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Resistin associated with higher cardiovascular events in intermediate grace score of acute coronary syndrome

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ABSTRACT

Previous studies revealed that inflammatory biomarkers have a role in the clinical outcomes of acute coronary syndromes (ACS) and also in prediction of cardiovascular events using GRACE score. Resistin, a recently identified inflammatory biomarker, also has a role in clinical outcomes of ACS but its role related to GRACE score risk stratification is unknown. Three risk stratifications of ACS based on GRACE scores were used i.e. low, intermediate, and high. Some studies reported that inflammatory biomarkers have a role in cardiovascular events of patients with low risk GRACE scores, but their role in the patients with intermediate risk still needs to be elucidated. This study aimed to investigate the role of resistin in cardiovascular events of ACS patients with intermediate risk GRACE score. This was an observational study using a cross-sectional design involving sixty-three patients with ACS who fulfilled the inclusion and exclusion criteria. Blood samples were drawn 24 h after onset. Resistin level was analyzed and classified according to its median values. The cardiovascular event was defined as mortality, ischemic events, acute heart failure or arrhythmia during hospitalization. The result showed that cardiovascular events were significantly higher in patients with resistin levels higher than median i.e. 23.8% compared to those with resistin levels similar or lower than median i.e. 11.1% (OR 3.348, 95%CI: 1.125-10.007 p=0.027). It can be concluded high resistin level is associated with an increase of cardiovascular events of ACS with intermediate risk GRACE score.

ABSTRAK

Penelitian sebelumnya menunjukkan bahwa penanda inflamasi berperan pada luaran klinik sindrom koroner akut (SKA) dan juga dalam memprediksi kejadian kardiovaskular menggunakan skor GRACE. Resistin sebagai salah satu penanda inflamasi juga berkaitan dengan kejadian kardiovaskular pada SKA namun perannya terhadap kejadian kardiovaskular berdasarkan skor GRACE belum pernah diteliti. Berdasarkan skor GRACE, SKA dibedakan dalam tiga stratifikasi risiko yaitu risiko rendah, sedang dan tinggi, Beberapa penelitian telah melaporkan penanda inflamasi berperan dalam kejadian kardiovaskular pada SKA dengan skor GRACE risiko rendah, tetapi perannya pada SKA dengan skor GRACE risiko sedang perlu dibuktikan. Penelitian ini bertujuan untuk mengkaji peran resistin sebagai salah satu penanda inflamasi, terhadap kejadian kardiovaskular pada SKA dengan skor GRACE risiko sedang. Penelitian ini merupakan penelitian observasi dengan rancangan potong lintang yang melibatkan 63 pasien SKA yang memenuhi kriteria inklusi dan eksklusi. Pengambilan sampel darah untuk pengukuran kadar resistin dilakukan dalam 24 jam pasca awitan serangan. Kadar resistin diukur dan dikelompokkan berdasarkan nilai mediannya. Kejadian kardiovaskular didefinisikan sebagai kematian, kejadian iskemik, gagal jantung akut dan aritmia yang terjadi selama perawatan di rumah sakit. Hasil penelitian menunjukkan kejadian kardiovaskular lebih tinggi secara bermakna pada kelompok kadar resistin di atas median yaitu 23,8% dibandingkan kelompok kadar resistin sama atau di bawah median yaitu 11,1% (RO 3,348, 95% IK 1,125-10,007 p=0,027). Dari penelitian ini dapat disimpulkan bahwa kadar resistin tinggi berkaitan dengan kenaikan kejadian kardiovaskular pada populasi SKA dengan skor GRACE risiko sedang.

