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3-YEARS OUTCOME OF FOLLOW-UP OF PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE SUCCESSFULLY TREATED BY PERCUTANEOUS CORONARY INTERVENTION DUE TO ACUTE CORONARY SYNDROME

Aim	To evaluate results of three-year follow-up in patients after acute coronary syndrome (ACS) associated with chronic obstructive pulmonary disease (COPD) and to identify predictors for delayed serious cardiovascular adverse (SCVAE) events.
Material and methods	This prospective cohort study included 119 patients with verified COPD who had ACS after a successful urgent percutaneous coronary intervention and were discharged from the hospital without in-hospital complications. Incidence of and time to SCVAE (cardiovascular death, myocardial infarction, stroke, repeated unscheduled myocardial revascularization) were recorded. SCVAE predictors were identified with the Cox regression by stepwise inclusion of variables into the model.
Results	SCVAE occurred in 33.6% of ACS patients with COPD. The high rate of repeated myocardial revascularization mostly contributed to the development of delayed SCVAEs (19.3% of patients). Independent predictors of SCVAE included the total number of stenoses in major coronary artery branches; ankle-brachial index; glomerular filtration rate calculated with the CKD-EPI equation; frequent COPD exacerbations; functional residual capacity of the lungs; and 6-min walk distance.
Conclusion	New independent predictors of SCVAE were identified in COPD patients after ACS with percutaneous coronary intervention and stenting, including distance in the 6-min walk test, frequent COPD exacerbations, and functional residual volume of the lungs as an index of pulmonary hyperinflation.

Keywords	Acute coronary syndrome; percutaneous coronary interventions; chronic obstructive pulmonary disease; serious adverse cardiovascular events; predictors
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Endovascular techniques used to treat acute and chronic coronary artery disease (CAD) have significantly improved prognosis in acute coronary syndrome (ACS) and quality of life in stable forms of CAD. However, the long-term results of percutaneous coronary interventions (PCI) largely depend on patient clinical characteristics and accompanying somatic pathologies, rather than the technological aspects of endovascular interventions. The contribution of diabetes mellitus and chronic kidney disease has been studied in detail and is reflected in the clinical guidelines for myocardial revascularization (MR) [1]. At the same time, the role of chronic obstructive pulmonary disease (COPD) is less well understood in the long-term prognosis for patients with ACS after successful endovascular MR. COPD is a systemic disease which can modify the course of cardiovascular pathology [2, 3]. The latest revisions of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the Federal Clinical Guidelines for COPD acknowledge a pronounced clinical heterogeneity of the disease. This requires more detailed characterization rather than the traditional classification of severity depending on the forced expiratory volume exhaled in 1 second (FEV1) [4]. This leads to an interest in finding predictors of unfavorable cardiovascular prognosis in patients with

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CAD and COPD. Clinical, laboratory and instrumental characteristics of COPD should be evaluated as possible predictors, such as indices of pulmonary function other than FEV1, exacerbation of COPD, and intensity rates of systemic inflammation.

Objective

To evaluate the results of a three-year follow-up of patients with COPD after ACS and to identify predictors of long-term cardiovascular serious adverse events (SAEs).

Material and methods

In accordance with the inclusion and exclusion criteria, the prospective cohort study consistently included 119 patients with ACS and concomitant COPD who underwent PCI for ACS in 2012–2014. Most of the interventions were performed in Research Institute Regional Clinical Hospital No. 1 named after Professor S. V. Ochapovskiy. The COPD patients were identified during spirography among 478 patients with ACS after successful PCI without in-hospital complications who had a long history of smoking.

Inclusion criteria were the age of 40 years or older; active smoking status at the time of admission or cessation of smoking within no more than a year before the current hospitalization; smoking history for at least 10 pack-years; ACS with a final diagnosis of myocardial infarction (MI) or unstable angina; PCI with the implantation of a bare-metal or drug-eluting stent within 24 hours after the onset of symptoms leading to hospital admission, resulting in the complete recovery of blood flow in the infarct-related artery; COPD diagnosed following the GOLD 2011 criteria [5], and signed informed consent.

