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Prediction of long-term adverse cardiovascular events after percutaneous coronary interventions in patients with coronary artery disease and concomitant chronic obstructive pulmonary disease

Aim To identify independent predictors for long-term serious adverse cardiovascular events following percutaneous coronary interventions (PCI) in patients with a combination of ischemic heart disease (IHD) and chronic obstructive pulmonary disease (COPD) and to develop a prognostic mathematical model.

Material and methods Design: a prospective cohort study. The study included 254 patients with IHD associated with COPD after PCI (in 119 patients, PCI was performed for acute coronary syndrome and in 135 patients, PCI was elective). Follow-up duration was up to 36 months. Composite endpoint included cardiovascular death, myocardial infarction, stroke or repeated, unscheduled myocardial revascularization. Cox regression with stepwise inclusion of variables was used for identification of predictors for the composite endpoint.

Results The following independent predictors of serious adverse cardiovascular events were identified: number of stenoses in major coronary artery branches, ankle-brachial index. glomerular filtration rate, age, distance in 6-min walk test, COPD phenotype with frequent exacerbations (FE), and functional residual capacity (FRC) of lungs. The mathematical model based on the Cox regression for prediction of serious adverse cardiovascular events had a 75% sensitivity and a 81% specificity.

Conclusion Incidence of long-term serious adverse cardiovascular events in patients with a combination of IHD and COPD after PCI depends not only on traditional cardiovascular risk factors but also on characteristics of COPD itself, such as the FE phenotype and the FRC indicative of lung hyperinflation. The proposed mathematical model based on the Cox regression can be used for evaluating the odds for adverse cardiovascular events after PCI in patients with a combination of IHD and COPD.

Keywords Ischemic heart disease; percutaneous coronary interventions; chronic obstructive pulmonary disease; serious adverse cardiovascular events; independent predictors; mathematical model

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The study of the effect of comorbidities on the long-term prognosis of acute and chronic coronary syndromes is one of the hottest topics in clinical medicine that is directly applicable to clinical practice. Such common combinations of comorbidities as coronary artery disease (CAD) and diabetes mellitus (DM), CAD and chronic kidney disease (CKD), CAD and hypertension, have been sufficiently studied to date, including their prognostic aspect. Therefore, these diseases are included in mathematical models used to calculate cardiovascular risks.

The management of coronary patients with a comorbid pathology is specified in particular sections of the European Guidelines on Acute and Chronic Coronary Syndromes [1, 2]. Chronic obstructive pulmonary disease (COPD) remains a common disease, which is rarely considered in the prospective analysis of cardiovascular prognosis due to the methods used in most such studies. Specifically, spirography is barely used to verify the diagnosis of COPD. Thus, cases of subclinical COPD usually remain undiagnosed.

Therefore, it remains a continuing challenge to estimate what role COPD plays in the long-term prognosis of patients with CAD, including in those after percutaneous coronary intervention (PCI). There are two prognostic models for the assessment of cardiovascular risks that take COPD into account as a predictor variable: 1) SYNTAXSCOREII score, based solely on total mortality for patients with multivessel CAD; 2) ACSrisk score, designed to predict the two-year risk of death after acute coronary syndrome (ACS) [3, 4].

The prevalence of COPD in the general population is barely different from that of DM or CKD, and the high rate of COPD and CAD comorbidity indicates the presence of common elements of pathogenesis [5–7]. However, there are far fewer publications reporting the effect of COPD on the prognosis in acute and chronic forms of CAD than in the case of DM and CKD. This is especially true for patients with clinically significant CAD treated with modern endovascular methods and techniques. PCI is currently the leading method of myocardial revascularization (MR). In developed countries, the ratio of PCI to coronary artery bypass grafting (CABG) varies from 2:1 to 6:1. There is reason to believe that the relative proportion of PCI in the treatment of CAD will further increase.

One of the main challenges in the application of PCI is to ensure good long-term results. Due to in-stent restenosis, the high recurrence rate of exertional angina has been, for a long time, the major drawback of endovascular intervention. This problem has been substantially resolved by next-generation drug-eluting stents. However, the elimination of local coronary stenosis by deploying a coronary stent does not solve all problems, and this continues to put patients with CAD at very high cardiovascular risk. Thus, the search for predictors associated with the worsening of the long-term cardiovascular prognosis after successful PCI is an urgent task.