Keywords:
resistin;
cardiovascular events;
acute coronary syndrome;
GRACE score;
biomarker;

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INTRODUCTION

Inflammatory markers have been proven to have role in cardiovascular events of acute coronary syndrome (ACS).[1,2] Resistin, an inflammatory marker recently found to be related to ACS, is a cysteine rich protein formerly found in mouse's adipocytes, correlated with insulin resistance.[3] It was stated that resistin had a role in cardiovascular events of ACS, however, there are still inconclusive.[4] Moreover, in the role pertaining to clinical outcomes of ACS, an inflammatory marker should prove not only its independent role towards cardiovascular events but also its role towards cardiovascular events in ACS according to some risk stratification methods.[5]

Among risk stratification methods in ACS, the guidelines recommended the application of the global registry of acute coronary events (GRACE) score.[6] The validation study of GRACE score reported that there is a gap of cardiovascular events incidence between GRACE score classifications. The prediction performance of intermediate and low risk was not as accurate as high risk. This was related to the possibility of other factors that affect the outcome, and one of them is the inflammatory biomarker.[7,8] Beygui *et al*.[9] reported that the inflammatory biomarker had additional prognostic value in the low-risk GRACE score. Therefore, there exists the need to investigate whether inflammatory markers such as resistin had an additional role in intermediate GRACE scores. This study aimed to evaluate whether resistin has a role in cardiovascular events in patients with ACS with intermediate-risk GRACE score.

MATERIALS AND METHODS

Population and samples

This was an observational study with a cross-sectional design conducted in the Cardiovascular Unit, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta, Indonesia for 6 months from October 2013 to April 2014. The inclusion criteria of this study were patients with ACS who have intermediate risk GRACE score, score 109-140 for non-ST elevation acute coronary syndrome (NSTEACS) and score 126-154 for ST elevation myocardial infarction (STEMI) and came to the hospital with onset less than 24 h and no previous definitive therapy for ACS. Definitive therapy was defined as anticoagulant or reperfusion given to the subject according to ACS guidelines.[6,10] The exclusion criteria were patients with sepsis, chronic renal disease, thyroid disease, chronic heart failure malignancy, underwent TZD (thiazoliendidione) therapy, underwent glucocorticoid therapy, concomitant diabetic complications, DKA (diabetic ketoacidosis) and HHS (hyperglycemia hyperosmolar state), stroke, pregnancy, cardiomyopathy, valvular heart disease, or in chronic anticoagulant therapy.

Resistin measurement

Serum resistin level was measured from venous blood taken within 24 h after symptoms onset. Two milliliters of venous blood sample was placed in EDTA vacutainer then being centrifuged at 1,000 G in 15 min and then serum was preserved in several aliquots and placed in -80º until analysis. The serum resistin level was analyzed using ELISA (enzyme link immunosorbent assay) with reagent kit human resistin R&D System, USA®.

Research protocols

Patients with ACS who met the inclusion and exclusion criteria and willing to participate in this study were

given definitive therapy according to the guidelines and hospital protocol. The primary outcome of this study was cardiovascular events which consisted of in hospital mortality, arrhythmia, acute heart failure and ischemic events. Ischemic events in this study were defined as persistent or residual angina, failed fibrinolysis, and reinfarction.

Cardiovascular events were observed during hospitalization in each subject with a specific time frame, immediately after reperfusion therapy for STEMI, one h after the first dose of unfractionated heparin (UFH) or six h after first dose low molecular weight heparin (LMWH) or 3 h after first dose of fondaparinux for NSTEACS and STEMI subjects who did not meet reperfusion criteria. Observation was stopped if the first cardiovascular event occurred but if no cardiovascular event occurred, observation was continued until discharge (FIGURE 1).