Exclusion criteria: heart defects if surgical correction is indicated; a history of coronary revascularization; indications for coronary artery bypass grafting (CABG), other than COPD lung disease; glomerular filtration rate (GFR) less than 30 mL/min/1.73 m^2; left ventricular ejection fraction less than 35% at the time of admission; cancer; lower limb pathology preventing from performing 6-minute walk test (6MWT); PCI complications: coronary artery dissection, perforation/rupture, no-reflow phenomenon; unwillingness/inability to take medication prescribed by the physician.

All patients underwent spirography and bronchodilation test with salbutamol 400 μg using a Spirovit SP-1 spirometer (Schiller, Switzerland) following the guidelines of the American Thoracic Society (2005), and measurement of static pulmonary volumes and capacities using the V6200 Autobox (SensorMedics, USA) or MasterScreen Body (Erich Jaeger, Germany). The following pulmonary functions were measured: FEV1, lung capacity (LC), vital capacity (VC), residual volume (RV), functional residual capacity (FRC).

The number of COPD exacerbations (GOLD, 2011) [5] was determined for the year prior to the current hospitalization.

Coronary angiography was performed using an AXIOM angiograph (Siemens, Germany) following the Judkins-Sones technique. Coronary angiograms were interpreted using a segment-by-segment analysis of atherosclerotic lesions. The number of hemodynamically significant stenotic lesions (≥50% of the vessel diameter), hemodynamically insignificant stenotic lesions (<50% of the vessel diameter), and the total number of all lesions were taken into account. The number of stenotic lesions of the main coronary branches was also considered. The SYNTAX score was calculated using an online calculator (http://www.syntaxscore.com).

The ankle-brachial index (ABI) was measured using a Sonos 7500 ultrasound system (Philips, Netherlands) and a cuff pressure gauge in all patients. 6MWT was performed before discharge from hospital. The biochemical profile included routine measurements taken in all patients with ACS at admission to hospital. Lipid profile, coagulogram, troponin I, glucose, creatinine, urea, transaminases, bilirubin, electrolytes, etc. GFR was calculated using the CKD-EPI formula and an online calculator: (http://www.qxmd.com/calculate-online/nephrology/ckd-epi-egfr). One month after discharge with decompensated COPD, blood levels of C-reactive protein (CRP) were measure at an outpatient visit the using high-sensitivity latex-enhanced immunoturbidimetry.

Drug therapy was ordered for all patients, including statins, double antiplatelet therapy, angiotensin-converting enzyme inhibitors (ACE) or sartans, as per indication, and beta-beta-blockers. Following the GOLD guidelines, COPD drug therapy was also administered. Patient follow-up included 1 phone call every 3 months on average, as well as scheduled clinic visits 1 and 12 months later and at the end of the follow-up period (up to 36-month). This could also include an unscheduled visit in the case of the onset of any of the reported clinical outcomes to be confirmed by clinical examination. The rate of cardiovascular SAEs was registered as a composite endpoint that included any of the following clinical outcomes: cardiovascular death, MI, stroke, MR (PCI or CABG). The time to cardiovascular SAE was registered in months.

Table 1. Baseline clinical characteristics of patients

Parameter	n=119
Age, years (M±SD)	58.6±7.8
Male, n (%)	113 (95)
ST-elevation ACS, n (%)	77 (65)
History of MI, n (%)	23 (19)
Hypertension, n (%)	88 (74)
DM, n (%)	24 (20)
Estimated GFR <60 mL/min/1.73 m^2, n (%)	17 (14)
6MWD, m (Me [Q1; Q3])	354 [296; 402]
ABI, Me [Q1; Q3]	0.92 [0.87; 1.01]
Total cholesterol, mmol/L (M±SD)	5.3±1.4
LDL-C, mmol/L (M±SD)	3.51±1.12
HDL, mmol/L (M±SD)	1.08±0.24
CRP, mg/L	2.36 [1.74; 3.44]
SYNTAX score	12 [7; 16.5]
Stenosis of the main coronary branches	3 [2; 4]

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

Table 2. Parameters of pulmonary function

Parameter		n=119
FEV_1, % of normal (Me [Q1; Q3])		72 [54; 86]
TLC, % of normal (Me [Q1; Q3])		103 [100; 109]
VC, % of normal (Me [Q1; Q3])		96 [85.5; 102.5]
RV, % of normal (Me [Q1; Q3])		123 [101; 158]
FRC, % of normal (Me [Q1; Q3])		113 [102; 133]
COPD severity, n (%)	Mild	50 (42)
	Moderate	42 (35)
	Severe	21 (18)
	Extremely severe	6 (5)

FEV_1, forced expiratory volume exhaled in 1 second; LC, lung capacity; VC, vital capacity; RV, residual volume; FRC, functional residual capacity; COPD, chronic obstructive pulmonary disease.

