Cent. Eur. J. Med. • 9(1) • 2014 • 21-27
DOI: 10.2478/s11536-013-0240-z

VERSITA

Central European Journal of **Medicine**

Usefulness of Reynolds Risk Score in men with stable angina

Research Article

Inga Pietka[1], Agata Sakowicz[2], Tadeusz Pietrucha[2], Anna Cichocka-Radwan[1], Malgorzata Lelonek*[1]

1 Department of Cardiology, Chair of Cardiology and Cardiac Surgery, Medical University of Lodz, Poland, Sterling Str. 1/3, 91-425 Lodz, Poland

2 Department of Medical Biotechnology, Medical University of Lodz, Poland, Zeligowskiego 7/9 Str., 90-752 Lodz, Poland

Received 19 January 2013; Accepted 3 June 2013

Abstract: Introduction. Recently several risk scores have been proposed that, beyond traditional risk factors, also include additional inflammatory biomarkers underlying atherothrombosis. The Reynolds Risk Score (RRS) is a point scale assessing the risk of cardiovascular events over 10 years, which takes into account for the first time high-sensitivity C-reactive protein. The aim of this study was to establish clinical usefulness of RRS in men with stable coronary artery disease and preserved left ventricular systolic function. Material and Methods. In total, 119 symptomatic non-diabetic man (mean age 63.9±9.23) who were directed for an elective coronary arteriography were enrolled in the study. Clinical data were collected including the elevated heart rate ≥70 bpm/min, basic laboratory results, placental growth factor and results of coronary angiography. Patients were analyzed related to RRS: low risk <10% (n=50), moderate risk 10-19% (n=46) and high risk >20% (n=23). Results. Opposite to high RRS patients, in the low risk group more often occurred marginal or none atherosclerotic coronary arteries (13% vs. 44%, P=0.0214). The findings have revealed the relationship between the higher risk score and the lower frequency of marginal or no atherosclerotic coronary arteries (OR=0.19, 95%CI 0.05-0.67). Conclusions. The Reynolds Risk Score appears to be useful in men with stable coronary artery disease and preserved left ventricular systolic function in stratifying the severity of coronary atherosclerosis.

Keywords: *Reynolds Risk Score • Stable coronary artery disease • Men*

1. Introduction

Recently several risk scores have been proposed that, beyond traditional risk factors, also include additional inflammatory biomarkers, what is related with understanding of the biological processes underlying atherothrombosis [1-3]. Although inflammation independently associates with future vascular risks, most of used global risk algorithms do not include information on that variable. In 2003, the Center for Disease Control and Prevention and the American Heart Association provided the first general guidelines for the use of inflammatory biomarkers in cardiovascular disease detection [4]. From 54 long-term prospective studies it is known that CRP (C-reactive protein) concentration has continuous associations with the risk of developing coronary heart disease, ischaemic stroke or vascular mortality [5].

Few years ago, a model was developed for assessing the risk of cardiovascular events and in the next 10 years is was called the Reynolds Risk Score (RRS) [6]. It was initially designed to develop and validate an algorithm for global cardiovascular risk in healthy women. Recently, RRS using male-specific equations was applied to healthy non-diabetic men with good results [7]. Similar to women, in the male population it was revealed that the addition of high-sensitivity CRP (hsCRP) and parental history of myocardial infarction (MI) before age

* *E-mail: mlelonek@poczta.fm*

60 years improved global cardiovascular risk prediction and reclassification of risk compared with the traditional Framingham Risk Score (FRS). In view of ongoing inflammatory processes in the wall of the coronary arteries, it seems that the risk scores, which takes into account the hsCRP level, might be especially useful for patients with stable coronary artery disease.

The aim of our study was to determine the clinical usefulness of RRS in men with stable coronary artery disease.

2. Material and Methods

The study included symptomatic, non-diabetic 119 men (mean age 63.9±9.23), with preserved left ventricular systolic function, who were directed for elective coronary angiography. The following data were analyzed: age, body mass index, smoking status, family history, heart rate, elevated heart rate (≥70 bpm), arterial blood pressure, basic laboratory results (serum lipids level, cholesterol ratio LDL/HDL, creatinine, hsTnT- high sensitivity troponin, hsCRP), and additionally serum concentration of the inflammatory marker- PlGF (placental growth factor), results of coronary angiography and concomitant cardiovascular diseases (arterial hypertension, previous stroke and peripheral arteries disease) were analysed.

