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ACUTE CORONARY SYNDROME IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

THESIS SUMMARY

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The defence materials are available in the library of the Medical University, Prof. Dr. P. Stoyanov" - Varna and are published on the official website of the University.

TABLE OF CONTENTS

ABBREVIATIONS

ACS – Acute coronary syndrome

ACE – Angiotensin converting enzyme

AFib – Atrial fibrillation

AH – Arterial hypertension

AMI – Acute myocardial infarction

ARNI – Angiotensin receptor- neprilysin inhibitor

ARBs – Angiotensin receptor blockers

ATS – American Thoracic Society

BB. – Beta-blocker

BP – Blood pressure

BMI – Body mass index

BODE – Body mass index, airflow obstruction, dyspnoea and exercise capacity

CAD – Coronary artery disease

CAT – COPD assessment test

CKD – Chronic kidney disease

COPD – Chronic Obstructive Pulmonary Disease

CRP – C - reactive protein

CVD. – Cardiovascular disease

DASI – The Duke Activity Status Index

DBP – Diastolic blood pressure

DM – Diabetes melitus

ECG – Electrocardiography

$FEV_{1.}$ – Forced expiratory volume per second

FVC – Forced vital capacity

FRS – Framingham Risk Score

GFR – Glomerular Filtration Rate

GRACE. – Global Registry of Acute Coronary Events

GOLD – Global Initiative for Chronic Obstructive Lung Disease

Hb – Hemoglobin

HDL – High-density lipoprotein

HF – Heart failure

ICD – Ischemic heart disease

LABA – Long-acting β_2 agonist

LAD – Left coronary artery

LAMA – Long-acting muscarinic antagonist

LCx – Left circumflex artery

LDL – Low-density lipoprotein

LVEF – Left ventricle ejection fraction

LVD-36 – Left Ventricle Dysfunction Test with 36 questions

mMRC – The Modified Medical Research Council Dyspnea Scale

NYHA – New York Heart Association

NSTEMI – Non-ST-Elevation Myocardial Infarction

PCI – Percutaneous coronary intervention

P_2Y_{12} – Adenosine diphosphate receptor

RCA – Right coronary artery

RF – Risk factor

SBP – Systolic blood pressure

SCA – Selective coronary angiography

STEMI – ST-Elevation Myocardial Infarction

WHO – World Health Organisation

INTRODUCTION

Acute coronary syndrome (ACS) and chronic obstructive pulmonary disease (COPD) are the leading causes of mortality and disability in the world. According to the National Statistical Institute, the number of deaths from COPD in Bulgaria in 2022 was 18.6 per 100,000 people, and the mortality rate from ACS amounted to 84.8 per 100,000 people. COPD is a disease of increasing social significance and, according to the World Health Organization (WHO) prognosis, is expected to become the third leading cause of death worldwide by 2030. Population-based studies have shown that cardiovascular diseases (CVD) are responsible for 20-30% of deaths in patients with COPD (Hujart et al., 2012).

Although it was initially believed that COPD affects only the respiratory tract and lungs, it is now accepted that the disease is complex and multi-component. Patients with pulmonary obstruction have up to five times the risk of developing CVD (Chen et al., 2015). The incidence of acute myocardial infarction (AMI) in these patients is 16% (Patel et al., 2012). Exacerbation of lung disease doubles the risk of AMI (Donohue et al., 2011).

The main mechanisms that determine the increased cardiovascular risk in patients with COPD are chronic inflammation, oxidative stress, obesity, decreased physical activity, smoking, and dyslipidemia (Leone et al., 2009). This makes this cohort of patients a risk group with high morbidity and mortality (Kjoller et al., 2004).

Studies on COPD as a risk factor (RF) for ACS have some limitations. Very often, the diagnosis of pulmonary obstruction is made based on medical documentation alone or the patient's data without being confirmed by spirometry. This, in turn, leads to an underestimation of the prevalence and importance of COPD in patients with ACS (Soriano et al., 2005; Arne et al., 2010). While the mortality rate in patients with ACS has fallen by half since 2000, it is increasing in patients with concomitant pulmonary obstruction (Bursi et al., 2010). A large population-based study involving 34,019 patients with COPD showed significantly higher mortality compared to controls, respectively for ST-segment non-elevation ACS (NSTEMI) HR 1.26 (95% CI: 1.17–1.35) and for ST-segment elevation ACS (STEMI) HR 1.25 (95% CI: 1.11–1.41) (Hawkins et al., 2022). The conclusions we can draw by analyzing data from other studies are primarily related to this cohort of patient’s age and risk profile. Patients with ACS and COPD are older, more impaired, and have a higher incidence of comorbidities (Curkendall et al., 2006). The most common comorbidities in COPD and ACS are anemia, type 2 diabetes mellitus, metabolic syndrome, cachexia, and atrial fibrillation (AFib) (Zairis et al., 2011). Each of them further worsens respiratory obstruction, which induces hypoxia, hypercapnia, and

endothelial dysfunction (Rabe et al., 2013). Another reason is the misperception of ACS symptoms as part of pulmonary obstruction. This can delay the diagnosis and timely administration of reperfusion therapy, which can worsen the prognosis and size of the infarction area. The data also show that the incidence of selective coronary angiography (SCA) in patients with COPD is lower even compared to patients with relative contraindications for coronary intervention, for example, with end-stage cancer or dementia (Rothnie et al., 2015).

Another therapeutic problem discussed in large observational studies is the non-adherence to the recommendations for secondary prevention after myocardial infarction, in particular, beta-blocker (BB) therapy, in patients with COPD (Selvaraj et al., 2005; Lazzeri et al., 2013; Salisbury et al., 2007; Stefan et al., 2012). These beliefs are based on brief reports or outdated data on the risk of bronchospasm after the administration of BB (Tattersfiel et al., 1986; Belli et al., 1995). Analyzing the results of current clinical trials, we conclude that cardioselective BB not only improves symptoms and prognosis in patients with ACS but can reduce mortality and reduce the risk of exacerbations in patients with COPD (Kornmann et al., 2011; Sial et al., 1994; Salpeter et al., 2003). This cohort of patients should not be deprived of the opportunity for full treatment of their cardiovascular disease. Data from Bulgaria confirm the negative trend of low adherence to the prescribed therapy in patients with CVD and COPD (Mitkova et al., 2017).

Despite its high prevalence, morbidity and mortality, COPD often goes unrecognized and creates serious difficulties in healthcare systems. Combined with ACS, it continues to be a diagnostic and therapeutic challenge for doctors in the 21st century. The peculiarities of the course of ACS in patients with COPD are the subject of extensive studies in the world literature, but there is a lack of data in this direction in Bulgaria. At present, there is no up-to-date registry for the follow-up of patients with ACS and COPD and adherence to their prescribed therapy, which could improve the prevention of fatal cardiovascular events.

Patients with ACS and concomitant COPD are a high-risk group in which a comprehensive approach is needed both in treatment and during follow-up. These patients consume more resources in primary and secondary medical care - consultations, emergency room visits, hospitalizations, and hospital stays. Strategies are needed to improve adherence to drug therapy, correct risk factors and reduce the incidence of complications and rehospitalizations.

AIM AND OBJECTIVES OF THE RESEARCH

1. Aim

The present study aimed to assess the clinical and demographic characteristics, adherence to the prescribed therapy, the causes of repeated hospitalizations, and mortality in patients with ACS and COPD.

2. Objectives

To achieve the aim, the following tasks were set:

1. To investigate the risk characteristics, clinical presentation, and therapeutic behavior in persons with acute coronary syndrome and accompanying COPD.

2. To make a comparison with a control group of patients with acute coronary syndrome with similar demographic and clinical characteristics, but without data on COPD.

3. To evaluate adherence to the prescribed therapy after hospitalization and in particular to treatment with beta-blockers.

4. To assess the quality of life in patients with ACS and COPD compared to the control group.

5. To determine the causes of hospitalizations.

6. To analyze the clinical and demographic characteristics of deceased patients with ACS.

MATERIALS AND METHODS

The clinical study was divided into two groups: patient and control, with participants selected using well-specified inclusion and exclusion criteria. The scientific study has been approved by the Commission on Research Ethics at the Medical University of Varna (minutes No. 84 / 27. 06. 2019) and is in line with the Helsinki Declaration.

1. Material base for the implementation of the dissertation

The study was conducted over 48 months. All examinations were performed from June 2019 to June 2023 in the Department of Cardiology in cooperation with the Second Internal Department of the Dobrich Hospital AD, Dobrich.

2. Study participants

A total of 140 consecutive patients diagnosed with ACS and hospitalized in the intensive care unit of the cardiology department at the Dobrich Hospital AD, Dobrich, were studied prospectively. The subjects studied were divided into two groups, depending on the presence of previously outpatients diagnosed with COPD:

- **Group A** includes 70 patients with ACS and known COPD. In persons without proven obst ructive disease but with evidence of dyspnea, chronic cough or sputum production, and/or a history of long-term smoking (more than 20 packages years), spirometry was performed because of the risk profile. According to the study, COPD was discovered in five patients (3.6%) of those with ACS, bringing the total number in group A to 75.
- **Group B** includes 65 people with ACS without COPD. The examined patients are categorized into both groups depending on the formulated inclusion and exclusion criteria necessary for the set goals.

3. Inclusion criteria:

All included patients are over 18 years of age and have confirmed their consent to participate in advance by filling out the form for informed consent and personal data protection

declaration. Both groups of patients were hospitalized for ACS. This includes one of the following clinical diagnoses:

- ACS without ST-elevation, including unstable angina pectoris and NSTEMI.
- ACS with ST-segment elevation.

4. Exclusion criteria:

1. Persons under 18 years of age.
2. Persons who have not given their informed consent.
3. Other forms of ischemic heart disease other than ACS - stable angina, silent myocardial ischemia, ischemic cardiomyopathy, and Prinzmetal's angina variant.
4. Chronic heart failure (HF) III and IV functional class according to the New York Heart Association (NYHA).
5. Concomitant oncological disease.