Statistical analysis was performed using the STATISTICA 10.0 software suite (StatSoft Inc., USA). In close-to-normal distribution, variables were expressed as mean (M) and standard deviation (SD), and in significant deviation from the normal distribution, as median (Me) and interquartile range [Q1; Q3]. The relative rates are presented as a percentage. Cox's regression was used with incremental variable inclusion at the significance level of 0.1, in order to identify variables being the predictors of cardiovascular SAEs.

Results

The initial clinical characteristic of patients is shown in Table 1. Indicators of pulmonary function are shown in Table 2. There were more patients with grade 1 and 2 COPD. Therefore, the relative proportion of patients with a history of frequent COPD exacerbations was relatively small (22%). On the other hand, the prevalence of grade 1 and 2 COPD affected the incidence of pulmonary hyperinflation (PH). For example, less than half of patients with COPD in our sample had PH. The blood levels of CRP were higher than 3 mg/L in patients of the upper quartile of the corresponding variable. Thus, a significant proportion of patients had a CRP level higher than a cutoff point. This is now considered an additional cardiovascular risk factor [6]. Our sample mostly included patients with low SYNTAX scores. This may be due to the absence of a long history of CAD in most patients (the ACS episode of interest was a debut of CAD in most cases), in the first place, and the fact that patients with severe CAD had scheduled CABG as the next stage of MR after PCI on an infarct-related artery, which was an exclusion criterion, in the second place.

The longest scheduled period of follow-up was 36 months, and the median was 20. The actual duration of follow-up was significantly longer than the median, since this value was significantly influenced by the onset of cardiovascular SARs in almost a third of patients. In that case the duration of follow-up was considered the period before any first cardiovascular SAEs. Five patients had more than one complication and/or event within the follow-up period. Thus, the composite endpoint rate, expressed as the relative proportion of patients who had at least one such event, is not equal to a simple sum of the rates (Table 3). Repeat MR for clinically significant stable exertional angina was the most common cardiovascular SAE (19.3%). Repeat PCI was performed in most cases|.

Twelve months after discharge, treatment compliance was evaluated to be 63.0% for statins, 93.3% for antiplatelet therapy, 52.9% for beta-blockers, 72.3% for ACE inhibitors or sartans. By this time, 23.5% of patients continued to smoke. Only 49.6% of patients used drug therapy for COPD (a combination of long-acting beta-agonists and inhaled glucocorticosteroids 14.3%, a combination of long-acting beta-agonists, inhaled glucocorticosteroids, and long-acting anticholinergic agent 5.0%, long-acting anticholinergic agents 5.9%, others took short-acting bronchodilators). Low COPD treatment compliance can be attributed to the prevalence of patients in our sample with mild to moderate COPD (77%).

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The step-by-step inclusion was used for variables from a set of quantitative and qualitative candidate variables statistically associated with the onset of cardiovascular SAEs, in a one-way analysis, at a level of significance $p<0.05$ (age, diabetes mellitus, GFR, 6MWT distance, the total number of coronary stenotic lesions, number of lesions of major coronary branches, SYNTAX scores, ABI, FRC, RV, CRP, history of frequent exacerbations of COPD). The corresponding STATISTICA 10.0 algorithm was used to select six variables included in Cox's regression model with a significance level <0.1 (Table 4). These variables predicting the onset of cardiovascular SAEs were (in descending order of significance) as follows:

1. Total number of all stenotic lesions of the main coronary branches
2. ABI
3. GFR
4. COPD phenotype with frequent exacerbations
5. FRC
6. 6MWT distance (measured before the discharge from hospital, after PCI).