PlGF levels were measured using Human PlGF Quantikine Kit Immunassay for in vitro quantitative measurements by ELISA.

The M-mode, 2-dimensional and Doppler echocardiographic examinations and conventional coronary arteriography using a femoral or radial approach were performed. Stenosis ≥50% of the left main and ≥70% of the three major coronary arteries (left anterior descending artery, left circumflex artery and right coronary artery and their branches), were considered significant and identified as 1-, 2- or 3-vessel disease. Marginal atherosclerotic plaques were defined as stenosis less than 50%. To calculate the sclerotic alteration in coronary arteries we evaluated the degree of luminal obstruction in conventional visual quantification of coronary arteriography.

In all cases, there was calculated value of RRS. The estimates were performed by using the interactive calculator website *www.reynoldsriskscore.org*. The RRS is composed of age, systolic blood pressure, smoking, total cholesterol and HDL-C, hsCRP, and parental history of MI before age 60 years [7]. RRS estimates the 10-year risk of cardiovascular events, which includes MI, ischemic stroke, coronary revascularization, and cardiovascular death. Patients were analysed depending on the RRS groups: <10% (low risk), 10% to 20% (moderate risk), and ≥20% (high risk) to predict cardiovascular events in the next 10 years.

Investigations were in accordance with the Declaration of Helsinki. The study was approved by Bioethics Committee.

3. Statistical methods

Statistical analyses were performed using STATISTICA PL software, version 9.0 and SPSS software, version 19. For continuous variables, arithmetic means and standard deviation (SD) or medians and interquartile range were calculated depending on the normality of distribution. For categorical variables the number of observations (N) and fraction (%) were calculated.

Normality was tested using the Shapiro – Wilk's test for normality.

Differences between two independent samples for continuous data were analyzed using U Mann-Whitney's test (since data distribution was different from normal). To compare more than two independent samples the Kruskal–Wallis test or parametric ANOVA (with post-hoc tests) were used. For categorical variables statistical analysis was based upon results of chi-squared test or chi-squared test with Yates' adjustment. P value <0.05 was considered significant.

4. Results

The baseline characteristics of patients are presented in Table 1. Most of the studied patients had arterial hypertension (80.67%), 31% were obese, almost half of the population had dyslipidemia (49.58%) and 22% were current smokers. There were not any significant differences between analyzed RRS groups in the basic laboratory tests results, heart rate, PlGF, hsCRP or hsTnT levels (Table 2, Table 3). Also there was not a difference in frequency of arterial hypertension (P=0.3954), dyslipidemia (P=0.4584), peripheral arteries disease (P= 0.7172) or current smoking (P= 0.1323) between all studied RRS groups. Opposite to patients with the high RRS, the low RRS patients were younger and had lower blood pressure and significantly higher frequency of marginal or no atherosclerotic changes in coronary arteries (13% vs. 44%) (Table 4). The relationship between RRS and the severity of coronary artery disease was revealed: the higher RRS the lower frequency of marginal or no atherosclerotic changes in coronary arteries (OR=0.19, 95%CI 0.05-0.67). There was not a

Table 1. Characteristic of the studied population.

Age (years) *	63.9±9.2 (44-84), Med. 63 (57-71)
Angina pectoris (CCS class)	
1	20 (16.8)
2	36 (30.3)
3	55 (46.2)
4	8 (6.7)
Positive family history	41(34.5)
Previous MI	29 (24.4)
Previous PCI	24 (20.5)
Current smoking	26 (22.0)
PAD	10 (8.4)
BMI [kg/m^2] *	28.44±4.0 (19.82-42.61), Med.27.83 (25.8-30.8)
Ejection fraction [%]	60.83±7.78 (60-46), Med. 60.0 (55-66)
Heart rate [bpm] *	68.64±11.59 (44-105), Med. 65.5 (60-75)
Heart rate ≥70 bpm *	55 (46.61)
Creatinine [mmol/l] *	0.74±0.16 (0.44-1.52), Med. 0.70 (0.63-0.8)
PlGF [pg/ml] *	31.27±21.11 (2.47-91.4), Med. 25.45 (14-45.87)
hsCRP[mg/l]*	2.88±5.07 (0.1-43), Med. 1.3 (0.8-3.0)
hsTnT [ng/ml*	0.012±0.016 (0.001-0.12), Med. 0.008 (0.005-0.013)
1-vessel CAD	31 (26.05)
2- vessels CAD	28 (23.53)
3- vessels CAD	21 (17.65)
Marginal atherosclerotic plaques	30 (25.21)
Without coronary artery stenosis	9 (7.56)

