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Serum corin is reduced and predicts adverse outcome in non-ST-elevation acute coronary syndrome

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Abstract

Background and objectives: The aim of the current study was to describe the role of corin, an enzyme that cleaves pro-atrial natriuretic peptide and pro-brain natriuretic peptide into their active peptides, in patients with acute coronary syndrome (ACS).

Methods: Serum corin level was studied in patients with non-ST-elevation ACS who underwent percutaneous coronary intervention (n=152) and in control volunteers (n=103).

Results: The corin level was lower in acute coronary syndrome patients (798±288 pg/ml) than in the controls (1165±613 pg/ml, p<0.0001). Those acute coronary syndrome patients who developed major adverse cardiovascular events (MACE; 60.9%) within 3 years of discharge had lower corin levels than the patients who did not experience major adverse cardiovascular events (698.16±233.67 vs. 952.1±297.81 pg/ml, p<0.0001). Using a multiple logistic regression model, corin level was a significant predictor of post-ACS MACE: p=0.0004 for 50 pg/ml steps, AUC 0.791, while p<0.0001, and AUC 0.804 using corin and brain natriuretic peptide as predictors.

Conclusions: Patients with non-ST-elevation ACS have lower serum corin levels than controls. Corin levels are lower in ACS patients who later experience MACE and thus might be predictor for MACE. This new putative biomarker may be useful, either alone or in combination with other biomarkers, for cardiovascular risk stratification assessment and outcome prediction in ACS patients.

Keywords

Acute coronary syndrome, brain natriuretic peptide, cardiovascular biomarker, corin

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Introduction

Cardiovascular diseases are the highest-incidence cause of death and morbidity in the general population.[1] Acute coronary syndrome (ACS) is a complex syndrome with heterogeneous etiology. New biomarkers that reflect the diverse pathobiology of acute ischaemic heart disease have emerged and are being investigated for use as noninvasive means to gain insight into the underlying causes and consequences of ACS.[1,2] The primary goals of therapy for patients with ACS are to reduce cardiovascular complications and prevent major adverse cardiac events (MACE), including death, non-fatal myocardial infarction (MI), and the need for urgent revascularization. A good biomarker should be sensitive and specific for the target disease and provide both diagnostic and prognostic information.

Brain natriuretic peptide (BNP) and pro-BNP are established cardiac biomarkers. The natriuretic peptides protect the cardiovascular system[3] and secreted into the circulation in inactive forms. Their levels increases predominantly in response to increased myocardial wall stress[4] and are used mainly to establish the diagnosis and predict the outcome

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of heart failure.[5] The role of BNP in unstable ACS per se (in the absence of heart failure, i.e. unstable angina, non-ST-elevation or ST-elevation MI) is well established.[6–8,9]

Corin is a type-II transmembrane serine protease that is highly expressed in both endothelial and myocardial cells in the heart.[10–12] Corin, furin, and meprin cleave pro-atrial natriuretic peptide (ANP) and pro-BNP into their active forms (ANP and BNP).[13] Corin is potentially involved in hypertension and cardiac hypertrophy[14] as well as in heart failure.[15–17] The corin level has been found to be markedly influenced by gender, being lower in females than in males[18–21] (as BNP level has been shown to depend on testosterone and age)[22–24] and in patients with heart failure.

We have recently established an enzyme-linked immunoabsorbent assay for the measurement of corin in human blood.[18] This can be achieved by the shedding and autocleavage of corin. As Jiang et al.[10] showed, corin shedding and autocleavage are closely correlated with activation, as it was low in heart failure.[10,20,21,25] This assay may facilitate the introduction of corin into clinical use. Corin protein and enzymatic activity have been determined in normal human circulation to be 195–2451 pg/ml (with coefficient of variation of 5.7%).[18] One step forward in the attempt to determine the clinical relevance of circulating corin levels was achieved by showing that patients with heart failure manifest reduced corin levels.[19–21]

The purpose of this study was to further investigate the potential role of corin as a cardiac biomarker in ACS and to improve our treatment of ACS patients undergoing percutaneous coronary intervention (PCI) by: (1) measuring the serum corin levels in patients with ACS in comparison with those of control; and (2) comparing corin levels in ACS patients with and without MACE after PCI.