The objective of this study was to identify independent predictors of long-term, serious, adverse cardiovascular events following PCI in patients with concomitant CAD and COPD and to create a mathematical model to estimate the probability of these events.

Material and methods

Patients at the Research Institute of Regional Clinical Hospital No. 1 named after Professor S.V. Ochapovskiy were included in the study. Patients during 2012–2014 with acute and chronic CAD and concomitant COPD were selected based on the following inclusion and exclusion criteria. The inclusion criteria were:

1) signed informed consent;
2) age ≥40 yrs;
3) the presence of any of the following diagnoses: acute MI, unstable angina, or stable exertional angina confirmed by a positive stress test;
4) PCI with coronary stent implantation during ongoing hospitalization;
5) a long smoking history (≥10 pack-years) and active smoking status at the time of inclusion or smoking cessation within the last year;
6) diagnosis of COPD made according to GOLD 2011 [8].

The exclusion criteria were:

1) a history of MR;
2) valvular heart disease with indications for surgical correction, left ventricular ejection fraction <35% by the end of the first week after MR;
3) glomerular filtration rate (GFR) <30 ml/min/m^2 calculated using CKD-EPI;
4) resistant hypertension;
5) lower limb pathology that prevented the patient from performing a stress test;
6) non-COPD lung diseases;
7) diffuse connective tissue disease;
8) cancer;
9) complications of PCI, i.e., CA dissection, perforation or rupture, or no-reflow phenomenon.

All patients underwent spirography to detect bronchial obstruction according to the guidelines of the American Thoracic Society (2005) using a SpirovitSP-1 spirograph (Schiller, Switzerland). In stable exertional angina, spirography was performed before PCI, following ACS on days 7–9 after the admission to the hospital. In the presence of bronchial obstruction, a bronchodilator test was done with salbutamol 400 mg delivered through a metered-dose inhaler. COPD was diagnosed according to the GOLD 2011 spirographic criteria, i.e., the ratio of the forced expiratory volume exhaled in 1 sec (FEV 1) to the forced vital capacity (FVC) at 15–30 min after salbutamol administration should be less than 0.70. The percentage of the reference values for FEV1 determined the COPD severity. According to the findings of spirography with the bronchodilator test, concomitant COPD was diagnosed in 261 patients, seven of whom subsequently experienced complications of scheduled PCI as described in the exclusion criteria. The static lung volumes and capacities, total lung capacity (TLC), functional residual capacity (FRC), and residual lung volume (RLV), were determined in all patients diagnosed with COPD using the V6200 Autobox (SensorMedics, USA) or the MasterScreenBody (ErichJaeger, Germany) body plethysmograph. The number of COPD exacerbations within the year before the inclusion was estimated according to the Gold 2011 guidelines [8]. The

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COPD frequent exacerbator phenotype was established in cases where the annual number of exacerbations was at least two.

Coronary angiography was performed using an AXIOM angiograph (Siemens, Germany) according to the Judkins-Sones technique. We performed a segment-by-segment analysis of atherosclerotic lesions. The total number of coronary stenotic lesions, hemodynamically significant stenosis (≥50% of the vessel diameter), stenosis of the main coronary branches, and hemodynamically significant stenosis of the main coronary branches was tabulated. The SYNTAX score was calculated using an online calculator (http://www.syntaxscore.com).

Transthoracic echocardiography was performed in M-mode, B-mode, and Doppler mode using the Siemens (Germany) or Sonos-7500 (Netherlands) echocardiograph. The left ventricular ejection fraction was measured using the Simpson method.

The ankle-brachial index (ABI) was measured using a Sonos 7500 ultrasound system (Philips, Netherlands) and a cuff pressure gauge. A six-minute walk test (6MWT) was performed using the generally accepted method before discharge from the hospital [9].

