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Predictive value of laboratory markers in the development of cardiac events in patients with stable coronary artery disease after elective endovascular revascularization

Aim	To reveal a relationship between preprocedural laboratory data and adverse cardiac outcomes (CO) in patients with stable ischemic heart disease (IHD) following elective endovascular revascularization (ER).
Material and methods	This study included 225 patients with IHD admitted for treatment to the Research Institute of Cardiology of the Tomsk National Research Medical Center. The study included patients with documented IHD and hemodynamically significant coronary stenoses requiring elective ER. Patients were divided into groups based on the presence of complications: group 1, 98 patients with adverse CO and group 2, 127 patients without adverse CO. Besides evaluation of complaints, history, and objective status, general clinical and biochemical tests were performed for all patients. Concentration of glycated hemoglobin (HbA1c) was measured by immunoturbidimetry (DiaSys Diagnostic Systems). Serum concentrations of insulin, interleukin-6 (IL-6), endothelin 1 (ET-1), and homocysteine were measured by enzyme immunoassay. Blood lipid profile was determined by enzymatic colorimetry (DiaSys). Content of non-high-density lipoprotein (non-HDL) cholesterol (CS) was calculated as: CS – HDL CS. Insulin resistance (IR) was assessed by the HOMA-IR index. IR was diagnosed at the index of 2.77. Statistical analyses were performed with Statistica 10.0 and Medcalc 19.2.6 software.
Results	A one-way regression analysis identified predictors for adverse CO following ER. The most significant predictors were fibrinogen (odds ratio (OR), 1.430; 95% confidence interval (CI), 1.027–1.990), HbA1c (OR 1.825; 95% CI, 1.283–2.598), homocysteine (OR, 1.555; 95% CI, 1.348–1.794), ET-1 (OR, 94.408; 95% CI, 16.762–531.720), triglycerides (TG)/glucose ratio (OR 1.815; 95% CI, 1.155–2.853). Based on selected factors, logistic regression models were constructed. However, not all models had a high prognostic power. Only concentrations of ET-1 and homocysteine showed a high prognostic capability in respect of the adverse outcome (88.3 and 85.7%, respectively).
Conclusion	For patients with IHD, the prognostic capability of ET-1 and homocysteine with respect of the risk for adverse CO following ER was the highest compared to other markers. The results of the study are completely consistent with data of literature and can be successfully used in clinical practice for optimizing the medical care of patients after elective ER.

Keywords	Ischemic heart disease; homocysteine; endothelin 1; prognosis; revascularization
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Cardiovascular disease (CVDs) remains the leading cause of mortality in the world's population. Increased incidence of coronary artery disease (CAD), advances in the development of stents and techniques for myocardial revascularization, and improved clinical efficacy have resulted in an increasing number of procedures performed using percutaneous coronary intervention (PCI). Regardless of the quality of interventions performed, repeated cardiovascular events remain a problem of current concern [1, 2].

In 2014, a meta-analysis of 95 studies (93,553 cases) found that the use of first-generation drug-eluting stents (Taxus, Cypher, Endeavor) showed a downward trend in mortality. Second-generation drug-eluting stents (Xience, Promus, Resolute) established the statistical significance of this trend. The decrease in mortality in the PCI group

compared to the conservative treatment group was 25–35% depending on the type of stent [3]. In order to reduce the risk of coronary and cerebral events and the likelihood of fatal outcomes, further research is needed to find the factors that determine the long-term outcomes of CAD after elective PCI.

Aim

To clarify the relationship of pre-procedural laboratory parameters in the occurrence of adverse cardiovascular outcomes in patients with stable CAD after elective endovascular revascularization (ER).

Material and methods

The study included 225 patients with CAD who underwent inpatient treatment at the Research Institute of Cardiology, Tomsk National Research Medical Center.

Inclusion criteria: the study included patients with documented stable CAD and hemodynamically significant coronary stenosis who needed elective ER.

Exclusion criteria: acute coronary or cerebrovascular events within past 6 months, uncontrolled arterial hypertension, cancer, hematological and immune diseases, acute inflammatory diseases, and administration of anti-coagulant drugs.