In all models, χ^2 was 46.4, and the degree of freedom was 6 ($p<0.0001$). The contribution of variables into the model is shown in Table 4.

Total number of stenotic lesions in the main coronary branches made the largest contribution in the regression model (Wald=8.1, $p<0.004$), and 6MWT distance made the smallest contribution (Wald=3.4, $p=0.066$).

Table 3. Relative proportion of patients with cardiovascular severe adverse events occurring in the long-term period after PCI for ACS in patients with COPD

Cardiovascular outcomes	n=119
Cardiovascular death, n (%)	5 (4.2)
MI, n (%)	10 (8.4)
Stroke, n (%)	5 (4.2)
CABG, n (%)	6 (5.0)
Repeat PCI, n (%)	18 (15.1)
Repeat MR (PCI or CABG), n (%)	23 (19.3)
Composite endpoint – all cardiovascular SAEs, n (%)	40 (33.6)

PCI, percutaneous coronary intervention;
ACS, acute coronary syndrome; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction;
CABG, coronary artery bypass grafting;
MR, myocardial revascularization;
SCCEs, severe cardiovascular complications and events.

Discussion

Unscheduled repeat MR was the most common event among long-term adverse outcomes in our sample, which was performed only in the case of clinically significant exertional angina, if it was caused by hemodynamically significant stenosis of the main coronary branches. Even a small plaque that may increase over time can initiate such stenosis creating a clinically significant obstruction of blood flow in any of the main coronary arteries. At the same time, stenosis of the second-order arteries, even hemodynamically significant, rarely leads to MR. On the other hand, rupture of a vulnerable plaque localized in a main coronary artery, even a small one, usually has serious consequences such as thrombosis and MI, i.e., one of the reported outcomes. Thrombosis of a second-order branch is much less likely to result in a clinically significant event. This can explain the most significant contribution of the total number of stenotic lesions of the main coronary branches in the regression model.

On the other hand, such a widely used prognostic variable as the SYNTAX score was not among the independent predictors. This may be explained by the fact that this score does not take into account hemodynamically insignificant stenosis (which can have prognostic value) and was developed mainly to choose a method of MR [7]. Moreover, patients with the highest SYNTAX scores had only a slight chance of inclusion in our study This is because after blood flow was restored in an infarct-related artery, almost all of them were subjected to scheduled CABG. Thus, whereas the SYNTAX score helps select the best MR strategy, the

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

Predictor	B	Standard error	Wald test	p	Exp (B)	95% CI limits for Exp (B)	
						Lower	Upper
X1. Stenosis	0.693	0.244	8.084	0.004	2.000	1.240	3.224
X2. GFR	-0.029	0.012	5.897	0.015	0.971	0.948	0.994
X3. 6MWT	-0.004	0.002	3.382	0.066	0.996	0.991	1.000
X4. ABI	-4.192	1.595	6.909	0.009	0.015	0.001	0.344
X5. FRC	0.020	0.009	4.915	0.027	1.020	1.002	1.039
X6. FEP	-0.820	0.369	4.925	0.026	0.441	0.214	0.909

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

total number of stenotic lesions of the main coronary branches is more closely related in multivariate analysis to the probability of long-term adverse cardiovascular SAEs.

ABI less than 0.90 is a reliable marker of peripheral atherosclerosis and is associated with major adverse coronary events, as well as with an increased risk of all-cause and cardiovascular mortality, which reflects the systemic nature of atherosclerotic lesions [8]. As all patients included in our study had ACS, a decreased ABI showed that they had atherosclerosis of at least two vascular systems. In the PEGASUS-TIMI54 study, multifocal atherosclerosis was associated with a two-fold risk of cardiovascular SAEs [9]. Despite the correlation between the number of coronary stenoses and ABI, in our study both variables turned out to be independent predictors of cardiovascular SAEs.

The 6-minute walk distance is a predictor of adverse outcomes in pulmonary hypertension and COPD, as well as in chronic heart failure [10–12]. Several publications showed that the 6MWT distance was a predictor of cardiovascular AEs in stable CAD [13, 14]. The 6MWT distance depends on such factors as age, completeness of MR, severity of peripheral atherosclerosis, anemia, obesity, chronic heart failure, etc. However, 6MWT demonstrated its contribution in a multivariate model as an independent predictor of cardiovascular SAEs.