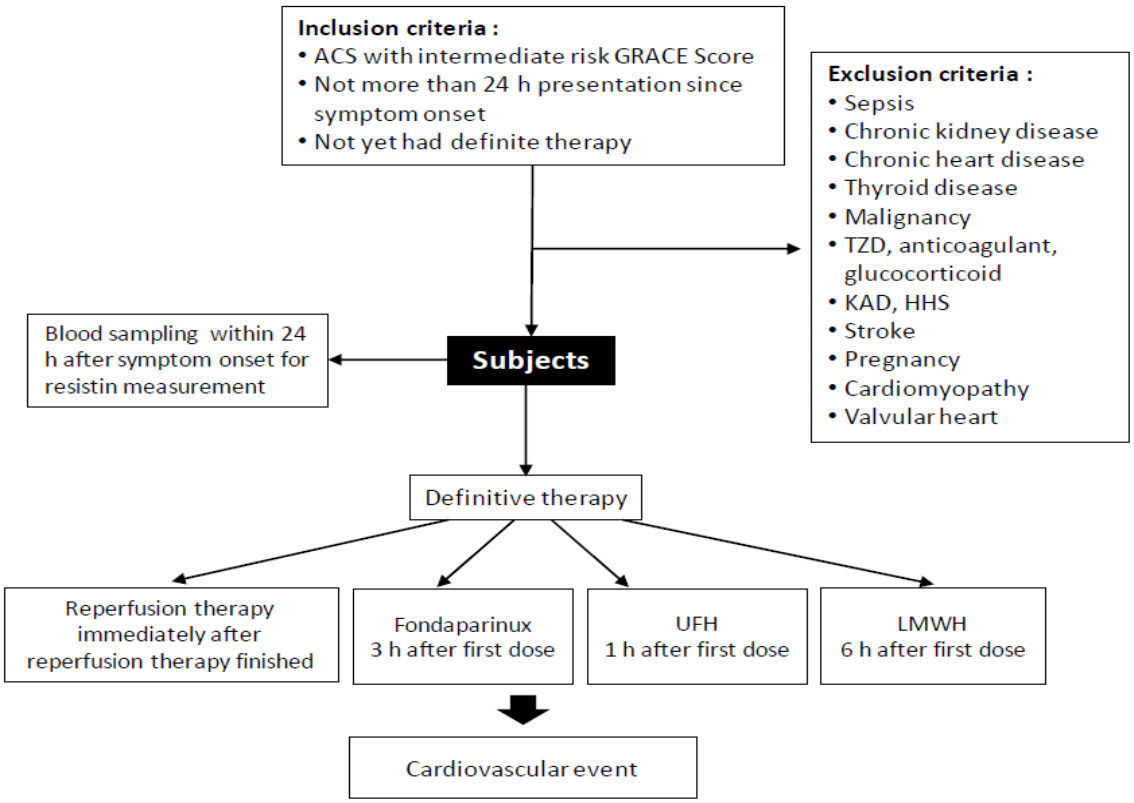

FIGURE 1. Research protocol

Statistical analysis

Categorical variables were analyzed with chi-squared and Fisher's exact tests. Continuous variables were analyzed using student t or Mann-Whitney U tests. This study applied 95% confidence level (CI) with p value <0.05 to be cosidered as a significant result. SPSS Program 15.0 (IBM Corp., Chicago) was applied for statistical analysis.

Ethical clearance

This study has been approved by the Medical and Health Research Ethic Committee, of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada /Dr. Sardjito Hospital General Hospital on September 6th, 2013.

RESULTS

Seventy two patients with ACS who met the inclusion were recruited. Nine patients were excluded due to stroke, chronic heart failure, malignancy, chronic kidney disease. One patient with an indication of intervention but it had not been performed. Therefore, 63 patients consisted of 39 patients (62%) with STEMI, and 24 patients (38 %) with NSTEACS. participated in this study.

The distribution of resistin levels is presented in the following histogram (FIGURE 2). The mean resistin level in this study was 1.97±1.69 ng/mL ranging between 0.71 to 9.05 ng/mL and the median was 1.36 ng/mL.