Data are expressed as N (%), mean ±SD and ranges, median and interquartile ranges (IQR) in nonnormal distribution (*). MI- myocardial infarction; PCI- percutaneous coronary intervention; BMI- body mass index; hsTnT- high- sensitivity troponin T; CRPhs- high- sensitivity C- reactive protein; PlGF- placental growth factor; CAD- coronary artery disease; PAD-peripheral artery disease.

correlation between number of atherosclerotic arteries and PlGF level (R= -0.0647; P=0.486).

5. Discussion

The main finding of our study was that symptomatic non-diabetic middle-aged men with arterial hypertension, dyslipidemia and with low RRS have more often had marginal or no atherosclerotic changes in their coronary arteries in comparison with patients with high RRS. Moreover, the relationship between RRS and severity of atherosclerosis in coronary arteries of these patients was observed. So far there has not been an article, which compared coronary artery angiography results with the RRS in men with stable coronary artery disease. In times of ongoing discussions as to whether to direct some of these patients for invasive diagnostic tests or not, a simple score as RRS appears to be a very useful tool in identification of those with marginal or no changes in coronary arteries. That might help to avoid an invasive diagnosis, which is burdened with complications.

In 2008, Ridker and colleagues analysed also non-diabetic men (N=10,724) in median age 63 years, who were followed up prospectively over 10 years [7]. Authors compared the test characteristics of global model fit, discrimination, calibration, and reclassification in 2 prediction models for incident of cardiovascular events, one based on age, blood pressure, smoking status, total cholesterol, and HDL-C (traditional model) and the other (RRS model) based on these risk factors plus hsCRP

Table 2. Patients characteristics related to Reynolds Risk Score (RRS).