Methods

Study participants

Two groups were included in the study: 152 ACS patients that were enrolled non-consecutively, who were admitted to the Cardiovascular Institute of the Baruch Padeh Medical Center, Poriya. The second group consisted of 103 control subjects recruited from healthy Poriya hospital staff volunteers with a very low prevalence of cardiovascular risk factors and who showed no clinical evidence of cardiovascular disease from the initial measurement through the 3-year follow up. We compared a smaller group of patients (n=83) aged 55.1±5.7 years to a smaller group of controls (n=60) aged 53.9±6.1 years (no difference between the ages, p=0.7).

The study protocol and the consent form were approved by the Institutional Review Board of the Baruch Padeh Medical Center, Poriya.

Inclusion criteria

Patients were admitted during an acute episode of non-ST-elevation ACS. The diagnosis was established on the basis of ischaemic chest pain, dynamic ST-T changes, transient ST-depression or T-wave changes, and/or elevated plasma troponin level. Coronary angiography was performed within 72 hours of admission demonstrating more than 70% stenosis. The creatinine level was <1.5 mg/dl. Signed informed consent was obtained. A limitation of this study was that patients were enrolled non-consecutively.

Exclusion criteria

Patients with non-significant coronary artery disease were excluded. Also excluded were patients with heart failure, defined by shortness of breath with evidence of pulmonary congestion on chest radiographs, prominent jugular veins or ankle oedema, or left ventricular ejection fraction <45%. ST-elevation MI patients with any ST-elevation during acute hospitalization were similarly excluded, as were patients with chronic renal failure (creatinine >1.5 mg/dl), or patients unable to give informed consent.

Patient definitions

The two populations were followed up at regular clinic visits or via telephone calls. Information about MACE (defined as non-fatal myocardial infarction, death, coronary revascularization, stroke, or unstable angina) was obtained for up to 3 years following discharge.

Patients were diagnosed with diabetes mellitus if they were treated with an oral hypoglycaemic agent or insulin. Hypertension and hyperlipidaemia were diagnosed if the patient had been previously diagnosed with such. Heavy smoking was defined as self-reported smoking of more than 10 cigarettes a day. Anaemia was diagnosed when the haemoglobin level was <12 g/dl in males or <11 g/dl in females.

Blood sample collection

Serum corin and BNP levels were measured in the control group at the subjects' convenience. Repeat measurements were obtained for corin in 69 individuals 4–6 years after the initial measurement. Blood samples for measurement of corin and BNP were collected from all ACS patients within 24 hours of acute admission (immediately before PCI). Blood samples for measurement of troponin were obtained both immediately upon admission and 6–10 hours later. The highest level measured was used for the analysis. Repeat measurements of corin and BNP were later performed in 86 patients when in a clinically stable condition, 4–6 years after the acute index episode.

Serum corin level

A 5-ml volume of blood was drawn from the antecubital vein into a non-gel plastic vacuum serum collection tube.

Table 1. Baseline characteristics of control and acute coronary syndrome patients.

	Control (*n*=103)	ACS (*n*=152)	*p*-value
Males (*n*, %)	51 (49.5)	120 (78.95)	<0.0001 (χ^2)
Age (years)	51.66±13.15 (31–95)	61.62±10.5 (40–92)	<0.0001
Blood pressure (mmHg)	123/75±14/8	140/77±24/12	Systole <0.0001, diastole 0.27
Hypertension	1	70.8	
Hyperlipidaemia	11	68.5	
Diabetes	0	43.42	
Anaemia	0	16.45	
Troponin I positive	–	42.76	
Current heavy smokers	21.74	21.71	0.99 (χ^2)
Corin (pg/ml)	195–2451	291–1941	
eGFR (ml/min/1.73 m^2)	–	91.9±25.7	

Values are mean±SD, range, or %.
EGFR, estimated glomerular filtration rate.