Each patient was followed up for a year with follow-up visits at the sixth and 12th months.

5. Research methods

5.1. Survey method

The sociodemographic details of the patients, such as age, gender, location, marital status, and education, have been incorporated into original questionnaires. Anthropometric measures, including height and weight, are also tracked at the end of the 12th month. Information was also collected about the prescribed main classes of medications, dosage, and adherence to the prescribed therapy.

The patients filled in the questionnaires at each of the visits to track the dynamics of their condition after the medication adjustments were made and recommendations were given.

5.2. Clinical examination

Every participant had their heart rate and blood pressure measured as part of a comprehensive clinical evaluation.

Blood pressure (BP) is recorded with a mechanical sphygmomanometer (Little Doctor 71 A) with a cuff size corresponding to the circumference of the armpit, taking into account systolic blood pressure (SBP) and diastolic blood pressure (DBP). For the analysis, an

arithmetic mean of two measurements every two minutes is used, separately for SBP and DBP. Taking into account the average age of the population we studied and according to the European recommendations for arterial hypertension (AH) in patients over 65 years of age, we took 130-139 mmHg of SBP and less than 80 mmHg for DBP as a target for BP (Garcia-Aymerich et al., 2003). Body weight is determined using a calibrated digital weighing scale (OMRON HN 289) in kilograms. The height was measured by a height meter in centimeters when the patient was standing upright. Based on the measurements, a body mass index (BMI) (kg/m2) was calculated for each participant according to the standard formula BMI = Weight (kg)/Height (m^2) (Kolimechkov et al., 2020). Individuals are classified into three categories based on their BMI: normal weight (18.5-25 kg/m2), overweight (25-29.99 kg/m2), and obese (greater than 30 kg/m2). The subjects of our study are people with a BMI ≥ 25 kg/m^2.

5.3. Risk factors for coronary artery disease

For all patients included in the study, information was obtained regarding the statute of limitations, control, and treatment of the main RF-AH and diabetes mellitus (DM). Data were taken on the statute of limitations of smoking the number of cigarettes per day. Taking into account the risk characteristics of patients with ACS in both groups, the 10-year risk of ischemic heart disease (IHD) was calculated using the Framingham Risk Score (FRS). It includes the most common six RFs for coronary artery disease – age, sex, total cholesterol, HDL cholesterol, smoking history, and BP values (Sohn et al., 2012).

5.4.Risk factors for chronic obstructive pulmonary disease

In our study, all patients previously diagnosed with COPD collected information about the statute of limitations, the number of exacerbations in the last year, as well as data on smoking in pack years. We calculated the pack years using the formula number of cigarettes per day, multiplied by the years of smoking by 20 in current and former smokers, and data on working in an environment with inhalation hazards (Guaraldi et al., 2015). We defined exacerbations as an acute event characterized by increased dyspnea and/or cough and expectoration, which worsens in less than 14 days and may be accompanied by tachypnea and/or tachycardia (Celli et al., 2021).

For a complex assessment of patients with COPD, we used a BODE index. It includes four risk indicators. These are the BMI – B; the degree of bronchial obstruction – O; the severity of dyspnea assessed by the Modified Dyspnea Rating Scale (mMRC) – D; physical endurance

measured by a six-minute walking test (6MWT) – E. According to the values of each of the four indicators, patients receive from 0 (minimum number) to 3 points (maximum number), which are summed up. The score ranges from 0 to 10 points, with a higher number of points being less favorable in terms of disease prognosis and a higher risk of mortality (Celli et al., 2012).

5.5. Health status assessment

To assess the health status and quality of life of each of the visits, we used the following questionnaires:

- Left Ventricle Dysfunction Test with 36 questions (LVD-36) - a questionnaire for assessing the health status and quality of life of patients with left ventricular dysfunction (O'Leary et al., 2000). It includes 36 statements that the patient must answer with "True" or "False." The total number of affirmative answers is summed up as a percentage, so 100 points is the worst possible outcome, and 0 points is the best.

- **The Duke Activity Status Index (DASI)** - evaluates the physical capacity of patients with CVD such as coronary artery disease (CAD), HF, or ACS (Caecilia et al., 2022). The questionnaire collected information on 12 common physical activities. Respondents should identify the daily task that demands the most effort from them.

- **COPD assessment test (CAT)** - evaluates the impact of obstructive pulmonary disease on the overall health status and quality of life of patients with COPD (Jones et al., 2013). It includes eight questions related to the presence of cough, phlegm, shortness of breath, and limitation in physical capacity. Depending on the result, information is obtained about the impact of COPD on the quality of life in these patients – respectively, 0 – 10 points is mild, 11 – 20 points is moderate, 21 – 30 points is severe and between 31 – 40 points is very severe.

- **The Modified Medical Research Council Dyspnea Scale (mMRC**) – scale for self-assessment of dyspnea in patients with COPD. Patients demonstrate minimal symptoms at levels of 0 or 1, and significant symptoms at values of 2 or above. Depending on the mMRC, individuals were classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification (Sanjaya et al., 2022).

5.6.Functional method

A functional examination of a six-minute load test was conducted in both patient groups using an American Thoracic Organisation (ATS)-validated methodology.

5.7. Instrumental method

All patients included in the study underwent 12-lead electrocardiography with a calibrated device (Contec ECG 1200 G). The presence of specific disorders in ventricular repolarization (ST–segment and T–wave) is targeted. There is a dynamic in the main rhythm during the different visits.

Transthoracic echocardiography: one-dimensional (M-mode), two-dimensional (B-mode), and Doppler examination was performed in all patients at the first and last visit (12th month) using the Esaote MyLabSix device. In all patients, the change in the telediastolic and telesystolic volume of the left ventricle and the dynamics in the left ventricular ejection fraction (LVEF) were monitored.

All patients with newly diagnosed or outpatient COPD underwent a functional lung examination with the Medical International Research Spirolab III device. The conducted spirometry aims to determine the forced vital capacity (FVC) and forced expiratory volume per second (FEV_1%) as the FEV_1/FVC ratio according to a standardized methodology according to the updated ATS recommendations (Graham L. et al. 2019). All patients were evaluated according to the ABCD (2017) and ABE (2023) group according to GOLD. Group A includes those with few symptoms and rare exacerbations, B – with more symptoms but rare exacerbations, C – with few symptoms but frequent exacerbations, and D – with severe and frequent exacerbations (Gruffydd et al., 2012). These recommendations were modified in 2023, with classifications C and D replaced by E to emphasize the relevance of the number of exacerbations each year.

All study participants underwent selective coronary angiography using Siemens Helathineeeralthinesas.

5.8. Laboratory method

All participants in the study had a blood sample taken for biochemical analysis. The laboratory tests were carried out in the MHAT Dobrich AD, Dobrich clinical laboratory using an automatic biochemical analyzer, Beckman Coulter AU 2700, Brea, CA, USA. For all persons at the first visit, the following is examined:

- complete blood count with 12 indicators;
- markers for myocardial injury – highly sensitive troponin I;
- creatinine, blood glucose, fibrinogen, C-reactive protein (CRP), and lipid profile.

5.9. Statistical analysis methods

The statistical analysis of the data was performed using the software product IBM SPSS MAC v. 29.0.1.0 (171), and Microsoft Excel for Mac Version 16.69.1, 2019 was used for the graphical representation.

We used descriptive statistics to calculate the indicators of relative share, averages, standard error, and standard deviation. Testing of the hypothesis for equality of mean values was done using Student-t and Paired t-test. A dispersion method was used for verification.

The determination of the categorical signs was performed by chi-square. The determination of the nature and degree of the relationship between the indicators was performed by correlation analysis. With a correct distribution and linear connection, the Pearson coefficient (parametric method) was used, and with an incorrect distribution, the Spearman coefficient (non-parametric method) was used.

Chi-square was used to assess the statistical reliability and the value of the significance level (P). This is the probability of rejecting the null hypothesis (H0) when it is true. Differences in significance level $p<0.05$ are considered significant.

RESULTS AND DISCUSSION

1. Demographic and clinical characteristics of study participants

Data from the demographic indicators of the 140 patients studied showed that they had an average age of 64.96 ± 9.50 years. Men predominate – 86 (61.4%), and women are 54 (38.6%), which was observed in other studies (Dimitrova et al., 2020).

The patients were divided into two groups. Group A includes 75 people with ACS and known COPD, with an average age of 66.36 ± 8.69 years. Of these, 31 (41.33%) are women, and 44 (58.67%) are men. Group B includes 65 people with ACS without COPD, with an average age of 63.39 ± 10.17 years, of which 23 (35.38%) are women and 42 (64.62%) are men, respectively.

Patients with COPD are older, probably due to the effect of long-term smoking, which leads to the manifestation of the disease at a later stage. Ferreira et al. also found a higher mean age among patients with COPD and ACS compared to those without lung disease (62 ± 9 vs 58 ± 10 years, p=0.028).

The male sex is predominant in most large studies examining patients with COPD. An unbalanced distribution between the sexes was also documented in Bulgarian research of people with COPD (male:female: 21.7% vs. 10.8%, p<0.001) (Pavlov et al., 2012). Our study is most similar to Sidney et al.'s in terms of the proportion of men in the COPD group, which was 55.4%.

For the follow-up period, a total of 32 deaths were registered, respectively, for group A, these are 19 (25.3%) patients, and for group B, 13 (20%). Five patients in all were unable to complete follow-up because of their incapacity. Based on the visits they were able to attend, the analysis incorporates the data from their tracking.

2. Risk factors for the development of ischemic heart disease

The VALIANT study found a higher incidence of classical RF (DM, dyslipidemia, and AH) among patients with ACS and COPD compared to the general population (Hawkins et al., 2009). The initial data for the risk characteristics of the studied population is presented in Table 1.