Parameters	RRS <10% (n=50)	RRS 10-20% (n=46)	RRS ≥20% (n=23)
Age [years]	57.84±6.47; Med. 57 (44-73)	66.63±8.20; Med.64.5 (61-74)*	71.61±8.04; Med. 74 (65-79)
BMI [kg/m^2]	28.57±4.29; Med. 27.78 (25.61 30.78)*	28.82 ±4.01; Med. 28.68 (21.97-41.03)	27.36 ±3.88; Med. 26.79 (19.82-37.98)
BPs [mmHg]	123.50 ±12.6; Med.120 (90-155)	134.46±14.65; Med. 130.0 (120-145)*	149.78±19.97; Med. 150 (120-190)
BPd [mmHg]	77.10±8.93; Med. 80.0 (70-80)*	78.59±10.15; Med. 75.0 (70-80)*	88.04±9.38; Med. 90.0 (80-100)*
HA	39 (78)	37 (80.43)	20 (86.96)
Dyslipidemia	24 (48)	22 (47.83)	13 (56.52)
PAD	4 (8.0)	4(8.7)	2 (8.7)
Ejection fraction [%]	61.72±8.90; Med.60.5 (46-79)	61.17±6.56; Med.60 (49-74)	58.22±7.15; Med. 60 (47-74)
Heart Rate [bpm]	50.9±9.41; Med.65 (45-90)	69.73±14.72; Med. 65 (60- 5)*	68.08±8.9; Med. 70 (46-80)
Heart rate ≥70 bpm	22 (44)	21 (46.67)	12 (52.17)
Total cholesterol level [mmol/l]	4.32±1.0; Med. 4.2 (3.7-4.99)	4.26±1.15; Med. 4.28 (2.5-6.5)	4.80±1.29; Med. 4.5 (2.6-8.3)
LDL- cholesterol [mmol/l]	2.22±0.77; Med. 2.2 (1.7-2.6)*	2.17±1.04; Med. 2.0 (1.4-2.6)*	2.71±1.13; Med. 2.6 (0.7-5.76)
HDL- cholesterol [mmol/l]	1.4±0.43; Med. 1.29 (1.05-1.61)*	1.34±0.38; Med.1.35 (1.12-2.09)	1.37±0.45; Med. 1.33 (0.62-2.13)
Triglycerides [mmol/l]	1.50±0.68; Med. 1.34 (0.98-1.9)*	1.64±0.89; Med. 1.27 (1.03-0.9)*	1.95±1.71; Med. 1.26 (0.80-2.85)
LDL/HDL index	1.71±0.72; Med. 1.56 (1.20-2.11)*	2.62±6.70; Med.1.43 (1.07-2.13)*	1.90±0.91; Med. 1.85 (0.0-3.70)
Creatinine [μmol/l]	0.71±0.14; Med. 0.67 (0.62-0.78)*	0.75±0.17; Med. 0.73 (0.63-0.81)*	0.77±0.17; Med. 0.75 (0.44-1.09)
PlGF [pg/ml]	32.47±23.66; Med. 24.60 (11.40-47.56)*	30.23±19.21; Med. 25.45 (15.20-42.47)*	30.69±19.49; Med. 25.50 (7.57-79.64)
hsCRP [mg/l]	2.71±4.03; Med. 1.2 (0.6-2.8)*	2.21±2.69; Med. 1.2 (0.8-2.8)*	4.59±9.10; Med. 1.6 (1.0-4.2)*
hsTnT [ng/ml]	0.014±0.024; Med. 0.007 (0.003-0.012)*	0.010±0.008; Med.0.009 (0.006-0.011)*	0.013 ±0.008; Med.0.011 (0.003-0.32)
1-vessel CAD	11 (22)	11 (23.9)	9 (39.13)
2-vessel CAD	14 (28)	8 (17.39)	6 (26.09)
3-vessel CAD	3 (6)	13 (28.6)	5 (21.74)
Marginal or none changes	22 (44)	14 (30.43)	3 (13.04)

Data are expressed as N (%), mean ±SD and ranges or median (Med) and interquartile ranges (IQR) in variables with nonnormal distribution (*). BMI- body mass index; BPs- systolic blood pressure; BPd- diastolic blood pressure; HA- arterial hypertension; PlGF- placental growth factor; CRPhs- high-sensitivity C- reactive protein; hsTnT- high- sensitivity troponin T. CAD- coronary artery disease; PAD-peripheral artery disease

and parental history of myocardial infarction before the age of 60 years [7]. For the end point of all cardiovascular events, the RRS had better global fit (P<0.001).

In order to improve risk prediction, the National Education Cholesterol Panel Adult Treatment Program (NCEP ATP III) has taken into account the incidence of diabetes, stroke, aortic aneurysms, and peripheral artery disease for the identification of high-risk individuals [8]. By searching for a better risk stratifying tool, the newer factors (metabolic, inflammatory, parental history) were also taken into account in CARRISMA Score (Cardiovascular Risk Management) [9], QRISK2 Score (risk score which uses the QRESEARCH database) [10,11], National Health and Nutrition Examination Survey (NHANES) [12] and RRS [6].

The Framingham Heart Study is well known for its 10-year risk score and FRS, for its prediction of cardiovascular disease events in the general population

Table 3. Results of comparison of Reynolds Risk Score (RRS) groups- analysis of variance ANOVA Kruskal- Wallis test.

Parameters	ANOVA	RRS <10% vs 10-19%	RRS 10-19% vs ≥20%	RRS <10% vs ≥20%
		P	P	P
BMI [kg/m^2]	0.4399	1.0000	1.0000	0.6119
BPd [mmHg]	0.0001	1.0000	0.0002	0.0007
EF [%]	0.3112	1.0000	0.4152	0.6113
Heart Rate [bpm]	0.9364	1.0000	1.0000	1.0000
LDL- cholesterol [mmol/l]	0.1081	1.0000	0.3498	0.1068
Triglycerides [mmol/l]	0.9377	1.0000	1.0000	1.0000
LDL/HDL index	0.2622	1.0000	0.8965	0.3076
Creatine [μmol/l]	0.2120	0.6399	0.3088	1.0000
PlGF [pg/ml]	0.9873	1.0000	1.0000	1.0000
hsTnT [ng/ml]	0.3078	0.8744	0.4396	1.0000

BMI- body mass index; BPd- diastolic blood pressure; PlGF- placental growth factor; CRPhs- high-sensitivity C-reactive protein; hsTnT- high sensitivity troponin.