All laboratory tests within the framework of this work, except for C-reactive protein (CRP), were performed routinely at admission to the Research Institute of Regional Clinical Hospital No. 1 with ACS or for scheduled PCI. These tests included concentrations of glucose, creatinine, total cholesterol, low-density and high-density lipoprotein cholesterol, transaminases, bilirubin, and troponin I. GFR was calculated by the CKD-EPI formula using an online calculator (http://www.qxmd.com/calculate-online/nephrology/ckd-epi-egfr). Concentrations of plasma CRP were determined using a high-sensitivity latex enhanced immunoturbidimetry assay in non-acute COPD exacerbation, i.e., at one month after discharge from the hospital in patients after ACS or before PCI in patients with chronic IBS.

Drug therapy, including statins and antiplatelet drugs (angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists (ARA II) as required, and beta-blockers) was ordered for all subjects. According to the GOLD guidelines, a respiratory physician ordered the drug therapy for COPD.

The follow-up included, on average, telephone contacts every 3 mos with standard questions to predict the onset of clinical outcomes of interest, smoking status, and compliance with the drug therapy. The follow-up also included repeated visits to the hospital at 1 mo for patients after ACS, and for all patients at 12 mos and at the end of the study. Patients were invited for unscheduled visits in case of onset of a clinical outcome of interest for clinical investigation. The rate and time to the onset of the composite endpoint were taken into account, including the following clinical outcomes: cardiovascular death, MI, stroke, scheduled MR, i.e., PCI and/or CABG.

Statistical analysis and modeling was performed using the application software packages STATISTICA 10.0 (StatSoft Inc., USA) and SPSS Statistics 20.0 (IBM, USA). Descriptive statistics for variables with normal distributions are presented as the mean (M) and the standard deviation (SD), otherwise in the form of the median (Me) and the interquartile range [Q1; Q3]. The Cox regression was applied with the incremental inclusion of variables (p=0.1) to identify predictors of the onset of the composite endpoint and build the prediction model.

Results

The clinical characteristics of patients at the time of inclusion are detailed in Table 1. A total of 254 patients were included in the study. PCI was performed for ACS in 119 (47%) patients and for chronic CAD in 135 (53%) patients. The mean number of stents implanted in these patients was 1.14 and 1.40, respectively. Drug-eluting stents were implanted in 26% of the patients. The sample was primarily composed of patients with a low SYNTAX score, which may be due to the preference for CABG in patients with severe coronary lesions, and which made it impossible to include such patients in the study.

The pulmonary function measurements of all patients are presented in Table 2. Patients with mild to moderate COPD were more numerous in this sample, as in the general population, because they included all consistently identified patients with COPD who met the inclusion criteria. This appeared to result from a small (21%) percentage of patients with a history of the COPD frequent exacerbator phenotype.

The blood CRP of patients in the upper quartile was higher than 3 mg/l, i.e., more than a quarter of patients had a higher level of CRP concentration, which is now considered as an additional cardiovascular risk factor [10].

During the 12 mos after discharge from the hospital, 64.6% of patients took statins, 91.7% used dual antiplatelet therapy (after the implantation of a drug-eluting stent), 70.1% used ACE inhibitors or ARA II, 52% used beta-blockers, and 53.5% took drugs for COPD.

The maximum duration of follow-up was 36 mos, and the median was 20 mos. In some cases, more than one adverse cardiovascular event was reported in the same patient during the follow-up period, which is why the relative rate of the composite endpoint is not equal to the sum of the relative rates of its components. No statistically significant differences were found for any of the events when the rates of individual events were compared between patients after scheduled PCI and those who were subjected to PCI for ACS (Table 3). Of the composite endpoint components, the most common cardiovascular event was a repeat, unscheduled MR not associated with ACS. This occurred in 21.3% of patients during the follow-up period.

The step-by-step inclusion of variables from the candidate variables (age, number of coronary stenosis lesions, number of stenosis lesions of the main coronary branches, SYNTAX score, DM, GFR, TLC, FRC, RLV, FEV1, 6MWD, CRP, history of COPD frequent exacerbator phenotype, etc.) was used in SPSS20.0 to select seven variables included in the Cox regression model ($p < 0.1$; Table 4).