The mean follow-up period was 14.5 (6; 23) months.

The study design was approved by the ethics committee. All included patients signed the informed consent to participate in the study.

All patients had previously received acetylsalicylic acid (ASA) 75 mg/day, and dual antiplatelet therapy was ordered immediately before ER: ASA 75 mg, and clopidogrel 600 mg/day loading dose followed by 75 mg/day maintenance dose for at least 6–12 months after coronary stenting.

During the study, adverse cardiovascular outcomes were recorded. These included death, non-fatal myocardial infarction (MI), acute coronary syndrome (ACS), stroke, recurrent angina pectoris with angiographically confirmed stent restenosis, progression of chronic heart failure (CHF) by one functional class or more, repeated (surgical, endovascular) coronary revascularization, ventricular arrhythmias, atrial fibrillation, and pacemaker implantation. Restenosis was the clinically significant (anginal pain) narrowing of the stent lumen by 50% or more or a 70% narrowing, in all cases when not indicative of recurrent angina. Hemodynamically significant narrowing of coronary arteries localized elsewhere was considered as the progression of atherosclerosis.

All deaths were considered as fatal cardiovascular outcomes, if no other cause was established. Control angiographic examination was performed 12 months later or when anginal pain and/or ischemia appeared, according to investigations.

All patients underwent standard general clinical and biochemical examinations, as well as the assessment of complaints, medical history, objective status. Fasting blood samples were collected from the peripheral veins 2 to 3 days before the PCI. Glycated hemoglobin (HbA1c) was measured using immunoturbidimetry (DiaSys Diagnostic Systems, Germany). Enzyme-linked immunosorbent assay (ELISA) was used to determine serum levels of insulin (Monobind Inc., US), interleukin-6 (IL-6; Vector-BEST, RF), endothelin-1 (ET-1: Biomedica, Austria), and homocysteine (Axis-Shield Diagnostics Ltd., GB). The blood lipid composition was determined by enzymatic colorimetry (DiaSys, Germany). The levels of non-high-density lipoprotein cholesterol (non-HDL–C) were calculated using the following formula: total cholesterol (TC) – high-density lipoprotein cholesterol (HDL–C). Insulin resistance (IR) was evaluated using the HOMA-IR index. IR was diagnosed, if the index was more than 2.77.

The data obtained was processed using the Statistica 10.0 and Medcalc 19.2.6 software suites. The quantitative data is expressed as the median and interquartile range (Me [Q1; Q3]). The categorical data is presented as the absolute and relative values (n (%)). The quantitative variables were compared using the Mann-Whitney U-test, and the categorical data was compared using Fisher's exact test and χ^2. Logistic regression analysis was used to construct prediction models. Odds ratio (OR) and 95% confidence interval (cardiovascular outcomes) were used as a quantitative measure to assess the influence of the factors of interest on the outcome. Differences were statistically significant if p was less than 0.05.

Results

The outcomes of PCI with stenting were assessed in all patients. Adverse cardiovascular outcomes were reported in 98 (43.5%) patients in the follow-up period: 3 (3.1%) sudden deaths; 14 (14.3%) cases of ACS, including 4 (4.1%) cases of MI. 25 (25.4%) patients underwent repeat revascularization due to progressing coronary atherosclerosis. The clinical picture of stable angina pectoris recurred in 18 (18.4%) patients, which was associated with stent restenosis. CHF progressed in 8 (8.2%) patients. Cerebral accidents occurred in 3 (3.1%) patients, life-threatening arrhythmias, cardioverter-defibrillator implantation in 18 (18.4%) and 5 (5%) patients, respectively.

All patients were grouped according to the presence of cardiovascular events: group 1 (adverse cardiovascular outcomes; n=98); and group 2 (no adverse cardiovascular outcomes – n=127). The clinical and angiographic characteristics of patients are provided in Table 1 and Table 2. There were no significant differences between

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the groups in the main clinical and demographic characteristics.

Drug therapy before and after ER did not differ statistically significantly between the groups (Figure 1).