Table 4. Significant differences between patients with low vs high Reynolds Risk Score (RRS).

Parameters	RRS<10% (n=50)	RRS≥20% (n=23)	P
Age [years]	57.84±6.47 Med. 57 (44-73)	71.61±8.04 Med.74.0 (65-79)*	0.0000
BPs [mmHg]	123.50±12.6 Med.120 (90-155)	149.78±19.97 Med. 150 (120-190)	0.0000
BPd [mmHg]	77.10±8.93 Med. 80 (70-80)*	88.04±9.38 Med. 90 (80-100)*	0.0002
1-vessel CAD 2 - vessel CAD 3 - vessel CAD Marginal or none changes	11 (22) 14 (28) 3 (6) 22 (44)	9 (39.13) 6 (26.09) 5 (21.74) 3 (13.04)	0.0214

Data are expressed as N (%), mean ±SD and ranges or median and IQR in nonnormal distribution (*). BPs- systolic blood pressure; BPd- diastolic blood pressure

[13]. The MESA (Multi-Ethnic Study of Atherosclerosis) was a prospective cohort study examining measures and progression of subclinical atherosclerosis but also conversion to clinical events among 6,814 participants (3,213 men and 3,601 women) who were between 45 to 84 years old, and free of clinical cardiovascular diseases at first examination from 4 different ethnic groups (white, black, Hispanic, and Chinese) in the USA [14]. The distribution of coronary artery calcium (CAC) levels, measured using electron-beam and multi-detector row computer tomography across FRS strata were examined in the MESA participants (total of 5,660 men and women, 79 years old or younger at baseline) by Okwuosa TM et colleagues [15]. They have shown that in very low-risk individuals (FRS≤ 5%), the yield of screening and probability of identifying persons with clinically significant levels of CAC is low, but becomes greater in low- and intermediate-risk persons (FRS 5.1% to 20%) [15]. Similar to their results, in our study patients with the low RRS mostly had marginal or no atherosclerotic changes in coronary arteries.

DeFilippis AP et al. compared the association of the FRS and RRS with subclinical atherosclerosis, assessed by incidence and progression of CAC in 5,140 MESA participants (mean age 61±10 years, 47% males, mean follow-up: 3.1±1.3 years) [16]. Both the FRS and RRS were significantly predictive of incidental CAC (relative risk RR=1.40; 95% CI 1.29-1.52 and RR=1.41; 95% CI 1.30-1.54 per 5% increase in risk, respectively) and CAC progression (mean CAC score change=6.92; 95% CI 5.31-8.54 and 6.82; 95% CI: 5.51-8.14 per 5% increase, respectively). Discordance in risk category classification (<10% or >10% per 10-year coronary heart disease risk) occurred in 13.7%, with only the RRS consistently adding predictive value for incidence and progression of CAC. These subclinical atherosclerosis findings were supported by the coronary heart disease events in 5.6 ±7 years of follow-up [16]. This is the only

article concerning what is occurring in the coronary arteries with respect of RRS.

An important role in cardiovascular risk stratification play also the biomarkers. PlGF is a strong candidate as a biomarker for plaque instability, myocardial ischemia, and prognosis for patients with ACS [17,18], and it seems to be useful also in stable coronary artery disease. Therefore we investigated its role in combination with RRS in stable coronary artery disease. We did not reveal a relationship between PlGF level either for the RRS or the severity of atherosclerosis in coronary arteries.

There still do not exist perfect non-invasive methods for predicting both severity of coronary artery disease and the risk of cardiovascular events in stable angina, although it would be of vital importance in new approach in prevention of cardiovascular events. New factors of pathogenesis of the coronary artery disease are still under investigations, such as epicardial adipose tissue (EAT), which is metabolically active tissue that accumulates around the coronary arteries and may contribute to local inflammatory load by increased synthesis of inflammatory cytokines [19]. In view of ongoing inflammatory processes in the wall of the coronary arteries, it seems that the risk scores, which take into account the hsCRP level as RRS, may be helpful in decision process for invasive diagnostic tests such as coronary angiography.