The χ^2-value for the whole model was 82.6, and there were 7 degrees of freedom ($p < 0.0001$). Stenosis of the main coronary branches made the largest contribution (Wald=13.3, $p < 0.001$), FRC made the smallest contribution (Wald=3.9, $p = 0.05$). The contribution of variables into the model is shown in Table 4. The Cox regression model is based on the equation linking independent predictors and a dependent variable of the risk function. The equation linking the seven identified predictor variables and the value of the risk function is as follows:

$$h_i(t) = h_0(t) \times \exp(0.045 \times \text{Age} + 0.487 \times \text{Stenosis} - 0.028 \times \text{GFR} - 0.004 \times \text{MWD} - 3.11 \times \text{ABI} + 0.012 \times \text{FRC} + 0.631 \times \text{COPD frequent exacerbator phenotype}).$$

The ROC curve for the resulting model is shown in Figure 1. If the risk function threshold of 0.501 is exceeded, an adverse outcome is likely (sensitivity 82.4%, specificity 60.0%; $p < 0.001$ (Table 5). However, this threshold is highly sensitive and moderately specific. This increases the probability of an overestimated risk error in predicting adverse events. If the risk function cut-off point is increased to 0.787, the model specificity will increase to 81.4%, and the sensitivity will remain as good as 75.3%, which seems the best possible for predicting adverse outcomes. In this case, judgment on the development of the adverse cardiovascular event within the period up to 3 yrs after PCI will be justified with the risk function hi (t) ≥0.787.

The constructed mathematical model was used to design a computer program [11] that permitted assessment of the risk of long-term adverse cardiovascular events in patients with concomitant CAD and COPD following PCI. The program has received a certificate of state registration. The program categorizes patients based on the initial parameter values, i.e., the above-described predictors of adverse prognosis. Patients are classified into two categories: high probability and low probability of long-term adverse cardiovascular events following PCI.

Discussion

There are numerous mathematical models, many of which are implemented as clinical scores to estimate

Table 1. Clinical characteristics of patients at the time of inclusion

Variable		n=254
Age, yrs (M±SD)		59.4±7.7
Male, n (%)		242 (95.3%)
Hypertension, n (%)		186 (73.2%)
History of MI, n (%)		99 (40.0%)
DM, n (%)		46 (18.1%)
Frequent COPD exacerbations, n (%)		54 (21.3%)
GFR <60 ml/min/1.73 m², n (%)		47 (18.5%)
TC, mmol/L (M±SD)		5.2±1.5
LDL, mmol/L (M±SD)		3.44±1.14
HDL, mmol/L (M±SD)		1.07±0.25
CRP, mg/L		2.33 [1.58; 3.36]
LVEF, %	>50%, n (%)	168 (66.1%)
	36–50%, n (%)	86 (33.9%)
6MWD, (Me [Q1; Q3])		362 [303; 416]
ABI, Me [Q1; Q3]		0.93 [0.87; 1.01]
SYNTAX, (Me [Q1; Q3])		12 [9; 16]
Coronary stenosis, total, (Me [Q1; Q3])		5 [4; 6]
Hemodynamically significant stenosis, total, (Me [Q1; Q3])		3 [2; 3]
Stenosis of the main coronary branches (Me [Q1; Q3])		4 [3; 4]
Hemodynamically significant stenosis of the main coronary branches, total, (Me [Q1; Q3])		2 [1; 3]

MI, myocardial infarction; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; 6MWD, six-minute walk distance; ABI, ankle-brachial index; CA, coronary arteries.

Table 2. Indices of pulmonary function

Variable, percentage of normal value (Me [Q1; Q3])		n=254
TLC		103 [99; 108]
VC		94 [82; 103]
RLV		123 [101; 158]
IC		95 [81; 103]
FRC		114 [101; 131]
FEV_1		72 [49; 87]
COPD severity, n (%)	I	110 (43.3)
	II	79 (31.1)
	III	47 (18.5)
	IV	18 (7.1)

TLC, total lung capacity; VC, vital capacity; RLV, residual lung volume; IC, inspiratory capacity; FRC, functional residual capacity; FEV1, forced expiratory volume in 1 second; COPD, chronic obstructive pulmonary disease.