In the group of patients with adverse cardiovascular outcomes during the prospective follow-up after stenting, higher initial values of blood lipid composition (TC, non-HDL–C), carbohydrate metabolism (basal glycemia, HOMA-IR) were established. Moreover, it was shown that patients with adverse cardiovascular outcomes initially had higher concentrations of IL-6, homocysteine, ET-1 (Table 3).

Logistic regression was then used to identify the main predictors which to a maximum extent determine the development of adverse cardiovascular outcomes in patients with CAD after revascularization. Models were constructed based on the selected factors. This allowed for OR to be calculated, in order to assess the isolated influence of the factors of interest on the development of adverse clinical outcomes.

Univariate regression analysis identified the following predictors which determine the development of adverse cardiovascular outcomes after PCI (Table 4).

Odds ratio (OR) of developing a favorable outcome versus an adverse outcome

Table 4 shows how many times OR increases when an indicator is increased by one. Thus, the study showed that when the indicators increase, in most cases the odds of developing adverse cardiovascular outcomes increase statistically significantly. The levels of fibrinogen, HbA1c, homocysteine, ET-1, and triglycerides/glucose ratio were the most significant indicators.

One-way logistic regression was used to construct the prediction model. This allows for a predict of the development of adverse cardiovascular outcomes to be made (Table 5).

Regression analysis found that not all models have high predictive power (Table 6).

Several logistic regression equations were obtained, from which only those with the highest correct prediction value (>80%) were selected. It was found that only ET-1 and homocysteine had high predictive power regarding both favorable and adverse outcomes. Models were constructed for these indicators, in order to assess the predictive probability p (X) of an adverse annual

Table 1. Clinical characteristics of the examined patients

Parameter	Group 1 (adverse cardiovascular outcomes), n=98	Group 2 (favorable cardiovascular outcomes), n=127	p
Sex (male/female)	83 (84.7)/15 (15.3)	108 (85.0)/19 (15.0)	0.544
Age, years	56 [51; 63]	56 [52; 62]	0.718
Obesity, n (%)	49 (50)	56 (44.1)	0.228
Diabetes mellitus, n (%)	48 (49)	55 (43.3)	0.397
Arterial hypertension, n (%)	93 (94.9)	124 (98.4)	0.134
Postinfarction cardiosclerosis, n (%)	60 (61.2)	88 (69.3)	0.131
Smoking, n (%)	48 (51.6)	55 (47.8)	0.587
Chronic kidney disease, n (%)	23 (23.5)	34 (26.8)	0.642
Left ventricular ejection fraction, %	61.5 [45; 64]	58 [45; 65]	0.362

The data are expressed as the median and interquartile range (Me [Q1; Q3]) unless otherwise specified.

Table 2. Angiographic characteristics of the examined patients

Parameter	Group 1 (adverse cardiovascular outcomes), n=98	Group 2 (favorable cardiovascular outcomes), n=127	p
SYNTAX, score	18.2 [11.5; 28]	16 [11; 24]	0.483
Number of arteries involved	2.1 [1.6; 2.4]	1.9 [1.4; 2.4]	0.421
Number of hemodynamically significant stenotic lesions per patient	2.1 [1.6; 2.4]	1.9 [1.4; 2.4]	0.421
Number of occlusions, n (%)	36 (36.7)	56 (44.1)	0.323
Bifurcation lesions, n (%)	34 (34.7)	56 (44.1)	0.213
Revascularization completeness, n (%)	87 (88.8)	107 (84.2)	0.314
Number of drug-eluting stents, n (%)	65 (66.3)	84 (66.1)	0.671
	Sirolimus – 47	Sirolimus – 62	
	Everolimus – 18	Everolimus – 22	
Протяженность стенозов, мм	16 [13; 19]	17 [13;21]	0.711

The data are expressed as the median and interquartile range (Me [Q1; Q3]) unless otherwise specified.