The samples were centrifuged at room temperature at 3000 rpm for 15 min within 1 hour of being drawn. The serum was stored at −30°C until analysis. The serum corin level was measured by enzyme-linked immunoabsorbent assay as previously described[18] (R&D Systems, Minneapolis, MN, USA). Normal range was 296–2451 pg/ml, mean 1165 pg/ml, coefficient of variation (CV) 5.7% inter-assay and 3.7% for intra-assay, minimum value 7.9 pg/ml, and maximum 5800 pg/ml.[18]

BNP measurements

Blood was collected in tubes containing EDTA plastic collection tubes. The plasma supernatant was stored at −30°C until analysis. Plasma BNP was measured by a microparticle enzyme immunoassay using the AxSYM system (Abbott Laboratories, Abbott Park, IL, USA) detecting the BNP-32 peptide with no cross-reactivity with atrial natriuretic peptide, C-type natriuretic peptide, or N-terminal pro-BNP. The intra- and inter-assay CV is 6.3–4.3% within runs. According to Abbott, the BNP reference for healthy patients is <100 pg/ml in 91.5%, with the 95th percentile = 135 pg/ml.

Troponin-I measurements

Troponin-I was measured in ACS patients. At least 6 hours after the index event, venous blood was drawn into lithium heparin-containing plastic tubes and troponin-I levels measured using the chemiluminescent immunometric Immulyte 2000 assay (Diagnostic Products, Los Angeles, CA, USA). Troponin-I assay was designed to have a precision ≤10% total CV with 95% confidence for concentrations from 0.27 to 4 ng/ml. The sensitivity limit of troponin-I is 0.02 ng/ml at the 95% level of confidence up to 22.78 ng/ml. The sensitivity is 0.02 ng/ml at the 95% level of confidence. There was no cross reactivity with troponin C or T. The 99th percentile of the normal population is at 0.04 ng/ml. The cut-off value on admission was 0.2 ng/ml to establish the diagnosis of non-ST-elevation ACS (according to laboratory standard reference range).

Statistical analysis

The data was analysed using SAS version 9.1 (SAS Institute, Cary, NC, USA). $p<0.05$ was considered significant. Continuous variables were reported as mean±SD or median (interquartile range). Between-group comparisons were performed using the T-test for normally distributed data (i.e. age/corin), the Wilcoxon rank–sum test for non-parametric data (i.e. BNP), and Satterthwaite's test for data with unequal variances (control group vs. patient group). Categorical data were reported as the number (%) and compared using the χ^2 test. The Spearman correlation was used to test the correlation between BNP and corin; Pearson correlation coefficients were used to test the correlations between corin and age and between corin and blood pressure. Logistic regression analysis was used for the MACE predictions. Linear regression analysis was used to determine the corin predictions.

Results

Control volunteers

The baseline characteristics of the 103 control subjects are presented in Table 1 and their corin and BNP results are presented in Table 2. There was no correlation between the corin level and the BNP level ($p=0.5$, $n=69$) or blood pressure ($p=0.81$ for systolic; $p=0.46$, for diastolic). Multiple linear regression analysis was performed using corin as the dependent variable and hypertension, age, BNP, and gender as independent variables. Gender and age were the only significant explanatory variables ($p<0.0001$ and $p=0.02$, respectively).

Table 2. Comparison of non-ACS control and ACS patients at baseline and 4–6 years later in stable state.

	Control		ACS		*p*-value
	Time 0	4–6 years later	Acute stage	4–6 years later	
Corin (pg/ml)					
At time 0	1165±613	–	798±288	–	<0.0001[a]
Males	1505±576	–	859±282	–	<0.0001[a]
Females	832±443	–	571±180	–	0.0003[a]
Age-matched	1173±659	–	840.6±293	–	0.0004[a]
Change in control group	1165±613	1145±572	–	–	0.54[b]
Change in ACS group	–	–	798±288	1030±394	<0.0001[c]
At 4–6 years later	–	1145±572	–	1030±394	0.07[a]
BNP (pg/ml)					
between groups	–	71.8±100.2	91±125	–	0.5[a]
Change in ACS group	–	–	91±125	181±220	0.0057[c]
At 4–6 years later	–	71.8±100.2	–	181±220	0.0057[a]

Values are mean±SD. Age-matched: n=64 in control group; n=83 in ACS group.
[a]Between controls and ACS patients.
[b]Between time 0 and after 4–6 years in control patients.
[c]Between acute stage and 4–6 years later in ACS patients.