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Table 3. The rate of long-term severe adverse cardiovascular events following PCI in patients with acute and chronic forms of CAD and concomitant COPD

Cardiovascular outcomes, %	ACS and COPD, n (%), n=119	CCAD and COPD, n (%), n=135	p	Total, n=254
Cardiovascular death	5 (4.2)	8 (5.9)	0.74	13 (5.1)
MI	10 (8.4)	10 (7.4)	0.95	20 (7.9)
Stroke	5 (4.2)	3 (2.2)	0.59	8 (3.2)
CABG	6 (5.0)	9 (6.7)	0.78	15 (5.9)
Repeat PCI	18 (15.1)	24 (17.8)	0.69	42 (16.5)
Repeat MR (PCI or CABG)	23 (19.3)	31 (23.0)	0.58	54 (21.3)
Composite endpoint	40 (33.6)	45 (33.3)	0.93	85 (33.5)

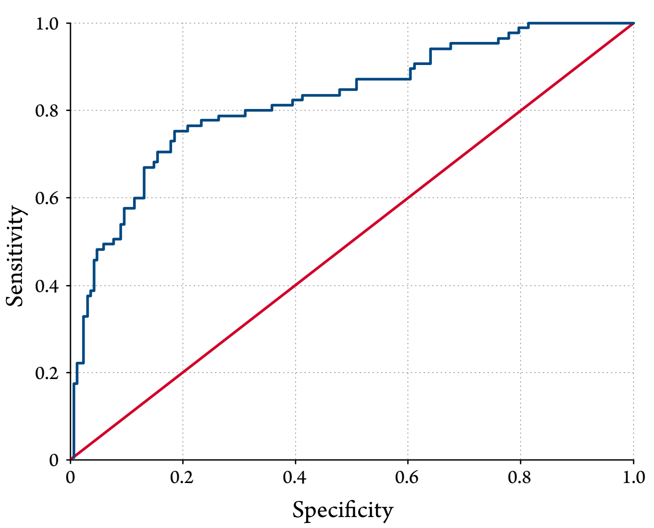
ACS, acute coronary syndrome; COPD, chronic obstructive pulmonary disease; CCAD, chronic coronary artery disease; MI, myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; MR, myocardial revascularization.

Table 4. Predictor variables of severe long-term adverse cardiovascular events following PCI in patients with CAD and concomitant COPD

Predictor	B	Standard error	Wald test	p	Exp (B)	95% CI limits for Exp (B)	
						Lower	Upper
X1. Age	0.045	0.017	6.770	0.009	1.047	1.011	1.083
X2. Stenosis	0.487	0.133	13.344	<0.001	1.628	1.253	2.114
X3. GFR	-0.028	0.008	11.862	0.001	0.972	0.957	0.988
X4. 6MWD	-0.004	0.001	8.781	0.003	0.996	0.993	0.999
X5. ABI	-3.106	0.870	12.763	<0.001	0.045	0.008	0.246
X6. FRC	0.012	0.006	3.851	0.050	1.012	1.000	1.025
X7. FED	0.631	0.241	6.838	0.009	1.880	1.171	3.018

B, regression equation coefficient; SE, standard error; Exp (B),exponent B; CI, confidence interval; FED, COPD with frequent exacerbations.

Figure 1. ROC curve of the risk function values.



the prognosis in patients with coronary lesions. They use different combinations of age, creatinine/GFR, ABI, 6MWD, various characteristics of coronary lesions, COPD (as a binary variable only) as predictors [3, 4, 12–14].

Of the risk factors identified, the «stenosis of the main coronary branches» variable made the most significant contribution to the prediction model. This fact can be interpreted as follows. The repeat unscheduled MR was the most common long-term adverse outcome in our study. If it was not associated with the development of ACS, MR was only performed in the case of an evident clinical aggravation during the course of chronic CAD, which is usually caused by hemodynamically significant stenosis in the main coronary branches. Even a relatively small plaque, which may enlarge over time, can initiate a stenosis that creates a clinically significant obstruction of blood flow [15, 16]. Stenosis of the second-order branches, even if hemodynamically significant, rarely require performing MR. On the other hand, if a small plaque is located in a main coronary branch ruptures, it will have grave consequences, such as MI or unstable angina, and it will result in one of the outcomes registered in our study. Thrombosis of a second-order branch is significantly less likely to cause a clinically significant event [17, 18].