Figure 1. Comparative characteristics of the main classes of drugs in patient groups (%)

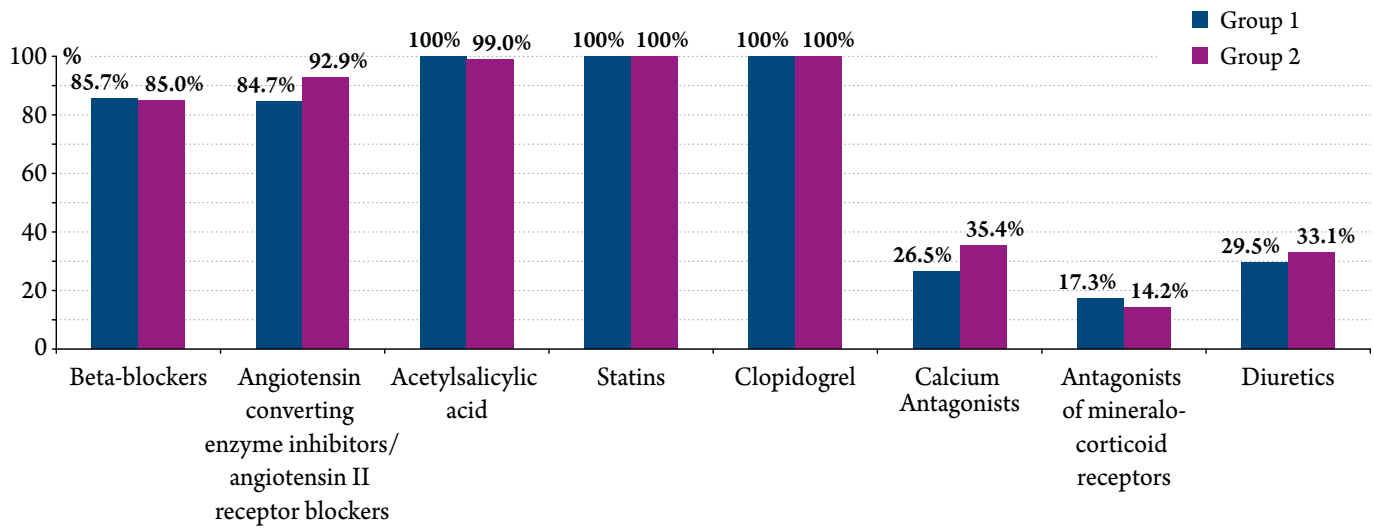

Table 3. Comparative characteristics of the parameters analyzed

Parameter	Group 1 (adverse cardiovascular outcomes), n=98	Group 2 (favorable cardiovascular outcomes), n=127	p
Fibrinogen, g/L	4.3 [3.4; 5.1]	3.8 [3.3; 4.3]	0.021
TC, mmol/L	6 [5.3; 6.7]	5.7 [4.6; 6.8]	0.0189
non-HDL-C, mmol/L	4.9 [4.3; 5.7]	4.6 [3.5; 5.6]	0.019
Basal glucose, mmol/L	6.5 [5.6; 7.7]	6 [5.5; 6.7]	0.016
HOMA-IR, units	4.8 [3.3; 6.6]	2.6 [2.2; 4.6]	0.000
IL-6, pg/mL	11.5 [6.3; 17.7]	3.6 [2.2; 8.7]	0.000
Homocysteine, μmol/L	19.9 [16.4; 24.6]	9.4 [8.3; 11.1]	0.000
Endothelin-1, fmol/mL	1.7 [1.1; 2.4]	0.4 [0.3; 0.6]	0.000

TC, total cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol;
HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; IL-6, interleukin-6.

Table 4. Univariate analysis of the indicators associated with adverse cardiovascular outcomes in patients after elective PCI (only statistically significant predictors)

Parameter	OR	95% CI
Endothelin-1	94.408	16.762–531.720
HbA1c	1.825	1.283–2.598
TG/glucose	1.815	1.155–2.853
Homocysteine	1.555	1.348–1.794
Fibrinogen	1.430	1.027–1.990
TC	1.332	1.061–1.672
Non-HDL-C	1.377	1.095–1.731
HOMA-IR	1.321	1.150–1.616
Basal glycemia	1.211	1.044–1.406
Insulin	1.101	1.050–1.154
IL-6	1.072	1.029–1.117