ACS patients

The baseline characteristics of the 152 ACS patients are presented in Table 1 and their corin and BNP results in Table 2 (including results for age-matched groups). There was no correlation between the corin level and the BNP level (p=0.91) or blood pressure (p=0.45 for systolic and p=0.52 for diastolic). We compared a smaller group of patients (n=83) aged 55.1±5.7 years to a smaller group of control patients (n=60) aged 53.9±6.1 years, subgroups from the described populations (matched ages, p=0.7) and corin was still significantly lower in the ACS group (Table 2). When multiple linear regression analysis was performed with corin as the dependent variable and hypertension, anaemia, age, BNP, gender, and troponin I as independent variables, gender and age were the only significant explanatory variables (p<0.0001 and p=0.022, respectively).

Corin and BNP after 4–6 years

The corin and BNP levels measured after 4–6 years are shown in Table 2. In the study group, both corin and BNP changed significantly.

Drug effects

To evaluate the putative effects of drugs commonly used in ACS patients, the corin levels were compared between patients who were or were not treated before sampling with selected medications (clopidogrel, aspirin, beta-blockers, alpha blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, and heparin). The corin levels did not differ between the patients who did or did not receive any of these medications, indicating that corin levels were not affected either by receiving these drugs or by heparin treatment. However, the sample size was probably too small to accurately assess the influences of drug treatment.

The MACE and non-MACE groups

The patient group was divided into two subgroups according to the occurrence of MACE during the 2–3 years of follow up; 92 patients (60.53%) developed late MACE. Of these, 52% required repeat PCI, 26% suffered from unstable angina pectoris, 4% underwent coronary artery bypass graft surgery, 7% had strokes, 7% had an AMI, and 4% died.

It is noteworthy that the MACE group had significantly lower corin levels than non-MACE, and higher proportions of females and hypertensive subjects (p=0.0001, 0.0004, and 0.03, respectively) than the non-MACE group. The presence of diabetes, anaemia, and troponin-I positivity (>1 ng/ml), were significantly different between these groups (p=0.019, 0.05, and 0.011, respectively). Hyperlipidaemia, BNP level, and the presence of smoking did not differ significantly between these groups (p=0.89, 0.9, and 0.9, respectively).

Multivariate analysis

To fit a logistic regression model for prediction of the later occurrence of MACE, we entered various potential predictors (age, gender, corin level, and other known risk factors for coronary artery disease, such as anaemia, troponin I positivity, BNP level, hyperlipidaemia, smoking, diabetes, and hypertension); corin level was entered using a stepwise method with 50 pg/ml steps. Corin was found to be a

Table 3. Baseline characteristics of patients with and without late MACE.

	MACE (*n*=92)	non-MACE (*n*=60)	*p*-value
Corin (pg/ml)	698.16±233.67	952.1±297.81	<0.0001
Corin (males)	761.67±227.47	970.45±299.15	<0.0001
Males	69.57 (64)	93.33 (56)	0.0004
Age (years)	62.18±11.04	61.22±9.92	0.34
Hypertension	77.17	61.02	0.03
Hyperlipidaemia	70.65	71.67	0.89
Diabetes	46.74	30.33	0.019
Anaemia	22.85	10.00	0.05
BNP (pg/ml)	92.70±123.72	98.74±131.40	0.90
Troponin I positive	54.1	35.0	0.011
Currently heavy smokers	21.74	21.67	0.9
eGFR (ml/min/1.73 m^2)	88.9±23.2	93.7±26.1	0.26

Values are mean±SD, % (*n*) or %. BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular events.

Table 4. Multiple logistic regression analysis of risk factors for late MACE following PCI.