The role of GFR reduction is a well-known marker of cardiovascular disease which increases the risk of cardiovascular AEs. Elevated markers of systemic inflammation and inductors of vascular calcification in CKD can damage the endothelium and vascular wall, which can contribute to the progression of atherosclerosis regardless of other risk factors [15].

The identified cardiovascular SAE predictors were indicators commonly viewed in the context of predicting pulmonological complications: frequent exacerbations of COPD and FRC [16]. The association has been earlier demonstrated between PH and total mortality in patients with COPD [17, 18], although the causes of death were not specified. At least half of deaths among patients with COPD are due to a cardiovascular pathology rather than respiratory failure. There are various adverse cardiovascular effects associated with PH. The contribution of PH in the onset / aggravation of left ventricular diastolic dysfunction is the most widely studied. It decreases diastolic filling, cardiac output and causes diastolic heart failure [19], which, in turn, can increase cardiovascular mortality. PH-related lesions of arterial bed cause endothelial dysfunction, and increases the stiffness of the artery wall and thickness of the intima-media complex [20–22]. The association between PH and elevated blood levels of systemic inflammation markers has been described: CRP, interleukin-6, interleukin-8, tumor necrosis factor-alpha [23]. On the one hand, the mentioned pathological phenomena are involved in the development of atherosclerotic process. On the other, the progression of atherosclerosis caused clinical outcomes which contributed most to the rate of the composite endpoint in our study (IM, stroke, and unscheduled repeat MR).

The pathological inflammatory response in patients with COPD damages blood vessels of the central circulatory system, as well as the pulmonary tissue [24, 25]. There are many macrophages and T-cells in the plaque rupture areas which play a significant role in atherothrombosis and ACS [26]. Thus, it is essential that exacerbation of COPD increases the blood levels of pro-inflammatory cytokines, leukotrienes, CRP, fibrinogen, and other biologically active molecules, and also activates leukocytes [3, 27, 28]. As these pathophysiological processes develop, the vascular bed is damaged, endothelium dysfunction worsens, and the risk of atherosclerotic plaque rupture increases. Several publications have confirmed the role of COPD exacerbation as a trigger of ACS and the progression of atherosclerosis. One of the possible mechanisms suggested was a massive release of activated neutrophils in the blood flow and activation of systemic inflammation [24, 29, 30]. Patients with frequent exacerbations of COPD are particularly vulnerable. Each exacerbation creates additional risks of worsening the course of the accompanying cardiovascular pathology. A phenotype of COPD with frequent exacerbations turned out to be an independent factor increasing the risk of cardiovascular SAEs in our study. The independent contribution of FRC and frequent COPD exacerbations to the regression model was not as significant as that of variables directly reflecting the severity of atherosclerosis (coronary stenosis and ABI). This may be partially due to a significant correlation between the incidence of COPD exacerbations and the severity of PH expressed by FRC.

Limitations

Firstly, the sample size of patients with COPD and a history of ACS was relatively small. Thus, the predictive value of the identified predictors of cardiovascular SAEs needs to be verified in larger studies.

Secondly, repeat coronary angiography performed subject to clinical indications only did not allow for evaluation of the progression of coronary atherosclerosis and stent restenosis in all included patients.

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Thirdly, a large proportion of patients had bare-metal stents installed, which is not entirely consistent with the current trend to use drug-eluting stents in all patients in need of PCI and stenting. However, this feature reflected the recent practice used in the Russian Federation, which has been common to many Russian health care providers having interventional radiology.

Conclusion

During the follow-up period lasting for up to three years, cardiovascular SAEs were reported in 33.6% with a history of ACS and concomitant COPD. The high rate of unscheduled repeat MR (19.3%) made the most significant contribution to the development of long-term cardiovascular SAEs. The long-term independent predictors of cardiovascular SAEs after performing PCI for ACS in patients with concomitant COPD are (in descending order of significance): a total number of stenotic lesions of the main coronary branches; ABI; GFR; a history of frequent exacerbations of COPD (COPD phenotype with frequent exacerbations); FRC; 6MWT distance.

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