Table 1. *Risk characteristics of patients in both groups.*

	Group A (n = 75)	Group B (n = 65)	p-value
Risk factors for IHD			
Arterial hypertension, (%)	98.7%	100%	0.350
Smoking, (%) - yes - ex-smoker - no	 57.3% 24% 18.7%	 47.7% 26.2% 26.1%	 0.459 0.765 0.288
Package per years	20.57±18.65	15.72±16.40	0.107
Dyslipidemia, (%)	45.2%	54.8%	0.258
Type 2 diabetes mellitus (%)	55.0%	45.0%	0.611
Overweight according to BMI >25 kg/m^2 (%)	55.8%	44.2%	0.445
10-year risk for IHD (FRS), (%) - Low risk <10% - Intermediate risk 10-20% - High risk >20%	 14.67% 45.33% 40%	 27.69% 49.23% 23.08%	 0.058 0.646 **0.033**
Laboratory indicators			
CRP mg/L	28.02±40.66	6.66±21.83	**0.0459**
Troponin I μg/L - in ACS without ST – elevation - in ACS with ST – elevation	 2.77±4.58 1.47±1.84	 0.403±1.01 4.72±7.90	 **0.019** 0.083

2.1. Arterial hypertension

Arterial hypertension occurs between 30 - 40% of patients with STEMI and 70% of patients with NSTEMI (Konstantinou et al., 2019). In patients with COPD, the incidence of hypertension is between 40-60%. Kim et al. discovered that 54.2% of the COPD study participants had hypertension. A sub-analysis of the PLATO (Platelet Inhibition and Patient Outcomes) found AH in 72.2% of patients with lung disease compared to 65% of those without it, p<0.001 (Andell et al., 2015). A research conducted in Bulgaria among 338 patients with

COPD found an incidence of hypertension in 70.5% (Stratev et al., 2018). In our study, AH was the most common RF in both groups (98.7% vs 100%, NS).

2.2. Smoking

Smoking is an independent RF, which, in combination with others, significantly increases the likelihood of ACS (Panaytov et al., 2013). A Japanese multicenter prospective study tracked the incidence of CVD in 995 smokers. In 25.9% of smokers with ACS, COPD was also found (Franssen et al., 2016). Similar results were found in another study. It followed 2730 smokers of both sexes with IHD, and 30.5% of them were diagnosed with COPD (Vozoris et al., 2012). When comparing patients with ACS and COPD and those without COPD, a significant difference was found in favor of patients with lung disease. Of those with COPD, 45.3% were found to be active smokers, while 35% of the control group stopped smoking (35.9% vs. 24%, $p<0.001$). (Kim et al., 2017). We found smoking in 57.3% of patients with ACS and COPD and 47.7% in those without COPD. To assess the cumulative effect on the cardiovascular and respiratory systems, we calculated the "package years" for each study group. COPD patients have a five-year longer statute of limitations than individuals without lung illness (20.57±18.65 vs 15.72±16.40, p=0.107). An observational study among 2164 patients with COPD found an average of 48.6 ± 27.1 package years (Agusti et al., 2010).

2.3. Dyslipidemia

A large retrospective study found a 1.48-fold higher risk of dyslipidemia in individuals with obstructive pulmonary disease compared to the healthy population (Yang et al., 2020). Another study found elevated LDL-cholesterol values in 43% of patients with COPD compared to controls (Bursi et al., 2010). In the population we studied, dyslipidemia is more common in the group of ACS without COPD 54.8% (n=32) compared to group A 45.2% (n=34), p=0.258.

2.4. Diabetes mellitus

Type 2 diabetes mellitus is more common in patients with COPD than in the general population (Rabe et al., 2013). In the NHANES study, its incidence was 29.6% in patients with lung disease compared to 15% in controls, $p<0.005$ (Wei et al., 2001). A high incidence of DM among patients with COPD was also found in Bulgaria OR 2.2 (95% CI, 0.38 – 12.5) (Pavlov et al., 2012). We found an incidence of DM in 55% (n=41) of patients with COPD, compared to 45% (n=30) in the control group, p=0.611. A study of 8167 patients with AMI with

obstructive lung illness in the Middle East confirms these findings. (48.2% vs 40%, p=0.001) (Hadi et al., 2010).

2.5. Obesity

Patients with COPD were more disadvantaged than controls with average BMI values. (29.1±7 kg/m2 vs 27.5 ± 5 kg/m2, p=0.001) (Hadi et al., 2010). In a Canadian national health survey, the incidence of obesity in patients with COPD was 24.6%, compared to 17.1% in patients without COPD (PEavlov et al., 2012). In our study, group A's average body weight was higher. (86.66 ± 21.49 kg vs 84.04 ± 18.09 kg, p=0.441). The incidence of obesity according to BMI is bigger in people with ACS and COPD (55.8% vs 44.2%, NS).

2.6. CRP

A study tracking cardiovascular risk in patients with COPD found higher CRP levels (3.70 ± 2.37 mg/L) than those without lung disease (2.39±2.23 mg/L), p=0.012. Using bivariate analysis, they found a strong positive correlation between CRP values and atherogenic risk (Sharma et al., 2019). Elevated inflammatory marker values are an independent predictor of ACS, with the relative risk in patients with CRP > 3 mg/L being 1.79 compared to individuals with CRP < 1 mg/L (Ridker et al., 2003). A meta-analysis of 14 studies investigating the relationship between COPD and systemic inflammation demonstrated an average difference in CRP values of 0.53 units (95% CI, 0.34 - 0.72, p=0.06), favoring individuals with lung disease. (Gan Hadi et al., 2005). Andell et al. also found higher CRP values among patients with concomitant COPD after myocardial infarction compared to those without pulmonary disease (38±60 mg/L vs 25±50 mg/L, p<0.001). We also found a statistically significant difference in the values of the inflammatory marker (28.02 ± 40.66 mg/L vs 6.66 ± 21.83 mg/L, p=0.0459).

2.7. Highly sensitive troponin

According to the fourth universal definition, myocardial infarction is considered to be the presence of acute myocardial damage, expressed in an increase and decrease by at least one troponin value above the 99th percentile URL (Thygesen et al., 2018). Troponin T and I are a component of the contractile apparatus of myocardial cells and are assumed to be strictly specific for myocardial tissue. However, high levels of troponin T have also been found in stable patients with COPD who have no CVD to date and are associated with high mortality (Soyseth et al., 2013). The protein values for myocardial damage correlate with the severity of bronchial obstruction. A prospective study of 50 patients hospitalized for exacerbation found

that patients with elevated troponin T values had a greater risk of CVD and left ventricular dysfunction compared with controls (Noorain, 2016). McAllister et al. found that out of 24 patients hospitalized for acute deterioration of COPD, 20 of them had high troponin values, chest pain, and changes in the electrocardiogram (ECG) corresponding to ACS. Most of them also meet the criteria for myocardial infarction of the second type (impaired oxygen supply due to tachycardia and hypoxia). The intergroup analysis revealed a statistically significant elevation in troponin I level in patients with ACS without ST elevation who also had COPD, compared to the control group (2.77±4.58 vs 0.403±1.01, p=0.019).

3. Comorbidities

Comorbidities are etiopathogenetically linked to chronic airway obstruction and progress concurrently, worsening the prognosis. According to NHANES 2013-2018, the most common comorbidities in patients with COPD are DM, chronic kidney disease (CKD), and stroke. The incidence of HF in patients with COPD was 18.9% compared to 2.8% of the general population. Patients with pulmonary obstruction also have more frequent DM (29.6% vs 15%) and stroke (14.1% vs 3.9%) compared to controls (Chen et al., 2023). Table 2 presents the most common concomitant diseases in the population we studied.

Table 2. *Comparison of groups according to comorbidities*

	Group A (n = 75)	**Group B (n = 65)**	**p-value**
Anaemia %	68.8%	31.3%	**P<0.0001**
Chronic kidney disease %	54.7%	38.4%	**0.0549**
Stroke %	20%	7.7%	**0.0388**

3.1. Anaemia

From the intergroup analysis, we found a higher incidence of anaemic syndrome among patients with COPD (68.8% vs 31.3%, p<0001). Pavlov et al. found a frequency of anemic syndrome in 34.4% of patients with COPD in the Pleven region. In a prospective study of 683 patients with stable COPD, hemoglobin (Hb) ≤ 130 g/L, and polycythemia, Cote, Celli, et al. found that anaemic syndrome is an independent predictor of decreased functional capacity. Anaemia is a well-described RF in patients with ACS. Back in 2001, Wu et al. stated that

anaemia impairs the hospital and outpatient prognosis of patients with ACS. They propose that the worsening prognosis in this patient population is due to both decreased oxygen supply to tissues and myocardium caused by anaemia and a higher incidence of comorbidities.

3.2. Chronic kidney disease

We also found borderline statistical significance for CKD as a concomitant disease in favor of patients with ACS and COPD (54.7% vs 38.4%, p=0.0549). Smoking causes vascular and parenchymal damage to the lungs and negatively impacts kidney function. Hypoxia, hypercapnia, and advanced age in patients with COPD play a key role in the development of CKD (Chen et al., 2015). Other investigations have also confirmed this pathogenetic connection, with a higher frequency of CKD in patients with obstructive lung disease. Rusnak et al. found kidney damage in 64% of patients with ACS and COPD compared to 50% of patients without lung disease, p<0.0013. Another study following 108 outpatients with stable COPD reported a 31% incidence of CKD compared to 8% of the healthy population (Yoshizawa et al., 2015).