Variable	*p*-value	OR	95% CI	c-statistic	Wald
Corin in 1 pg/ml steps	0.0004	0.996	0.994–0.998	0.767	0.002
Corin in 50 pg/ml steps	0.0004	0.834	0.754–0.922	0.791	0.002
Gender (female)	0.04	0.466	0.129–1.68		
Age	0.15	0.968	0.925–1.013		
Hypertension (systolic)	0.04	0.997	0.980–1.014		
Hyperlipidaemia	0.19	0.997	0.980–1.014		
Diabetes	0.51	1.338	0.553–3.236		
Anaemia	0.05	1.645	0.451–6.004		
BNP (cut off 100 ng/ml)	0.25	0.999	0.996–1.002		
Troponin I (cut off 0.2 pg/ml)	0.05	1.691	0.669–4.277		
Smoking	0.24	0.541	0.190–1.536		

Female consider risk factor for MACE, 30.43% of the MACE group were female and 6.67% in the non-MACE group (20.05% female in all ACS patients).

significant predictor (p=0.0004, odds ratio, OR, 0.83, 95% CI 0.75–0.92, c-statistics 0.791 for all subjects and 0.717 for males alone) in all trials. When using corin and BNP as the only predictors, corin level was a significant predictor of post-ACS MACE (p<0.0001, OR 0.828, 95% CI 0.764–0.896 for 50 pg/ml steps, c-statistic 0.804). The presence of anaemia, hypertension, gender, and troponin I positivity showed significance for prediction of recurrent events both in the univariate analysis (Table 3) and the multivariate analysis (Table 4; p=0.05, 0.04, 0.04, and 0.05, respectively). When age and gender were forced together, they were a significant predictor. When we matched age in both groups, with 83 patients and 60 healthy controls with mean age 55 years in the test group and 54 years in the control group (p=0.7), corin levels was still significantly different (p=0.0004). If we had matched gender, increasing females in the group obviously would have reduced the corin level as well. The ability of corin level to predict later MACE was evaluated using the receiver operating characteristic (ROC) curve. The areas under the curve (AUC) in ROCs were for the whole cohort (0.791) and the males-only stratum (0.717). When using corin and BNP as the only predictors, corin level was a significant predictor of post-ACS MACE (p<0.0001, OR 0.828, 95% CI 0.764–0.896 for 50 pg/ml steps, AUC 0.804).

The optimal discriminatory value of corin for predicting long-term MACE was identified as the corin value for which the combined sensitivity/specificity was the smallest distance from 0/0 to 100/100%, respectively. This was derived from the regression fit with a probability level of 0.62 for a corin level of 797.4 pg/ml, which had a sensitivity of 70.7%, specificity of 62.7%, positive predictive value of 74.7%, and negative predictive value of 57.8% for prediction of later MACE in the entire group.

Discussion

Corin is a type-II transmembrane protein that plays a pivotal role in the natriuretic peptide system.[19] Due to its mode of attachment to the cell membrane, corin may conceivably

be detached from the endothelial cells or cardiac myocytes and appear in the blood.[10] We previously established an assay to measure corin in the blood.[18] In the present report, we determined the serum corin levels in patients with ACS and in an apparently control population. The corin level was significantly lower in our ACS group than in our control group and was also significantly lower in ACS patients who later experienced MACE than in ACS patients with no MACE after PCI. Gender markedly influences corin level, with females having lower levels than males[18–21] except in subjects older than 55 years; however, our ACS groups had small percentages of females to influence the results and were notably old.

A reduced corin level has been suggested to indicate a lower rate of active BNP production. If so, the resulting reduced tissue level of BNP might offer less protection to the injured vasculature or myocardium, leading to an increased incidence of later cardiovascular events. In contrast, the amount of BNP found in the plasma may be more dependent on the amount of pro-BNP secreted by the heart. Pro-BNP secretion depends on myocardial wall stress, hence the role of blood BNP as a marker of heart failure. BNP level may predict the outcome of ACS via an heart failure mechanism (increased wall stress), whereas corin is more an indicator of vascular protection.