PCI, percutaneous coronary intervention;
OR, odds ratio; CI, confidence interval; HbA1c, glycated hemoglobin; TG, triglyceride; TC, total cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; IL-6, interleukin-6.

prognosis. Thus, the following equations with the highest predictive value of factors were obtained.

$$p=\frac{1}{1+e^{-y}},$$

where Y= –6.132 + 0.441·homocysteine, – 6.132 and 0.441 are regression coefficients, and e is a mathematical constant equal to 2.718;

The result was considered as favorable with p>0.5 and adverse with p<0.5. Variable coefficient significance is<0.0001. Model significance is<0.0001.

The second equation is as follows:

$$Y = – 3{,}623+4{,}548\cdot ET\text{-}1,$$

where –3.623 and 4.548 are regression coefficients, and e is a mathematical constant equal to 2.718;

The variable coefficient significance is <0.0001. Model significance is <0.0001.

Logistic regression analysis as a method of mathematical modeling allows not only for predictors of events to be

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Table 5. Prediction models

Parameter	Equation (Y)	Variable coefficient significance	Model significance
Homocysteine	–6.132+0.441·X	<0.0001	<0.0001
Endothelin-1	–3.623+4.548·X	<0.0001	<0.0001
Insulin	–1.142+0.096·X	<0.0001	<0.0001
HOMA-IR	–0.964+0.278·X	0.0001	<0.0001
TG/glucose	–3.944+0.596·X	0.0010	0.0077
IL-6	–0.417+0.070·X	0.0009	0.0003
HbA1c	–3.877+0.602·X	0.0007	0.0004
Basal glucose	–1.034+0.192·X	0.0117	0.0061
Non-HDL-C	–1.319+0.320·X	0.0064	0.0047
Fibrinogen	–1.101+0.357·X	0.0344	0.0281
TC	–1.427+0.287·X	0.0136	0.0109

HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; TG, triglycerides;
IL, interleukin; HbA1c, glycated hemoglobin; non-HDL-C, non-high-density lipoprotein cholesterol; TC, total cholesterol.

Table 6. Model predictive value

Parameter	% of correctly predicted adverse events	% of correctly predicted favorable events	% of correctly predicted events	Model significance
Homocysteine	88.3	83	86.2	<0.0001
Endothelin-1	85.7	92.5	88.5	<0.0001
IL-6	75.7	72.3	72.4	0.0003
HOMA-IR	70.1	66.3	68.4	<0.0001
HbA1c	76.4	57.9	64.5	0.0004
Insulin	73.8	62.7	65	<0.0001
TC	88.2	32.7	64	0.0109
Non-HDL-C	85.2	38.8	64.5	0.0047
Fibrinogen	87.6	19.1	59.5	0.0281
TG/glucose ratio	80	27.6	57.4	0.0077
Basal glycemia	81.1	16.3	52.9	0.0061

IL, interleukin; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; HbA1c, glycated hemoglobin;
TC, total cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; TG, triglycerides.

defined, but also for a prediction model that covers several parameters to be constructed. It is impossible to include statistically related attributes in one prediction model. Therefore, the prognostic attributes for collinearity need to be verified. Correlations and associations between attributes need to be identified, before creating a mathematical model that includes more than one predictor.

Checking for collinearity showed that almost all parameters correlated with each other. This is why we were unable to build a prediction model that included several parameters (Table 7).

Discussion

Endothelium is a complex and multifunctional organ with an area of >5000 m^2 and weighs 2–3 kg. It forms a barrier between blood and vessel smooth muscles and acts as an active modulator of vascular functions [4].

ET-1 is produced by the vascular endothelium in the heart and mainly acts through two receptors: endothelin receptors type A and B. Endothelin receptors type A have a high affinity for ET-1 and are expressed in vascular smooth muscle cells and the myocardium [5].

ET-1 is a functional peptide with a powerful peripheral and coronary vasoconstrictor through the stimulation of vascular smooth muscle cells. It also has a vasodilating effect in both vascular systems by stimulating nitric oxide. This ensures the stability of vascular tone in the coronary vessels and the systemic circulation. High plasma levels of ET-1 are a prognostic marker of CHF progression [6, 7].