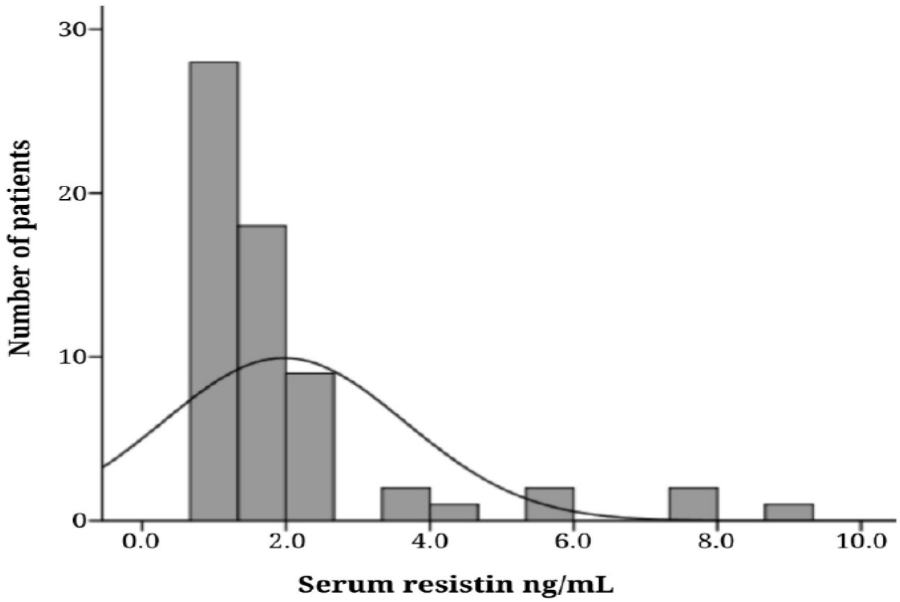

FIGURE 2. Distribution of serum resistin level in ACS with intermediate risk GRACE score.

FIGURE 2 shows the distribution of resistin among patients involved in this study. An abnormal distribution of resistin where the curve with right skewness was observed. Based on this result, the resistin level was classified into two groups according to its median i.e the low level group which the resistin level similar or lower than the median resistin level and the high level group which the resistin level higher than the median resistin level. TABLE 1 presents baseline characteristics of patients according to the resistin level.

TABLE 1. Baseline characteristics of subjects

Variables	≤ median (≤1.36 ng/mL) n=32	> median (>1.36 ng/mL) n=31	p
Demography			
• Age (mean ± SD years)	57.7± 8.2	59.6 ± 8.0	0.360
• Male [n (%)]	27 (84.4)	21 (67.7)	0.121
• Female [n (%)]	5 (15.6)	10 (32.3)	
• BMI [kg/m^2 (median-range]	22.5 (17.6-28)	23.1 (17.7-36.7)	0.740
Risk factors			
• Smoker [n (%)]	12 (19)	7 (11.1)	0.363
• Dyslipidemia [n (%)]	22 (34.9)	18 (28.6)	0.378
• Hypertension [n (%)]	19 (30.2)	20 (31.7)	0.674
• Diabetes mellitus [n (%)]	9 (14.3)	7 (11.1)	0.613
• Family history [n (%)]	2 (3.2)	0	0.157
Medical history			
• MI (n,%)	6 (7.9)	5 (9.5)	0.523
• PCI (n,%)	3 (4.8)	1 (1.6)	0.319
• Onset [hours (median-range)]	6 (1-24)	4.5 (2-24)	0.507
Therapy before admission			
• Insulin [n (%)]	4 (6.3)	4 (6.3)	0.628
• CCB dihydropyridine [n (%)]	0	1(1.6)	0.492
• ACEi [n (%)]	2 (3.2)	2 (3.2)	0.681
• \Statin [n (%)]	4 (6.3)	0	0.113
Laboratory			
• Creatinine (mean±SD mg/dL)	0.9±0.27	1.08±0.33	0.222
• Blood glucose on admission [mg/ml (median-range)]	135 (80-387)	137 (73-468)	0.478
Definitive therapy			
• Thrombolytics [(n (%)]	7 (11.1)	13 (20.6)	0.087
• PCI [n (%)]	11 (17.5)	9 (14.3)	0.649
• Heparin [n (%)]	30 (47.6)	29 (46)	0.681
Medications during hospitalization			
• Beta blockers [n (%)]	26 (42.3)	24 (38.1%)	0.707
• Statin [n (%)]	31 (49.2)	31 (49.2%)	0.508
• ACEi [n (%)]	22 (35.5)	19 (30.6%)	0.652
• ARB [n (%)]	5 (7.9)	4 (6.3%)	0.521