There was no correlation between serum corin and BNP levels in the present study. Similar results were reported by Shrestha et al.[25] These findings are consistent with the hypothesis that plasma and tissue levels of BNP differ.[15,26] Nevertheless, it is of interest that the BNP level rose concomitant with the recovery of the corin level in the stabilized post-ACS patients. This finding is similar to that in the study by Voors et al.,[27] which showed a late rise in BNP in patients recuperating from non-ST-elevation MI. It could be postulated that the depressed corin level during the acute episode does not allow an adequate increase in protective BNP, which then appears following clinical stabilization, with the restoration of the corin level. Another possible explanation is that cardiac hypertrophy or occult worsening of cardiac function develops and that secretion of the hormone increases with the increased wall stress.

The BNP levels in this study did not differ between the MACE and non-MACE subgroups, which may be because the assay was less specific[26] (cross-reacting with pro-BNP), because of differences in sample size, which may have biased our results, or because of our limitation that BNP (and corin) was drawn within 24 hours and not on admission. An elevated troponin level following PCI has also been shown to be associated with a worse prognosis.[28–31] Elevated troponin I at admission was shown to be a significant predictor of late post-PCI MACE in our model.

Previous reports have indicated that anaemia[32] and hypertension[8] contribute to an increased risk of post-discharge MACE in ACS patients. Both showed significance in this study in univariate and multivariate analyses. Our study should be regarded as a proof-of-concept study rather than a study that establishes the value of corin in ACS. The mere fact that corin was indeed a significant predictor indicates that this cardiovascular biomarker may be a potential contributor to any model predicting late MACE post ACS.

Study limitations are that patients were enrolled non-consecutively and there was a delay from symptom onset to blood sampling and from admission to blood sampling.

Conflict of interest

None.

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References

1. Battistoni A, Rubattu S and Volpe M. Circulating biomarkers with preventive, diagnostic and prognostic implications in cardiovascular diseases. *Int J Cardiol* 2012; 157: 160–168.
2. Morrow DA, Cannon CP, Jesse RL, et al. National academy of clinical biochemistry laboratory medicine practice guidelines: clinical characteristics and utilization of biochemical markers in acute coronary syndromes. *Clin Chem* 2007; 53: 552–574.
3. Burnett JC Jr. Novel therapeutic directions for the natriuretic peptides in cardiovascular disease: what's on the horizon? *Cardiology* 2006; 48: 235–241.
4. Munagala VK, Burnett JC Jr and Redfield MM. The natriuretic peptides in cardiovascular medicine. *Curr Probl Cardiol* 2004; 29: 769–707.
5. Daniels LB and Maisel AS. Natriuretic peptides. *J Am Coll Cardiol* 2007; 50: 2357–2368.
6. Dries DL. Process matters: emerging concepts underlying impaired natriuretic peptide system function in heart failure. *Circ Heart Fail* 2011; 4: 107–110.
7. Eggers KM, Lagerqvist B, Venge P, et al. Prognostic value of biomarkers during and after non–ST-segment elevation acute coronary syndrome. *J Am Coll Cardiol* 2009; 54: 357–364.
8. Galvani M, Ottani F, Oltrona L, et al. N-terminal pro-brain natriuretic peptide on admission has prognostic value across the whole spectrum of acute coronary syndromes. *Circulation* 2004; 110: 128–134.
9. O'Connor RE, Brady W, Brooks SC, et al. Part 10: acute coronary syndromes: 2010 American association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010; 122: S787–S817.
10. Jiang J, Wu S, Wang W, et al. Ectoderm shedding and autocleavage of the cardiac membrane protease corin. *J Bio Chem* 2011; 286: 10066–10072.
11. Huntley BK, Heublein DM and Burnett JC Jr. Corin expression in specific human cardiac endothelial cells and cardiac fibroblasts. *J Cardiology Failure* 2003; 9: S41.
12. Yan W, Wu F, Morser J, et al. Corin, a transmembrane cardiac serine protease, acts as a pro-atrial natriuretic peptide–converting enzyme. *Proc Natl Acad Sci USA* 2000; 97: 8525–8529.