Li et al. [8] have shown increased plasma levels of ET-1 as a prognostic factor in the development of ventricular arrhythmias in patients with implantable cardioverter-defibrillators.

ET-1 levels increase in acute MI. Hartopo et al. [9] showed that elevated serum levels of ET-1 were independently associated with adverse cardiovascular outcomes in patients with non-ST segment elevation MI. Serum concentration was almost 5 times as high as in patients without adverse outcomes. It was found that the ET-1 levels of >2.59 pg/mL were a predictor of hospital adverse cardiovascular outcomes

(adjusted OR 44.4395% CI: 1.44–1372.99; p<0.03), and the incidence of such events was 13.6% [9].

Hyperhomocysteinemia is a marker of cardiovascular and cerebrovascular risk, as well as other modifiable and unmodifiable factors [10]. According to some researchers, homocysteine levels of more than 10 μmol/L are associated with CAD risk [11]. A 25% increase in plasma homocysteine levels is associated with a 10% increase in cardiovascular risk and a 20% increase in the risk of stroke. Another meta-analysis showed that decreased serum levels of homocysteine by 3 μmol/L led to a decrease in the incidence of CAD by 16%. A 5 μmol/L elevation increases the relative risk (RR) of developing CAD 1.6–1.8 times [12]. Another meta-analysis found that a 5 μmol/L increase in homocysteine levels was associated with a 32% increase in the risk of death and a 52% increase in the risk of developing CVD [13].

Li et al. [14] found that elevated homocysteine levels are an independent predictor of clinically significant cardiovascular and cerebrovascular events in patients with CAD after PCI.

A meta-analysis by Zhang et al. [15] showed that higher levels of homocysteine were not associated with an increased risk of stent restenosis (RR 1.10; 95% CI: 0.90–1.33), but increased the risk of restenosis after angioplasty and the risk of all-cause death 3.19 times on average (RR 3.19; 95% CI: 1.90–5.34; p=0.000), the risk of major adverse outcomes – 1.51 times (RR 1.51; 95% CI: 1.23–1.85; p=0.000), and the risk of cardiac death – 2.76 times (RR 2.76; 95% CI: 1.44–5.32; p=0.000).

Hyperhomocysteinemia can cause CVDs by increasing the proliferation of muscle cells, and vasoconstriction. This can result in the altered coagulant properties of blood, damaging the artery walls and vascular endothelium [14].

Table 7. Correlations of the parameters analyzed

Parameter	Endothelin-1	Homocysteine
Fibrinogen	r=0.104; p=0.23	r=0.081; p=0.36
TC	r=0.072; p=0.41	r=0.025; p=0.76
Non-HDL-C	r=0.065; p=0.46	r=0.014; p=0.88
Basal glucose	r=0.074; p=0.39	r=0.183; p=0.04
HbA1c	r=0.344; p=0.008	r=0.324; p=0.01
Insulin	r=0.676; p=0.000	r=0.611; p=0.000
HOMA-IR	r=0.633; p=0.000	r=0.622; p=0.000
IL-6	r=0.668; p=0.000	r=0.671; p=0.000
Homocysteine	r=0.891; p=0.000	1
Endothelin-1	1	r=0.891; p=0.000
TG/glucose	r=0.06; p=0.45	r=0.014; p=0.193

TC, total cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; IL-6, interleukin-6; TG, triglycerides.

Conclusion

This study established that endothelin-1 and homocysteine have the highest predictive ability regarding the risk of adverse outcomes in patients with stable coronary artery disease after elective percutaneous coronary intervention, when compared with other markers studied. Our findings are entirely consistent with the literature and can be successfully used in clinical practice, in order to optimize approaches to the medical care of patients who have undergone elective percutaneous coronary intervention. Further research is needed to find factors which determine the long-term outcomes of coronary artery disease after elective percutaneous coronary intervention, in order to reduce the risk of coronary and cerebral events and the likelihood of a fatal outcome.

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