BMI: body mass index; MI: myocardial infarction; PCI: percutaneous coronary intervention; CCB: calcium channel blocker; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; SD: standard deviation

There were more male subjects than females in this study with a mean of 59 y.o. Hypertension and dyslipidemia were dominant as risk factors for all subjects. Baseline characteristics showed no significant differences of demography, risk factors, previous therapy, laboratory, definitive therapy, and medication during hospitalization between the two resistin groups.

During observation, there were 22 (34.9%) cardiovascular events that occurred during hospitalization and the majorities were ischemic events (86.4%). There was no in hospital mortality during the observation, 2 (9.1%) subjects had acute heart failure (9.1%,) and 1 (4.5%) subject had arrhythmia ventricular tachycardia (FIGURE 3). The ischemic events that occurred in this study were predominately residual angina (20.3%) followed by failed thrombolysis and reinfarction (FIGURE 4).

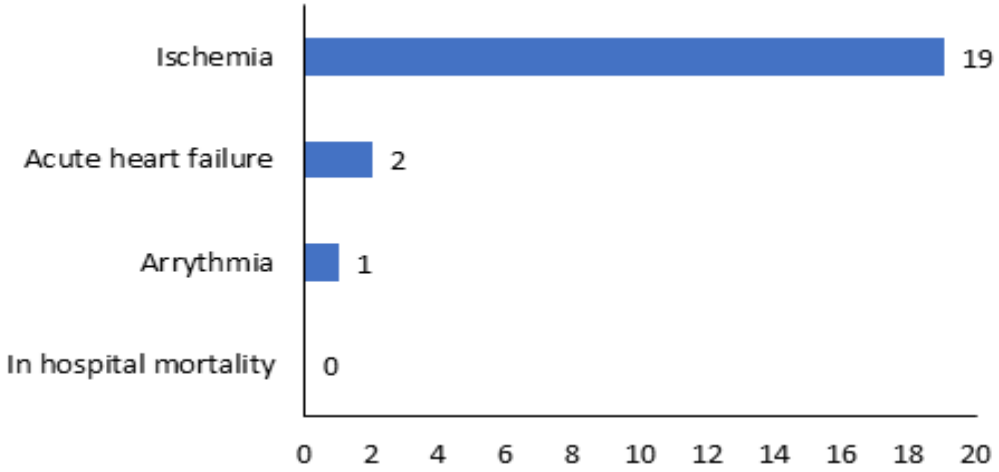

FIGURE 3. Cardiovascular events in acute coronary syndrome with Intermediate GRACE Score.