3.3. Stroke

More than 30% of COPD patients reported the presence of comorbidities, with 14% having a stroke (McAllister et al., 2012). The incidence of stroke in patients with COPD is between 6.9% and 9.9% (Curkendall et al., 2006). Another study found a twofold higher incidence of this comorbidity than controls (4.2% vs 2.6%, p=0.001) (Kim et al., 2017). In our study, 20% of the patients with ACS and COPD had a history of stroke. A meta-analysis of 1,204,100 patients found that 9.9% of patients with COPD had cerebrovascular disease, compared to 3.2% in the general population. (Engstorm et al., 2010). The NHANES study found that 14.1% of patients with respiratory obstruction had a stroke (Chen et al., 2023). An increased risk of ischemic MI has been reported depending on the degree of airway obstruction. For the first GOLD stage, this is RR 0.6 (95% CI, 0.3-1.1), for the second RR 1.7 (95% CI, 1.1-2.5) and for the third and fourth RR 1.5 (95% CI, 0.7-3.0) (Lange et al., 2010). The acute worsening of respiratory obstruction during exacerbation explains the exponentially increased risk of AMI and stroke in patients with COPD. (Portegies et al., 2016).

4. Characteristics of patients with concomitant COPD

4.1. Statute of limitations of the disease

Group A patients with concomitant COPD had an average duration of the disease of 11± 2.33 years, which correlates with the results of another study conducted in Bulgaria (Pavlov et al., 2012).

4.2. Classification of patients based on GOLD stage

The new GOLD criteria state functional breathing testing is necessary for COPD staging. Patients are classified into four stages based on the degree of obstruction, which defines the disease's severity and prognosis.

Observational research conducted in Bulgaria in 2020 found that patients were distributed according to the GOLD stage as follows: 7% in the first stage, 35% in the second, 15% in the third, and 43% in the fourth stage (Dimitrova et al., 2020). Another study conducted in the Pleven region produced similar results: GOLD 1 - 52.3%; GOLD 2 - 28.5%; GOLD 3 - 13.9%; and GOLD 4 - 5.3% (Pavlov et al., 2012).

In our study, all COPD patients have fixed obstructions. The mean value of FEV_1 after bronchodilation is 52.52±15.78%. The results confirm another survey conducted in the country with an average FEO_1 score of 52.1 ± 19.7% (Yanev et al., 2016). A 2023 study found an average FEO_1 value of 53.1±20.8% (Wei et al., 2023). Doldson et al. also find similar values - 55.9%. According to the spirometry classification, 16% of our patients have a mild obstruction (FEV_1<80%), 44% have moderate (50≤FEV_1<79%), 29% have severe (30≤FEV_1<49%), and 11% have a very severe obstruction (FEV_1<30%)– Figure 1.

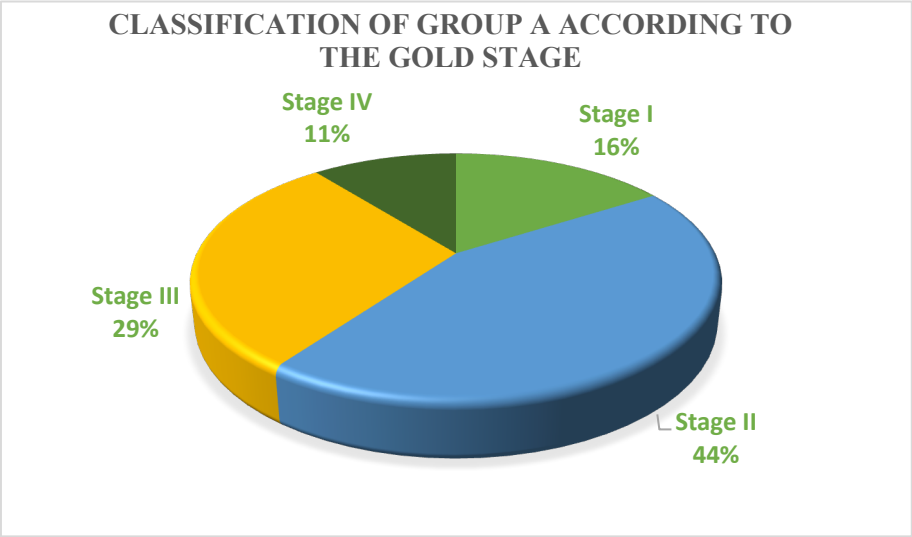

Fig. 1. *Distribution of patients according to the GOLD stage at their dehospitalization.*

Our results are close to those of the Norwegian Nord-Trøndelag Health Study, conducted between 1995 and 1997. In contrast to the ABCD grouping, the participant distribution was - 28% in the first stage (GOLD, 2007), 57% in the second stage, 13% in the third stage, and 2% in the fourth stage. And 61% in group A; 18% in group B; 12% in group C; and 10% in group D (Tevik et al., 2019). These findings have been confirmed by a longitudinal analysis of 117 patients with coronary artery disease from 2015 to 2021. The authors discovered mild obstruction in 34.1% of the patients, moderate in 52.3%, and severe in 13.6% (Ferreira et al., 2023).

4.3. Combined assessment of COPD patients

Patients with the same FEV_1 values may have varying perceptions of their condition. FEO_1 evaluates only one aspect of the disease: the degree of obstruction, which has a poor correlation with the patient's quality of life and subjective feeling of shortness of breath. (GOLD, 2021). In 2011, the ABCD classification was introduced to assess mortality based on GOLD criteria. In our study, according to the ABCD group of GOLD, 10.7% fell into group A, 42.7% into group B, 30.7% into C, and 15.9% into D. Group B had the most patients (42.7%), whereas group A had the fewest (10.7%). The distribution is shown in Figure 2.

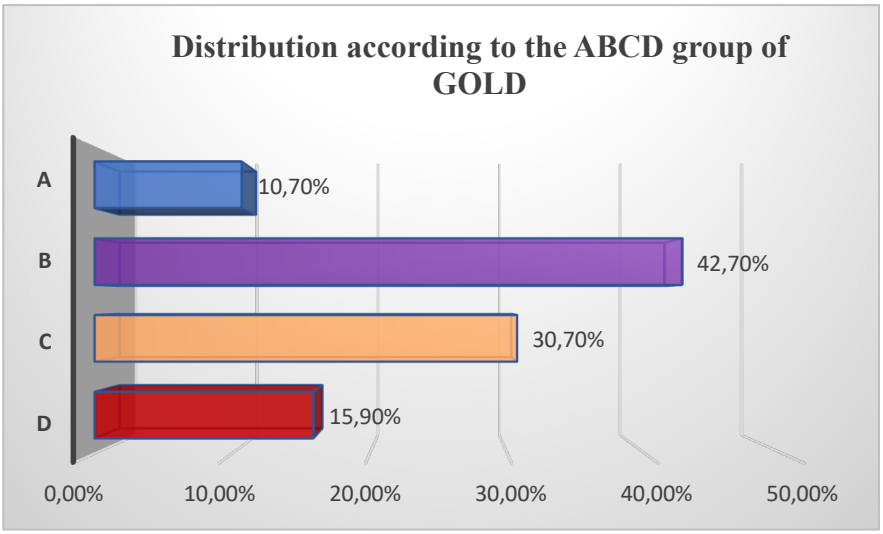

Fig. 2. *Distribution of patients according to the ABCD group according to the GOLD classification at the beginning of the study.*

In 2023, the recommendations were updated, and classes C and D were replaced by E – to highlight the importance of the number of exacerbations per year (GOLD, 2023). According to the ABE GOLD group, the distribution of patients showed that 10.7% had few

symptoms and fell into group A, 42.7% into group B, and group E with the most exacerbations – 46.7% – Figure 3.

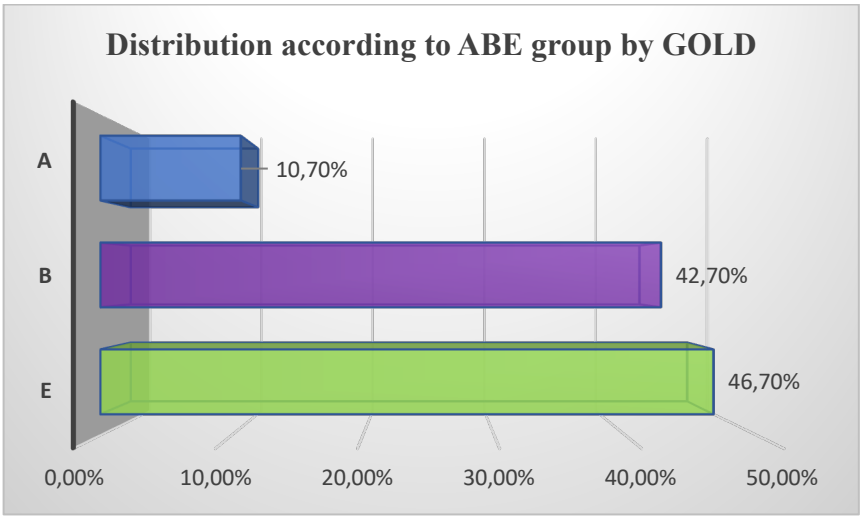

Fig. 3. *Distribution of COPD patients according to the ABE GOLD group at the beginning of the study.*

A study tracking 2,499 patients with COPD were staged according to GOLD 2017 and reclassified according to the 2023 recommendations. According to ABCD, in 2017, 8.4% fell into group A, 44.8% into group B, 2.9% into C, and 43.9% into group D. The new recommendations introduce a GOLD group of ABE, according to which patients from groups A and B remain 8.4% and 44.8%, respectively, and 46.8% already fall into group E (Wie et al., 2023).

The majority of the COPD patients analyzed by us had pulmonary obstruction, which corresponds to stage II GOLD and has the most severe symptoms according to the ABE group. Studies have shown that these patients often have a higher incidence of long-term adverse cardiovascular events than those with mild obstruction (Ferreira et al., 2023).

5. Clinical characteristics of patients from both groups according to the type of acute event

Patients with COPD have twice the risk of CVD compared to those without COPD (OR 2.7, 95% CI: 2.3–3.2) (Finkelstein et al., 2009). An analysis of the APPROACH (Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease) database found an incidence of CHD in the COPD group at 86.6% (Yongzhe et al., 2019). Finkelstein et al.

detected IHD in 16% of patients with COPD compared to 6% in the control group, p<0.0001. Age, low social status, hypertension, DM, and dyslipidemia increase the possibility of ACS in patients with obstructive pulmonary disease. A higher degree of education and more physical activity can reduce this risk. The incidence of ACS in COPD patients in the global population ranges between 10-17% depending on the design of the studies (Rothnie et al., 2015; Kara et al., 2000).

