENSINI scores. On the other hand, we have demonstrated that cardiac markers such as CK, CK-MB and troponin I had significant correlations with apelin levels. NSTEMI-ACS group's apelin and CK, CK-MB, troponin I levels were correlated positively. However it was vice versa in the STEMI group. To the best of our knowledge, such a correlation has been shown for the first time in medical literature. Apelin is largely produced and released from intact coronary endothelium and myocardial cells of the heart, so apelin production is reduced in myocardial infarction as a consequence of myocardial and coronary endothelial loss. In STEMI, generally larger amounts of myocardial cells are subjected to infarction compared to NSTEMI-ACS, which may explain why apelin levels decrease with increasing CK, CK-MB and troponin I levels in STEMI patients. In NSTEMI-ACS patients, more myocardial cells are subjected to ischaemia with lower amounts of infarction. Since apelin may be increased in cases of ischaemia for protection of the heart, smaller increases in cardiac markers may be seen together with increased apelin levels. We suggest that these correlations may be related to the quantity of live cells and extension of ischaemia.

#### Limitations of the study

The limitations of this study include the relatively small number of patients, short follow-up duration, and low number of encountered clinical end points. Since apelin levels were measured only once during hospitalisation for myocardial infarction, we could not evaluate changes in apelin concentrations in response to treatment due to lack of serial measurements. The lack of assessment of correlation between apelin levels and functional status in ACS patients is another limitation.

#### CONCLUSIONS

Prognostic score systems such as TIMI, GRACE and GENSINI which are used in ACS and inflammatory markers such as hsCRP showed no relationship with apelin levels. We did not find apelin to be a useful prognostic marker in ACS, after a follow-up period of one year. Nevertheless, the role of apelin as a prognostic marker in this setting requires further studies with a larger group of patients. Interestingly, we found that apelin was positively correlated with cardiac biomarkers in patients with NSTEMI-ACS but negatively correlated in patients with STEMI. In STEMI, generally larger amounts of myocardial cells are subjected to infarction compared to NSTEMI-ACS, which may explain why apelin levels decrease with increasing CK, CK-MB and troponin I levels in STEMI patients.

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## Stężenie apeliny u chorych z ostrymi zespołami wieńcowymi z uniesieniem odcinka ST i bez uniesienia odcinka ST: nowe dane

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### Streszczenie

**Wstęp:** Apelina jest nowym endogennym peptydem o działaniu inotropowym dodatnim i wazodylatacyjnym.

**Cel:** Celem badania były ocena rokowniczego znaczenia apeliny u pacjentów z ostrym zespołem wieńcowym (ACS) i określenie zależności między stężeniem apeliny oraz innymi wskaźnikami diagnostycznymi i prognostycznymi.

**Metody:** U 76 chorych z ACS (średnia wieku 62,1 ± 10 lat) wykonano badania w celu oceny stężenia apeliny-36 w osoczu, frakcji wyrzutowej (EF) oraz stężeń białka C-reaktywnego mierzonego metodą wysokoczułą (hsCRP), kinazy kreatynowej (CK), CK-MB i troponiny I. Badana grupa składała się z 35 chorych z zawałem serca z uniesieniem odcinka ST (STEMI) i 41 chorych z ACS bez uniesienia odcinka ST (NSTEMI-ACS). Chorych obserwowano przez rok pod kątem zdarzeń sercowo-naczyniowych.

**Wyniki:** Ani w grupie STEMI, ani w grupie NSTEMI-ACS nie stwierdzono istotnych zależności między stężeniem apeliny a punktacją w skalach TIMI, GRACE i GENSINI, stężeniem hsCRP oraz EF ( $p > 0,05$ ). U pacjentów z NSTEMI-ACS wykazano dodatnią korelację między stężeniem apeliny a stężeniami CK, CK-MB i troponiny I, natomiast u pacjentów ze STEMI korelacja ta była ujemna ( $p < 0,05$ ). Po roku nie stwierdzono istotnych statystycznie różnic pod względem stężenia apeliny między pacjentami, u których wystąpił złożony punkt końcowy.

**Wnioski:** Apelina korelowała dodatnio z biomarkerami sercowymi u osób z NSTEMI-ACS, jednak u pacjentów ze STEMI korelacja ta była ujemna. U chorych ze STEMI martwicy ulega na ogół większa liczba komórek miokardium niż w przypadku NSTEMI-ACS, co może tłumaczyć redukcję stężenia apeliny przy zwiększonych stężeniach CK, CK-MB i troponin u pacjentów ze STEMI.

**Słowa kluczowe:** ostry zespół wieńcowy, apelina, rokowanie, troponina

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