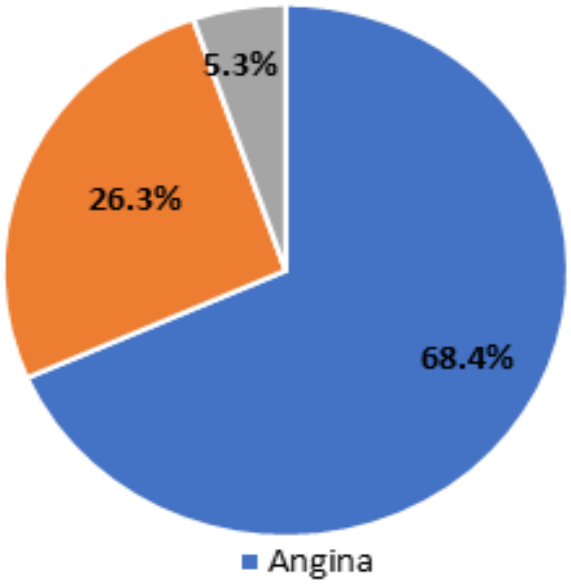

FIGURE 4. Proportion of ischemic events

The differences in cardiovascular events between the two resistin groups were analyzed by using chi-squared test (TABLE 2). The result showed that the resistin level is significantly associated with cardiovascular events in ACS with intermediate risk GRACE score (p= 0.027).

TABLE 2. Resistin level and cardiovascular event of ACS with intermediate risk GRACE score.

Variables	Cardiovascular event (+) [n (%)]	Cardiovascular event (-) [n (%)]	OR	95%CI	p
Resistin > median (> 1.36 ng/mL) n=31	15 (23.8)	16 (25.4)	3.348	1.120-10.007	0.027
Resistin ≤ median (≤1.36 ng/mL) n=32	7 (11.1)	25 (39.7)			
n	22 (24.9)	41 (65.1)			

OR: odds ratio, CI: confidence interval

The cardiovascular events were higher in subjects with the high resistin level compared with those with the low resistin level for the ACS population in this study with odds ratio (OR) 3.348 (95% CI: 1.120-10.007; p=0.027). Furthermore, analysis was conducted to evaluate the difference of cardiovascular events between the two resistin groups in the sub populations of STEMI and Non-ST Elevation ACS (NSTEACS) (TABLE 3 and 4). In the STEMI subpopulation, the cardiovascular events were higher in the high resistin level group compared to those the low resistin level according to its median with OR 5.564 (95% CI: 1.255-25.294; p=0.02). The opposite was found in the NSTEACS subpopulation, indicating that there were no differences in cardiovascular events between the both resistin groups (p=0.698).

TABLE 3. Resistin and cardiovascular events in subpopulation STEMI with intermediate risk GRACE score.

Variables	Cardiovascular event (+) [n (%)]	Cardiovascular event (-) [n (%)]	OR	95%CI	p
Resistin > median (> 1.36 ng/mL) n=31	13 (33.3)	3 (7.7)	5.564	1.255-25.294	0.020
Resistin ≤ median (≤1.36 ng/mL) n=32	10 (25.6)	13 (33.3)			
n	23 (59.0)	16 (41.0)			

OR: odds ratio, CI: confidence interval

TABLE 4. Resistin and cardiovascular events in subpopulation NSTEACS with intermediate risk GRACE score.

Variables	Cardiovascular event (+) [n (%)]	Cardiovascular event (-) [n (%)]	OR	95%CI	p
Resistin > median (> 1.36 ng/mL) n=31	2 (8.3)	6 (25.0)	1.000	0.141-7.099	0.698
Resistin ≤ median (≤1.36 ng/mL) n=32	4 (16.7)	12 (50.0)			
n	8 (25.0)	18 (75.0)			

OR: odds ratio, CI: confidence interval

DISCUSSION

The main results of this study showed that there was a significant difference in cardiovascular events between the bot resistin groups. Patients with high resistin level had more cardiovascular events compared to those with low resistin level. This finding was consistent in the STEMI subpopulation and in all subjects who had intermediate GRACE Score.

Based on findings from a study conducted by Correia *et al.*,[11] in 2010, inflammatory markers have an additional prognostic value to GRACE score. The study established a scoring model of inflammatory markers and added to GRACE score, this additional scoring had net reclassification improvement of 13%. Based on Lubos *et al.*,[12] in 2007, high resistin level was correlated to 1.19 times (95%CI: 0.98-1.45) increment of cardiovascular death however that result was statistically insignificant with p=0.08. Furthermore, Lee *et al.*,[13] in 2009 conducted a prognostic study with time of follow-up at 12 months and concluded that resistin was significantly correlated with 1.16 (95% CI: 1.12-2.28) times increment of all causes of death with p=0.01 but there was no significant correlation with cardiovascular death in the patients with ACS. Discrepancies of our finding with those previous findings was likely because there was no in hospital mortality events observed, and in our study the most dominant cardiovascular event was ischemia particularly residual angina. These discrepancies in mortality finding could be due to differences in the population of study, since in our study we specifically chose subjects with ACS with intermediate GRACE score.