Patients with COPD are more often presented with ACS without ST-elevation. Bursi et al. found an incidence of NSTEMI in 75% of the subjects with pulmonary obstruction compared to 65% in the control group (p=0.01). A study tracking patients with ACS and COPD found a statistically significant prevalence of ACS without ST-elevation in the group with lung disease (59.9% vs 54.2%, p=0.001) (Andell et al., 2014). Compared to the control group, patients with COPD are more likely to be older, active smokers and have more cardiovascular comorbidities. Less commonly, they have a typical clinical manifestation and a later peak in troponin levels (Enriquez et al., 2013). Rothnie et al. found that patients with COPD present themselves more often with NSTEMI than with STEMI and, accordingly, have lower values of markers of myocardial damage – troponin and creatinine kinase. Another study found a higher incidence of unstable angina in patients with pulmonary obstruction compared to those without (11.7% vs 3.9%, p<0.0001) (Finkelstein et al., 2009). An analysis of the results of NHANES revealed unstable angina in 15.8% of the studied patients with lung disease compared to 2.6%, p<0.001 (Wei et al., 1988). In our study, we also found that patients with COPD presented more often with ACS without ST-elevation (74.67 % vs 36.92%, p<0.0001). Compared to them, patients from group B have a more frequent manifestation of ACS with ST-elevation (25.33% vs 63.08%, p<0.0001) – Figure 4.

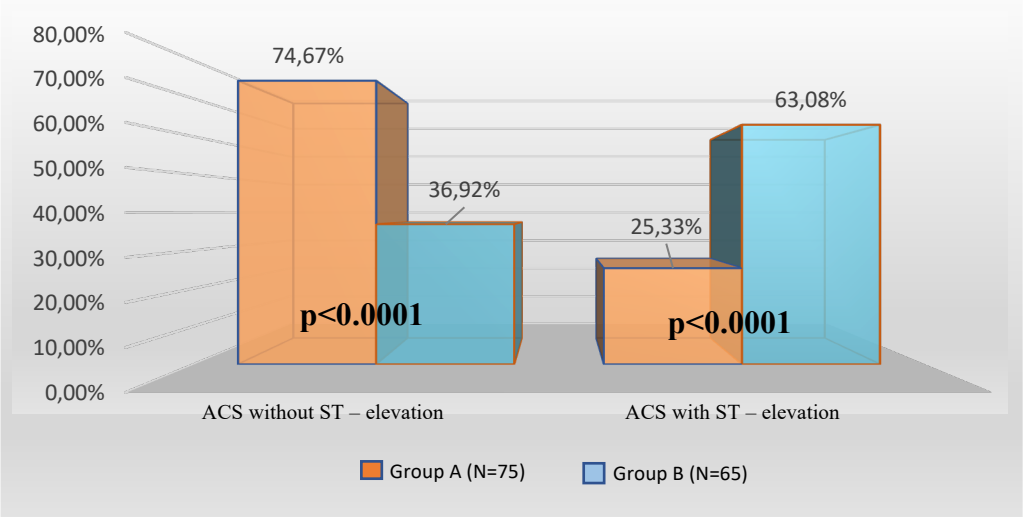

Fig. 4. *Distribution of patients from both groups according to the type of acute event.*

A large American. study using data from the national CVD registry (ACTION) compared 22,624 patients with ACS and pulmonary obstruction with 136,266 controls. The results showed a higher incidence of ACS with ST-elevation in the non-COPD group (Di Martino et al., 2016). Dziewierz et al. found STEMI in 38.3% of patients with pulmonary obstruction compared to 47.9% of subjects in the control group (Dziewierz et al., 2010). Similar to the results of the study by Andel et al., the manifestation of STEMI is more common in the group without COPD (35.5% vs 26.7%, p=0.001).

6. Distribution according to the diagnostic and therapeutic strategy undertaken

6.1. Distribution of patients according to invasive coronary angiography

According to the current recommendations of the European Society of Cardiology for treating acute coronary syndrome, revascularization is the main treatment method (Borja et al., 2018). In our group A population, 92% (n=69) and 100% of group B were interventionists, p=0.020 – Figure 5.

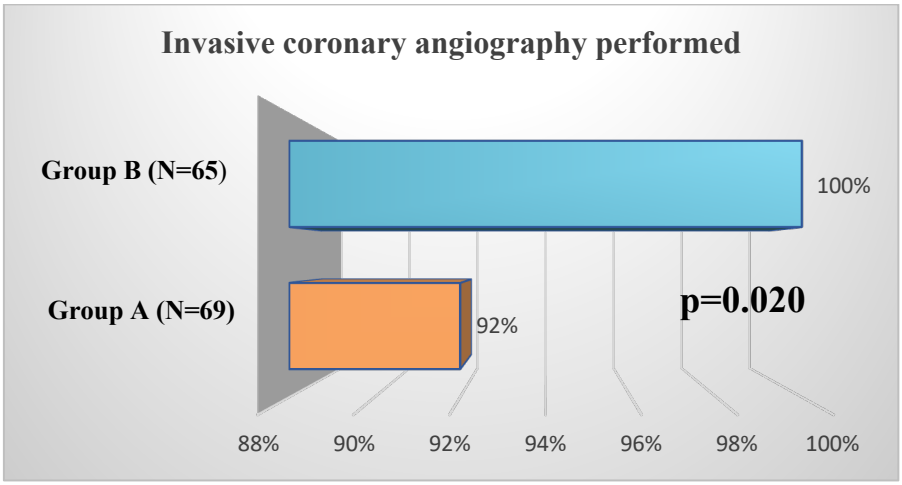

Fig. 5. *Distribution of patients according to diagnostic strategy*

Six patients with ACS and COPD weren't assessed for SCA, despite being at moderate to high risk, according to the Global Registry of Acute Coronary Events (GRACE). As a contraindication for invasive coronary angiography, two of the patients had a high-grade renal failure with a Glomerular Filtration Rate (GFR)<15 ml/min/1.73m2, three had severe anemic

syndrome with Hb<70 g/l and one was diagnosed with a severely damaged condition with pronounced hypercapnea.

Our data resonate with the results of other large studies (Andell et al., 2014; Rothnie et al., 2015; McAllister et al., 2012). The results of the national Swedish registry SWEDEHEART show that patients with ACS and COPD are less likely to get SCA compared to patients without COPD (37.7% vs 55.7%, p<0.001). The share of patients with COPD who receive stenting is also smaller (35.9% vs 53.3%, p<0.001). As a reason, the authors point to advanced age and the presence of more concomitant diseases. The lack of invasive diagnosis and treatment correlates with the higher incidence of reinfarction during hospital stay in patients with pulmonary obstruction (1.4% vs 1.3%, p=0.44) (Andell et al., 2014). A study tracking therapeutic strategies in patients with ACS and COPD found that the group with lung disease had a higher percentage of incorrect initial diagnosis and a longer time to reperfusion therapy compared to controls, respectively (153 min vs 109 min). A probable cause may be that patients with COPD are older and more impaired compared to controls. However, even after excluding these contraindicated patients, the percentage of patients with COPD who received SCA was lower (Rothnie et al., 2015). Another disturbing factor is that only 8% of patients with ACS and COPD hospitalized for acute exacerbations meet the definition of AMI (McAllister et al., 2012). The study by Bursi et al. found that 51% of patients with ACS and COPD underwent selective angiography compared to 59% of those without lung disease, p<0.01. Of these, they received revascularization respectively (41% vs 52%, p<0.01). PREMIER (Prospective Registry Evaluating Myocardial Infarction: Event and Recovery) again reported a statistically significant difference between the two groups. Percutaneous coronary intervention (PCI) was performed in 50.9% of patients with COPD compared with 62.9% in those without lung disease, p<0.001 (Salisbury et al., 2007).

6.2. Revascularization strategy in patients with obstructive CAB

Group A and B patients have significant differences in coronary pathology identified during interventional treatment. Univascular CAD predominates in patients with ACS and COPD (65.22% vs 33.85%, p=0.0003). Bilateral coronary pathology is more common in patients with ACS without COPD (15.94% vs 43.08%, p=0.0006). Although statistically insignificant in group A, multivascular CAD is more common than in group B (17.39% vs 15.38%, p=0.754) – Figure 6.

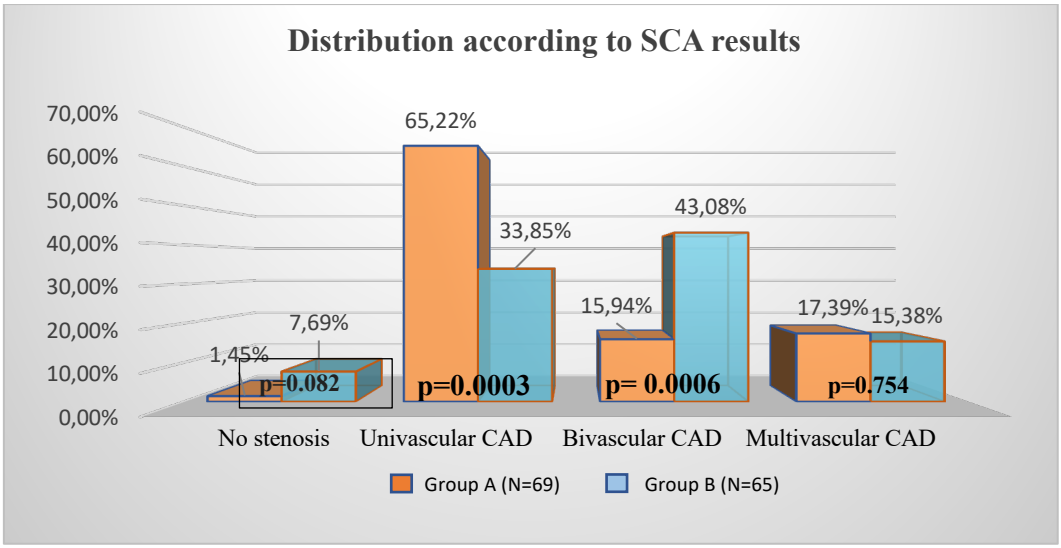

Fig. 6. *Distribution of patients according to SCA results*

APPROACH data showed a higher incidence of significant coronary stenosis in patients with COPD compared to the control group, p<0.001 (Yongzhe et al., 2019). Rusnak et al. found a predominance of univascular CAD in patients with ACS and COPD (25% vs 23%, p=0.416) and bivascular in the group without COPD (17% vs 24%, p=0.416). Stenosis of the three coronary arteries was recorded in 32% of patients with pulmonary obstruction compared to 29% in controls. Ferreira et al. discovered that multivascular CAD was more prevalent in COPD patients versus controls.