However, the SYNTAX score used in the multidimensional analysis was not significant for the prognosis. Firstly, both variables, the total number of coronary stenotic lesions and the SYNTAX score, correlated strongly with each other, which significantly reduced the probability of their simultaneous inclusion in the multidimensional

Table 5. Operational characteristics of the regression model based on the assessment of risk function

Parameter	AUC±SE (95% CI)	p	Risk function threshold	Sensitivity (Sen) and specificity (Spec)	
				Sen (%)	Spec (%)
Risk function	0.823±0.029 (0.767–0.880)	<0.001	0.501; 0.787	82.4; 75.3	60; 81.4

AUC, the area under the curve; SE, standard error; CI, confidence interval.

regression model. Secondly, the SYNTAX score was created primarily to choose an MR technique [19] and does not take into account hemodynamically insignificant stenosis, which nonetheless can have a predictive role. Thirdly, patients with the most adverse prognosis and a high SYNTAX score had a small chance of being included in the study, as their overwhelming number had undergone CABG. Thus, the SYNTAX score helps to select the best MR strategy, and the total number of stenosis lesions of the main coronary branches in patients with concomitant COPD is more closely related to the probability of a long-term adverse cardiovascular outcome in multidimensional statistical analysis when the influence of other variables is taken into account.

ABI is another predictor variable associated with atherosclerosis. ABI <0.90 is considered to be a reliable marker of peripheral atherosclerosis and is associated with an increased risk of all-cause and cardiovascular mortality, as well as with significant coronary events [20]. As all patients included in our study had CAD, reduced ABI meant that they had multifocal atherosclerosis, which was associated with a two-fold increase in the risk of serious adverse cardiovascular events in the large trial PEGASUS-TIMI54 [21].

6MWD is used as a predictor of adverse outcomes in chronic heart failure, pulmonary hypertension, and COPD [22–24]. Several works have been published in which 6MWD was a predictor of adverse cardiovascular events in patients with stable CAD [25, 26]. 6MWD is influenced by many factors: age, completeness of MR, the severity of peripheral atherosclerosis, obesity, heart failure, anemia, and other comorbidities. Nonetheless, it has its own independent prognostic value. A significant decrease in 6MWD not only shows the patient's poor functional abilities but also acts as an adverse prognostic factor for cardiovascular events.

A decrease in GFR less than 60 ml/min/1.73 m^2 is a well-known risk factor of an adverse cardiovascular prognosis [27, 28]. CKD is associated with elevated levels of inflammation markers and calcification activating factors, which causes damage to the endothelium and vascular wall and can underlie the progression of atherosclerosis even when traditional risk factors are taken into account [29]. Kidney failure most often results from such diseases as hypertension, systemic atherosclerosis, and DM. However, new evidence has recently been found that shows a relationship between COPD and kidney damage [30]. Hypoxemia, hypercapnia, systemic inflammation, oxidative stress, activation of the renin-angiotensin-aldosterone system are considered as factors that cause kidney damage in COPD.

An important finding is the detected effect on the cardiovascular prognosis of the predictor variables, which are traditionally considered in the context of predicting pulmonological complications rather than cardiovascular events, i.e., COPD with frequent exacerbations and FRC characterizing pulmonary hyperinflation. The adverse prognostic potential of COPD exacerbations, especially in the presence of the COPD frequent exacerbator phenotype, can be assumed to be particularly characteristic of patients with multiple coronary plaques. Even small plaques, which are not of interest to interventional cardiologists and cardiac surgeons, may be potentially dangerous for these patients, since each COPD exacerbation creates additional risk of plaque destabilization [31–34]. All mechanisms of damage and ulceration of atherosclerotic plaque are involved during COPD exacerbation, a condition that leads, among other things, to prothrombotic changes on the hemostasis system [35, 36].

Conclusion

The following independent predictors of serious adverse cardiovascular events were established in patients with concomitant CAD and COPD:

1) the number of stenotic lesions of the main coronary branches;
2) ABI;
3) GFR; 4) age;
5) 6MWD;
6) COPD of the frequent exacerbator phenotype;
7) FRC. It is appropriate to apply the proposed mathematical model based on Cox regression, with good operational characteristics (sensitivity 75%, specificity 81%), to estimate the probability of adverse cardiovascular events following PCI in patients with concomitant CAD and COPD.

No conflict of interest is reported.

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