Regarding our finding of ischemia as the highest cardiovascular event, according to literature, high resistin would increase oxidative stress and decrease endothelial nitric oxide (eNOS), which is a coronary vasodilator. Additionally, resistin is also known to have a role in decreasing coronary sensitivity to the relaxation effect of bradykinin This would enhance vasoconstriction and decrease myocardial oxygen supply contributing to ischemia and angina.[14,15] Furthermore, resistin was found to have a role in exaggerating platelet aggregation and thrombosis.[16-18]

Differences in the cardiovascular events between STEMI and NSTEACS still need to be confirmed by further research, whether it was due to differences of resistin level among subsets of ACS[19,20] or to determine if there were differences of resistin level in the coronary artery. This was postulated by Langheim *et al.*,[21] in 2010 proposing that there was the secretion of resistin from epicardial adipose tissue.

One limitation of this study was the unavailability of other inflammatory markers' data such as C-Reactive Protein, Interleukin 6, and Tumor Necrosis Factor-α for comparison or as confounding factors to analyze the role of resistin in ACS.

CONCLUSIONS

Serum resistin level is associated with higher cardiovascular events in ACS patients with intermediate risk GRACE score.

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REFERENCES

1. Battistoni A, Rubattu S, Volpe M. Circulating biomarkers with preventive, diagnostic and prognostic implications in cardiovascular diseases. Int J Cardiol 2012; 157(2):160-8. https://doi.org/10.1016/j.ijcard.2011.06.066
2. Blake GJ, Ridker PM. C-Reactive protein and other inflammatory risk markers in acute coronary syndromes. J Am Coll Cardiology 2003; 41(4 Suppl S):37S-42S. https://doi.org/10.1016/S0735-1097(02)02953-4
3. Steppan CM, Lazar MA. Resistin and obesity-associated insulin resistance. Trends Endocrinol Metab 2002; 13(1):18-23. https://doi.org/10.1016/S1043-2760(01)00522-7
4. Ding Q, White SP, Ling C, Zhou W. Resistin and cardiovascular disease. Trends Cardiovasc Med 2011; 21(1):20-7. https://doi.org/10.1016/j.tcm.2012.01.004
5. Correia LCL, Andrade BB, Borges VM, Clarencio J, Bittencourt AP, Freitas R, *et al*. Prognostic value of cytokines and chemokines in addition to the GRACE score in non-ST-elevation acute coronary syndromes. Clin Chima Acta 2010; 411(7-8):540-5. https://doi.org/10.1016/j.cca.2010.01.011
6. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, *et al*. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 61(4):e78-140. https://doi.org/10.1161/CIR.0b013e3182742cf6
7. Elbarouni B, Goodman SG, Yan RT, Welsh RC, Kornder JM, DeYoung JP, *et al*. Validation of the Global Registry of Acute Coronary Event (GRACE) risk score for in-hospital mortality in patients with acute coronary syndrome in Canada. Am Heart J 2009; 158(3):392-9. https://doi.org/10.1016/j.ahj.2009.06.010
8. Granger CB. Predictors of hospital mortality in the Global Registry of Acute Coronary Events. Arch Intern Med 2003; 163(19):2345-53. https://doi.org/10.1001/archinte.163.19.2345
9. Beygui F, Silvain J, Pena A, Bellemain-Appaix A, Collet JP, Drexler H, *et al*. Usefulness of biomarker strategy to improve GRACE score's prediction performance in patients with non–ST-segment elevation acute coronary syndrome and low event rates. Am J Cardiol 2010; 106(5):650-8. https://doi.org/10.1016/j.amjcard.2010.04.019
10. Jneid H. The 2012 ACCF/AHA Focused Update of the Unstable Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI) guideline: a critical appraisal. Methodist DeBakey Cardiovasc J 2012; 8(3):26-30. https://dx.doi.org/10.14797%2Fmdcj-8-3-26
11. Correia LCL, Freitas R, Bittencourt AP, Souza AC, Almeida MC, Leal J, *et al*. [Prognostic value of GRACE scores versus TIMI score in acute coronary syndromes]. Arq Bras Cardiol 2010; 94(5):613-9. https://doi.org/10.1590/s0066-782x2010005000036
12. Lubos E, Messow CM, Schnabel R, Rupprecht HJ, Espinola-Klein C, Bickel C, *et al*. Resistin, acute coronary syndrome and prognosis results from the AtheroGene study. Atherosclerosis 2007; 193(1):121-8. https://doi.org/10.1016/j.atherosclerosis.2006.05.039
13. Lee SH, Ha JW, Kim JS, Choi EY, Park S, Kang SM, *et al*. Plasma adiponectin and resistin levels as predictors