Compared to 50 patients in group B, 56 patients in group A were assessed for PCI (82.35% vs. 83.33%, p=NS). 17.65% of patients with ACS and COPD and 16.67% of patients without pulmonary obstruction were assessed for later aortocoronary bypass surgery (p=0.754). – Figure 7.

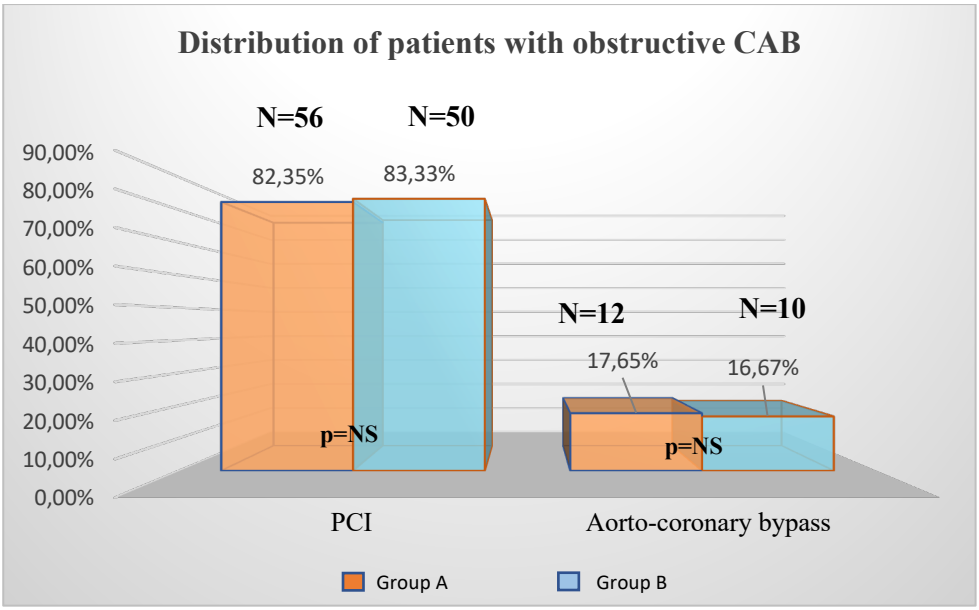

Fig. 7. *Distribution of patients with obstructive coronary artery disease.*

6.3. Distribution of patients according to the type of artery affected

The left coronary artery (LAD) is the most common cause of group B disease (53.2% vs 38%, p=0.0800). In the group with ACS and COPD, the right coronary artery (RCA) involvement predominates, respectively (39.4% vs 29%, p=0.210) – Figure 8.

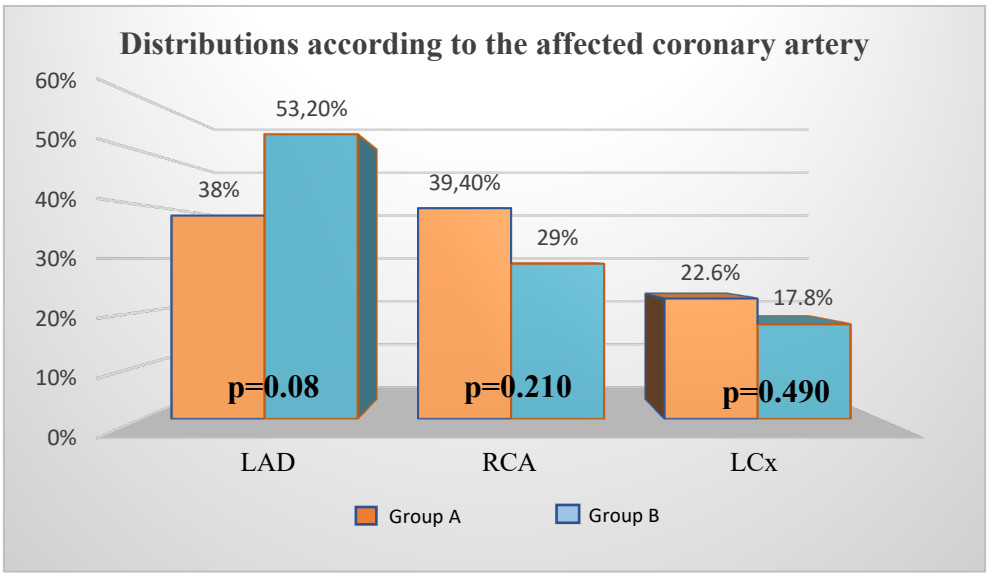

Fig. 8. *Distribution of patients from both groups according to angiographic findings.*

The results are close to those found by Rusnak et al. They identified stenosis of the LAD in 51% of individuals with ACS and 40% in ACS with COPD (p=0.160). Right coronary

pathology dominates in patients with COPD (38% vs 37%, p=0.873). Left circumflex artery (LCx) involvement is also more common in patients with pulmonary obstruction (29% vs 24%, p=0.474).

7. Follow-up of patients in both groups one year after ACS

7.1. Dynamics in risk factors for IHD one year after ACS

7.1.1. Arterial hypertension

Arterial hypertension is the most common comorbidity in individuals with COPD. It is responsible for 35% to 60% of all concurrent diseases. Patients with AH and obstructive pulmonary disease have an increased cardiovascular risk (Divo et al., 2012).

We analyzed blood pressure measurements and adherence to the prescribed therapy at each visit. The statistical analysis was done using a chi-square test – Figure 9.

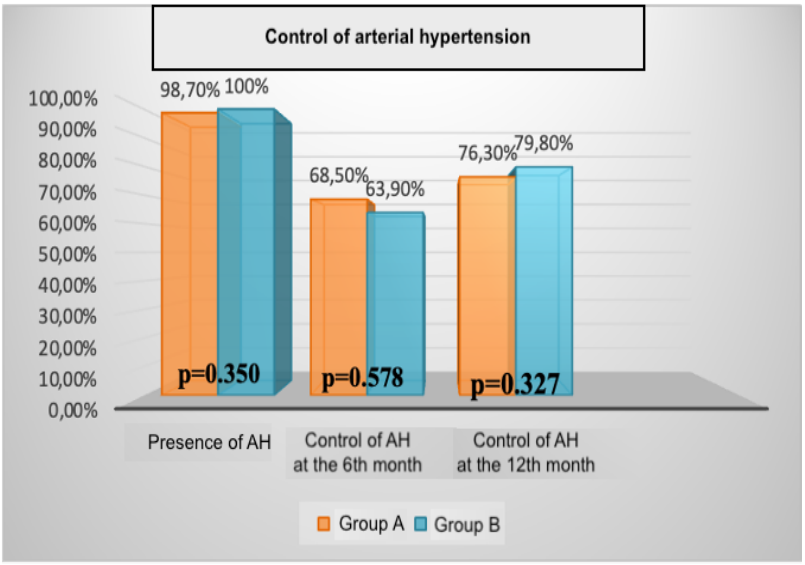

Fig. 9. *Distribution of patients according to the achieved control of hypertension during the follow-up period.*

During follow-up of patients, we found that at the first visit, optimal control of hypertension was more often achieved in group A (68.50% vs 63.90%, p=0.578). By the end of the 12th month, a larger share of patients from group B achieved the blood pressure target (76.3% vs 79.8%, p=0.327). A study following patients with COPD in the period from 2013 to

2018 found an increase in the proportion of hypertensive patients from 67.8% to 71.8%, p<0.001. The authors reported an average increase in SBP from 131.1 mmHg to 132.2 mmHg by p<0.0001. By the end of the trial, AH control had declined from 64.6% in the first years following enrolment to 60.8% (p < 0.0001) (Hawkins et al., 2022). A large 25-year study in patients after myocardial infarction or stroke found a decrease in SBP values from 140 mmHg to 129 mmHg and achievement of AH control (Shan et al., 2021). Another studio observes the control of hypertension in patients with ACS for 1,197 days. Patients with blood pressure control below 130/80 mmHg were 59.6% (95% CI: 54.3-64.9%) and below 140/90 mmHg were 83.7% (95% CI: 80.3-87.2%) (Shan et al., 2020).

7.1.2. Smoking

Smoking in patients with COPD and IHD is often associated with worsening shortness of breath and airway obstruction. Quitting smoking is extremely important for patients with ACS. The data show that one year without tobacco smoke reduces the relative risk of a second heart attack by 36% compared to controls RR 0.64 (95% CI, 0.58-0.71) (Nowak Shan и сътр., 1987). A study among patients with COPD found an average annual decrease in smokers by 13.6% (Hawkins Shan et al., 2022). In patients after ACS, this percentage is greater than 25% (Shah Shan et al., 2021). We found a statistically significant larger number of patients from group B who reduced or stopped smoking for one year after ACS compared to group A, respectively (39.53% vs 64.52%, p=0.035) - Figure 10.