13. Semenov AG, Tamm NN, Seferian KR, et al. Processing of pro-B-type natriuretic peptide: furin and corin as candidate convertase. *Clin Chem* 2010; 56: 1166–1176.
14. Wang W, Liao X, Fukuda K, et al. Corin variant associated with hypertension and cardiac hypertrophy exhibits impaired zymogen activation and natriuretic peptide processing activity. *Circulation Res* 2008; 103: 502–508.
15. Chen S, Sen S, Young D, et al. Protease corin expression and activity in failing hearts. *Am J Physiol Heart Circ Physiol* 2010; 299: H1687–9H1682.
16. Wu Q. The serine protease corin in cardiovascular biology and disease. *Front Biosci* 2007; 12: 4179–4190.
17. Dong N, Chen S, Yang J, et al. Plasma soluble corin in patients with heart failure. *Circ Heart Fail* 2010; 3: 207–211.
18. Peleg A, Jaffe AS and Hasin Y. Enzyme-linked immunoabsorbent assay for detection of human serine protease corin in blood. *Clin Chim Acta* 2009; 409: 85–89.
19. Ichiki T, Huntly BK, Heublein DM, et al. Corin is present in the normal human heart, kidney, and blood, with pro-B-type natriuretic peptide processing in the circulation. *Clin Chem* 2011; 57: 40–47.
20. Ibebuogu UN, Gladysheva IN, Houng AK, et al. Decompensated heart failure is associated with reduced corin levels and decreased cleavage of pro-atrial natriuretic peptide. *Circ Heart Fail* 2011; 4: 114–120.
21. Dong N, Chen S, Wang W, et al. Corin in laboratory diagnostics. *Clin Chim Acta* 2012; 413: 378–383.
22. Chang AY, Shuaib AM, Tulika J, et al. Associations among androgens, estrogens, and natriuretic peptides in young women: observations from the Dallas Heart Study. *J Am Coll Cardiol* 2007; 49: 109–116.
23. Redfield MM, Rodeheffer RJ, Jacobson SJ, et al. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol* 2002; 40: 976–982.
24. Saenger AK, Dalenberg DA, Bryant SC, et al. Pediatric brain natriuretic peptide concentrations vary with age and sex and appear to be modulated by testosterone. *Clin Chem* 2009; 55: 1869–1875.
25. Shrestha KAB, Troughton RW, Borowski AG, et al. Plasma corin levels provide minimal prognostic utility incremental to natriuretic peptides in chronic systolic heart failure. *J Card Fail* 2010; 16: 621–627.
26. Clerico A, Fontana M, Zyw L, et al. Comparison of the diagnostic accuracy of brain natriuretic peptide (BNP) and the N-terminal part of the pro-peptide of BNP immunoassays in chronic and acute heart failure: a systematic review. *Clin Chem* 2007; 53: 813–822.
27. Voors AA, Belonje AMS, Zijlstra F, et al. A single dose of erythropoietin in ST-elevation myocardial infarction. *Eur Heart J* 2010; 31: 2593–2600.
28. Miller WL, Garratt KN, Burritt MF, et al. Baseline troponin level: key to understanding the importance of post PCI troponin elevations. *Eur Heart J* 2006; 27: 1061–1069.
29. Babuin L and Jaffe AS. Troponin: the biomarker of choice for detection of cardiac injury. *CMAJ* 2005; 173: 1191–1202.
30. Nageh T, Sherwood RA, Harris BM, et al. Cardiac troponin T and I and creatine kinase-MB as markers of myocardial injury and predictors of outcome following percutaneous coronary intervention. *Int J Cardiol* 2003; 92: 285–293.
31. Thygesen K, Mair J, Katus H, et al. Recommendations for the use of cardiac troponin measurement in acute cardiac care. *Eur Heart J* 2010; 31, 2197–2204.
32. Hasin T, Sorkin A, Markiewicz W, et al. Prevalence and prognostic significance of transient, persistent, and new-onset anemia after acute myocardial infarction. *Am J Cardiol* 2009; 104: 486–491.