of mortality in patients with acute myocardial infarction: data from infarction prognosis study registry. Coron Artery Dis 2009; 20(1):33-9. https://doi.org/10.1097/mca.0b013e328318ecb0
14. Chen C, Jiang J, Lu JM, Chai H, Wang X, Lin PH, *et al.* Resistin decreases expression of endothelial nitric oxide synthase through oxidative stress in human coronary artery endothelial cells. Am J Physiol Heart Circ Physiol 2010; 299(1):H193-201. https://doi.org/10.1152/ajpheart.00431.2009
15. Kougias P, Chai H, Lin PH, Lumsden AB, Yao Q, Chen C. Adipocyte-derived cytokine resistin causes endothelial dysfunction of porcine coronary arteries. J Vasc Surg 2005; 41(4):691-8. https://doi.org/10.1016/j.jvs.2004.12.046
16. Calabro P, Cirillo P, Limongelli G, Maddaloni V, Riegler L, Palmieri R, *et al*. Tissue factor is induced by resistin in human coronary artery endothelial cells by the NF-kB-dependent pathway. J Vasc Res 2011; 48(1):59-66. https://doi.org/10.1159/000318775
17. Chen N, Wang X, Zhang1 Q, Qiu1 W, Yin J, Lin J, et al. Resistin stimulates platelet P-selectin expression via p38 MAPK signal pathway. Circulation 2011; 124.
18. Fang WQ, Zhang Q, Peng YB, Chen M, Lin XP, Wu JH, *et al*. Resistin level is positively correlated with thrombotic complications in Southern Chinese metabolic syndrome patients. J Endocrinol Invest 2011; 34(2):e36-42. https://doi.org/10.1007/bf03347059
19. Qiao XZ, Yang YM, Xu ZR, Yang LA. Relationship between resistin level in serum and acute coronary syndrome or stable angina pectoris. J Zhejiang Univ Scie B 2007; 8(12):875-80. https://dx.doi.org/10.1631%2Fjzus.2007.B0875
20. Chu S, Ding W, Li K, Pang Y, Tang C. Plasma resistin associated with myocardium injury in patients with acute coronary syndrome. Circ J 2008; 72(8):1249-53. https://doi.org/10.1253/circj.72.1249
21. Langheim S, Dreas L, Veschini L, Maisano F, Foglieni C, Ferrarello S, *et al*. Increased expression and secretion of resistin in epicardial adipose tissue of patients with acute coronary syndrome. Am J Physiol Heart Circ Physiol 2010; 298(3):H746-53. https://doi.org/10.1152/ajpheart.00617.2009