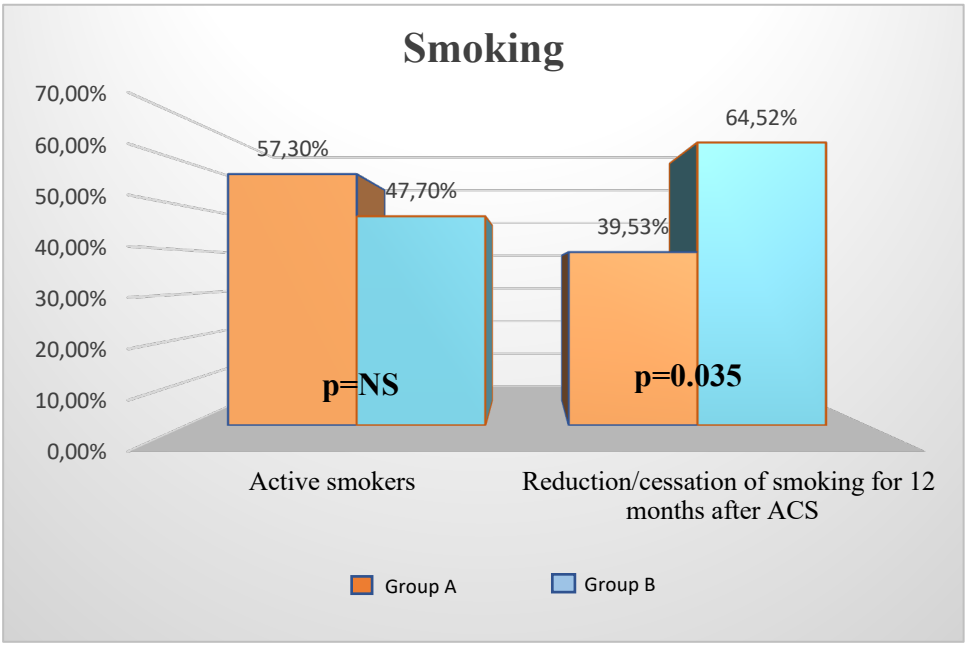

Fig. 10. *Cessation or reduction of smoking for a period of one year after ACS in both study groups.*

7.1.3. Dyslipidemia

It is known that there is a logarithmic, linear relationship between absolute changes in plasma LDL levels and the risk of ACS. Achieving the target values of the lipid profile is essential to reduce the risk of a recurrent cardiovascular event. Reducing LDL cholesterol by 1.0 mmol/l lowers the risk of a major vascular accident by 20%. (Fulcher Shan et al., 2015). In our study, at the sixth month of follow-up, about 24% of patients in both groups achieved a 50% reduction from baseline LDL-cholesterol levels. In particular, 31% of patients with ACS and COPD acquire control compared to 17.2% of patients without COPD, which is statistically significant ($x^2 = 5.94$, $p = 0.015$) – Figure 11.

These results are close to the data of Salwa et al., which establish the achievement of the target for patients with ACS and COPD 47% and for those without lung disease - 26%, p=0.02 at the twelfth month of follow-up, respectively.

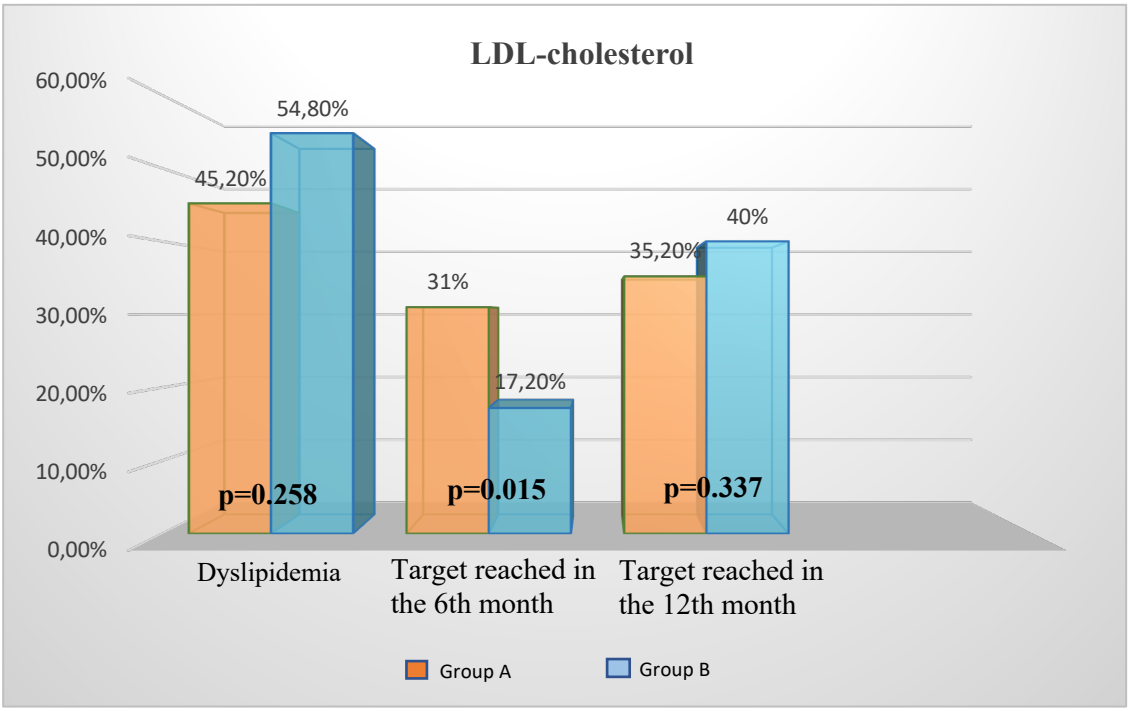

Fig. 11. *Control of LDL-cholesterol in both groups of patients.*

At the end of the trial, the obtained LDL-cholesterol control remained in nearly the same proportion of patients from group A - 35.20%, but we notice a higher rate of adherence to target values in group B - 40%.

A study following patients with COPD found that LDL-cholesterol targets were achieved in patients with COPD from 42.5% at baseline to 46.6% at the end of the five-year follow-up (Hawkins et al., 2022).

7.1.4. Diabetes mellitus

Diabetes mellitus is characterized by elevated blood glucose levels, which raise the risk of microvascular damage. A retrospective analysis examining the relationship between COPD and various comorbidities in a database of Italian general practitioners found a 10.5% higher risk of developing diabetes compared to the general population (Cazzola et al., 2017). Our study found higher mean glucose values among patients without COPD (17.79 ± 71.17 mmol/l.) compared to patients with COPD (8.37 ± 3.94 mmol/l.), but these differences showed no statistical significance ($t=1.14$, $p=0.254$). Group B had a higher incidence of STEMI compared to group A. (25.3% vs 63.08%, $p<0.0001$). The reason for this is probably that acute coronary syndromes cause dysglycemia even in patients with normal baseline blood sugar levels (WHO, 2006).

We discovered diabetes in 55% (n=41) of the participants in group A and 45% (n=30) of the persons in group B, based on data acquired from medical records during hospitalization. Retrospective analysis found an 18.5% higher risk of developing diabetes in individuals with COPD compared to the healthy population (El Sayed et al., 2023). Blood glucose control is important for the stratification of patients with CVD and COPD. According to the recommendations of the European Endocrinological Society, 4.4-7.2 mmol/l is taken as a target for preprandial plasma glucose and 10 mmol/l for postprandial < (Monnier et al., 2006).

Following our patients, we found that 10% of individuals with COPD and DM achieved blood sugar control compared to 13.3% of those without COPD. In the 12th month of the study, we found a higher percentage of control achieved in group A compared to group B (24.4% vs 19.5%, $p=0.829$) - Figure 12.

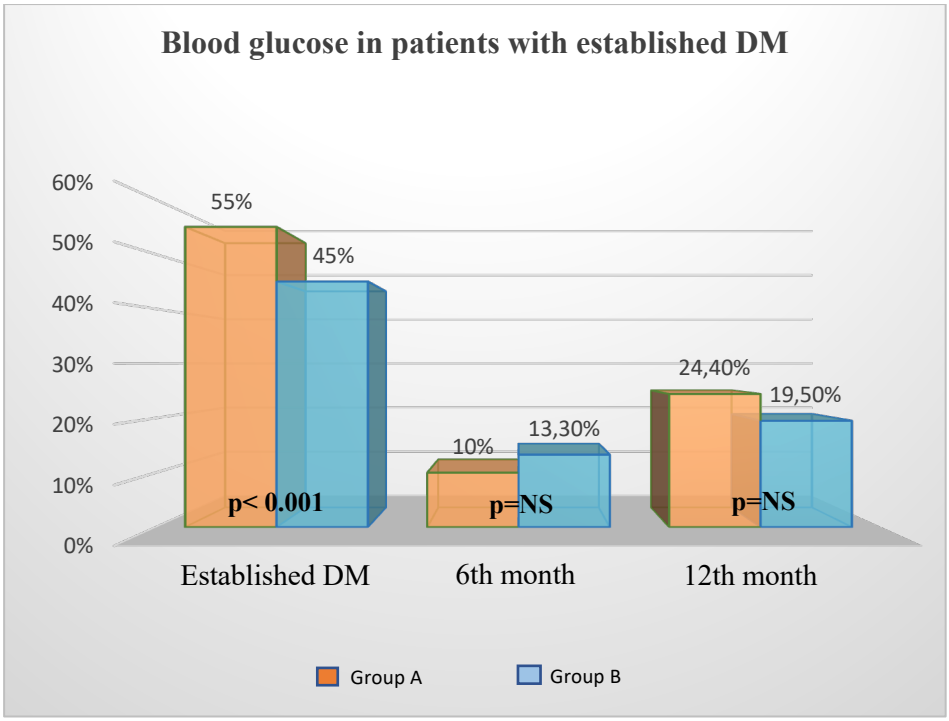

Fig. 12. *Blood glucose control was achieved in patients with established DM from both groups.*

7.1.5. Obesity

Obesity is one of the main risk factors for IHD and COPD. Data from the Global Burden of Disease Study found cardiovascular mortality in more than 2/3 of obese people (Cazzola et al., 2010). In an epidemiological study called the Copenhagen City Heart Study, obesity was associated with over a 20% increase in the relative risk of death in patients with COPD (GBD, 2015). Patients' symptoms, physical tolerance, and general wellness are significantly improved by pulmonary rehabilitation and physical activity. (Aguib et al., 2015). To reduce the risk of a fatal cardiovascular event, we recommended a healthy diet and regular physical activity at each visit, following the European Society of Cardiology (Pelliccia et al., 2021). As a result, the control weight of all participants in the twelfth month, although minimally reduced, was reduced (83.62 ± 19.75 kg vs 83.05 ± 17.87 kg, p = 0.874). Only 7.14% (n=3) of the 42 participants in group B achieved a BMI <25 kg/m^2. An interesting result is in patients from group A, in whom weight gain was registered in 9.43% of patients (n=5).