6. Limitations

The main limitation of this study was the small number of patients. There is also lack of prospective evaluation. The next limitation is that the visual quantification of coronary arteriography lesions did not include quantitative analysis and fractional flow reserve.

7. Conclusions

It would appear that the Reynolds Risk Score may be considered as a useful stratifying tool in men with stable coronary artery disease and the preserved left ventricular systolic function.

Acknowledgements

The study was supported from Medical University of Lodz grant (Nr 502-03/1-005-02/502-14-091).

Conflict of interest

None declared.

References

[1] Ridker PM, Brown NJ, Vaughan DE, Harrison DG, Mehta JL, Established and emerging plasma biomarkers in the prediction of first atherothrombotic events. Circulation, 2004, 109(1): IV6-19

[2] Hansson GK, Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med, 2005, 352,1685-1695

[3] Libby P, Theroux P, Pathophysiology of coronary artery disease. Circulation, 2005, 111,3481-3488

[4] Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, et al., Centers for Disease Control and Prevention; American Heart Association, Markers of Inflammation and Cardiovascular Disease Application to Clinical and Public Health Practice: A Statement for Healthcare Professionals From the Centers for Disease Control and Prevention and the American Heart Association. Circulation, 2003, 107,499-511

[5] Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, et al., C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet, 2010, 375,132-140

[6] Ridker PM, Buring JE, Rifai N, Cook NR, Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. JAMA, 2007, 297,611-619

[7] Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR, C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. Circulation, 2008, 118,2243-2245

[8] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), JAMA, 2001, 285,2486-2497

[9] Gohlke H, Winter M, Karoff M, Held K, CARRISMA: a new tool to improve risk stratification and

guidance of patients in cardiovascular risk management in primary prevention. Eur J Cardiovasc Prev Rehabil, 2007, 14,141-148

[10] Collins GS, Altman DG, An independent external validation and evaluation of QRISK cardiovascular risk prediction: a prospective open cohort study. Br Med J, 2009, 339,b2584-b2593

[11] Collins GS, Altman DG, An independent and external validation of QRISK2 cardiovascular disease risk score: a prospective open cohort study. Br Med J, 2010, 340,c2442-c2450

[12] Gaziano TA, Young CR, Fitzmaurice G, Atwood S, Gaziano JM, Laboratory- based versus non-laboratory-based method for assessment of cardiovascular disease risk: the NHANES I Follow-up Study cohort. Lancet, 2008, 371,923-931

[13] O'Donnell CJ, Elosua R, Cardiovascular risk factors. Insights from Framingham Heart Study. Rev Esp Cardiol, 2008, 61,299-310

[14] Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, et al., Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol, 2002, 156, 871-881

[15] Okwuosa TM, Greenland P, Ning H, Liu K, Bild DE, Burke GL, Eng J, et al., Distribution of coronary artery calcium scores by Framingham 10-Year risk strata in the MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol, 2011, 57,1838-1845

[16] DeFilippis AP, Blaha MJ, Ndumele CE, Budoff MJ, Lloyd-Jones DM, McClelland RL, et al., The association of Framingham and Reynolds Risk Scores with incidence and progression of coronary artery calcification in MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol, 2011,58,2076-2083

[17] Heeschen C, Dimmeler S, Fichtlscherer S, Hamm CW, Berger J, Simoons ML, et al., CAPTURE Investigators, Prognostic value of placental growth factor in patients with acute chest pain. JAMA, 2004,291, 435-441

[18] Lenderink T, Heeschen C, Fichtlscherer S, Dimmeler S, Hamm CW, Zeiher AM, et al., CAPTURE Investigators: Elevated placental growth factor levels are associated with adverse outcomes at four-year follow-up in patients with acute coronary syndromes. J Am Coll Cardiol, 2006, 47,307-311

[19] Silaghi AC, Pais R, Valea A, Mironiuc AI, Silaghi H, Epicardial adipose tissue and relationship with coronary artery disease. Centr Eur J Med, 2011, 6,251-262