An increase in BMI was also observed in another cohort of patients after ACS, from 27.2 kg/m^2 to 28.1 kg/m^2 (Shah et al., 2021). A study following patients with COPD showed average weight values of 98.6 ± 100.1 kg. Of these, approximately 10% manage to reduce their weight within a year, but only 1% reach a normal BMI (Hawkins et al., 2022).

7.2. Follow-up of COPD patients one year after ACS

7.2.1. Dynamics in the values of FEV1, FEV1 and FEV1 / FVC in % one year after the ACS

Observing the dynamics of FEO_1 over time provides information about the disease's course and predicts mortality. The authors' team of Casanova and Co. discovered an average decrease in FEV_1 values of 23 ml per year (95% CI 14-32 ml/year, p=0.002), which varies depending on the stage of the disease. In the second stage, FEV_1 decreases by an average of 40 ml. per year (95% CI 20-70 ml/year, p = 0.011), while in the third stage of GOLD a decrease of only 10 ml. (95% CI 4-20 ml/year, p = 0.017), and in the fourth FEO_1 does not decrease. After a five-year follow-up, the results were similar – for GOLD 2, an average drop of 46 ml/year. (95% CI 22-70 ml/year, p = 0.006), for GOLD 3 – 31 ml/year. (95% CI -18-80 ml/year, p = 0.158) and for GOLD 4 – 27 ml. /Yr. (95% CI 1-53 mL/yr/., p = 0.047). A study conducted in Indonesia found a one-year decrease in FEV_1 and FEV_1/FVC by 83.9% and 51.6%, respectively, in individuals with COPD (Ariawan et al., 2019). In the Baltimore Longitudinal Study of Ageing, patients with a faster decline in FEO_1 were five times more likely to die from any cause (Ferrucci et al., 2008). Our study found a decrease in FEV_1 by 3.9% in one year. An analysis of patients from the Lung Health Study proved that patients with lower baseline lung function (measured by the FEV_1/FVC ratio) had a faster decline in FEV_1 (Buist et al., 1997). The patients we studied showed a statistically significant decrease in FEV_1/FVC by approximately 4.09% – Table 3 and Figure 13.

Table 3. *Monitoring of pulmonary function test for one year*

	At the beginning of the study (N=75)	**On the 12th month (N=53)**	**p value**
FEV_1 % ref.	55.61±14.47	52.52±15.70	0.2596
FVC % ref.	59.68±21.67	55.49±20.14	0.2695
FEV1/FVC %	59.28±7.56	55.11±8.50	**0.005**

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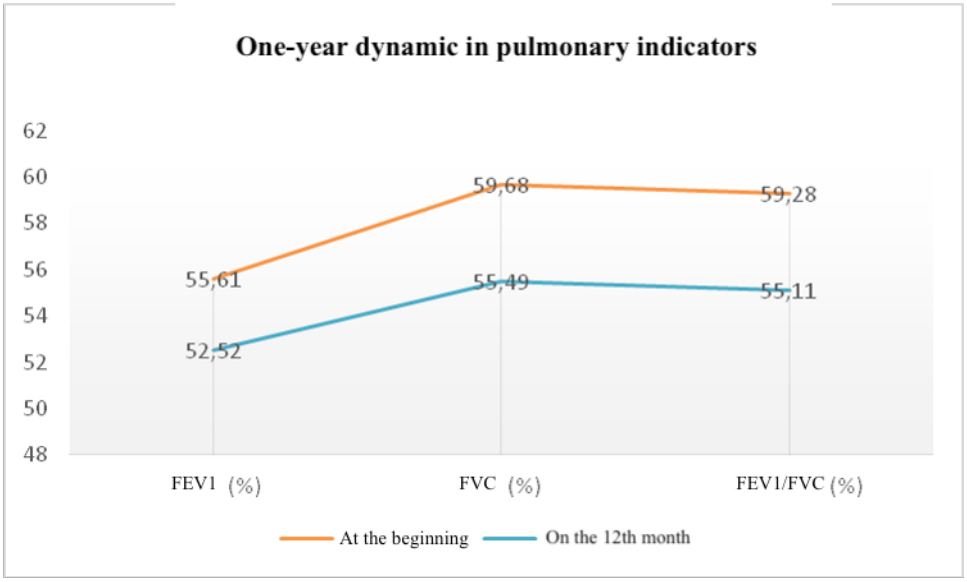

Fig. 13. *Dynamics in spirometry parameters for one year.*

Smoking harms patients with lung disease and significantly impairs their respiratory function. A study by Fletcher et al. conducted in 1977 described the progressive decline of FEV_1 in patients with COPD, especially in those who were active smokers. In our study, the decline in FEV_1 was also correlated with smoking. A one-year decline in pulmonary parameters was observed in 56.6% (n=30) of current smokers and 15.1% (n=8) of former smokers. Stefanova et al. also found a greater decrease in FEV_1 in current smokers compared to former smokers (t=2.377; p=0.043).

7.2.2. Classification of COPD patients according to GOLD one year after ACS.

At the end of follow-up, patients were classified by obstruction severity using the GOLD spirometry classification, which is based on FEV_1 values as a percentage of expected value. It is appropriate to note that the number of patients examined decreased during the follow-up period, most commonly due to death and, in just a small percentage of cases, due to a lack of data. In the first stage 16.7% (n=9) of the examined, in the second – 46.30% (n=24), in the third stage – 31.50% (n=17), and 5.5% (n=3) in the fourth – Figure 14.

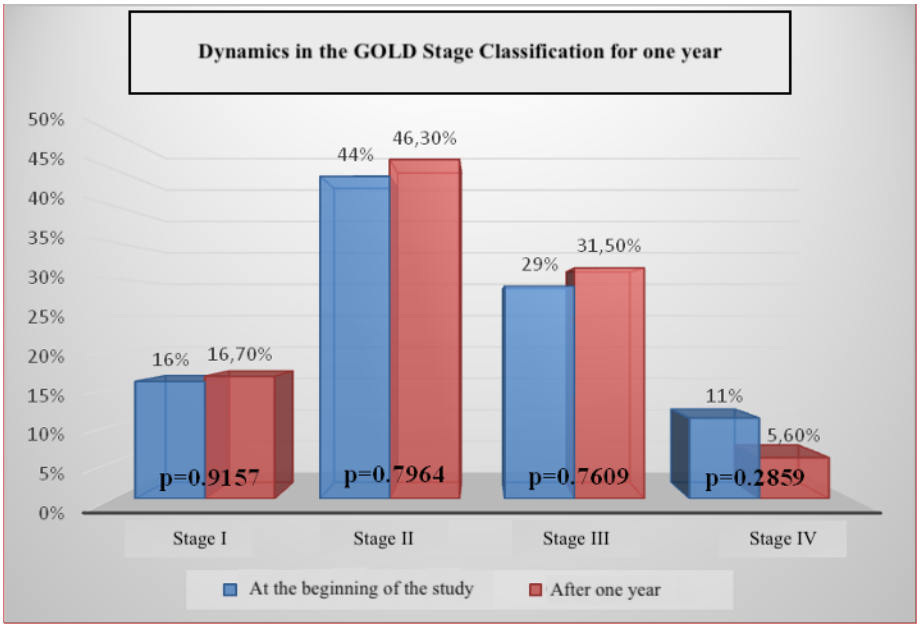

Fig. 14. *Dynamics in the classification of patients with COPD according to the GOLD stage one year after ACS.*

Dynamics in obstruction determine the reclassification of COPD patients according to GOLD during follow-up, which determines the degree of deterioration and prognosis. A longitudinal study conducted over two years found 39 patients with deterioration and reclassification according to GOLD 2011 (Gruffydd-Jones et al., 2012) at a higher stage, 47 with improvement and 160 without change. Patients with deterioration were assigned to GOLD A – 34.1%, GOLD B – 28.9%, and GOLD C – 37%, respectively. At the end of the study, the overall distribution of patients showed that 23.5% fell into stage A, 15.1% into stage B, 7.6% into stage C and 53.8% into stage D. Most of the patients classified at the beginning of the study in stages A and D remained so after the second year, pronounced dynamics and reclassification was observed in patients with stages B and C (Bernabeu-Mora et al., 2020).

During our investigation, we observed a rise in the number of patients in the second and third stages of GOLD compared to the beginning, with the second stage (44% vs 46.30%, p=0.796) and the third (29% vs 31.50%, p=0.760).

Yanev et al. also discuss the dynamics and classifications of groupings based on GOLD. They found a statistically significant difference at the end of the follow-up with a tendency to decrease the stage due to deteriorated lung metrics. (Yanev, 2016). A high CAT score may predict individual patients' stage worsening, mMRC >2, more than two exacerbations per year, and the presence of comorbidities. (Bernabeu-Mora et al., 2020).

7.2.3. Dynamics in symptom assessment for one year after ACS

At the end of the follow-up, patients with COPD completed the symptom objectification questionnaires - CAT and mMRC. It is also important to point out that all questionnaires were completed in the stable condition of patients. The average point sum of the 12th month of the CAT test follow-up is 21.09±7.96 points, and the mMRC is 2.32±0.87 points – Figure 15.

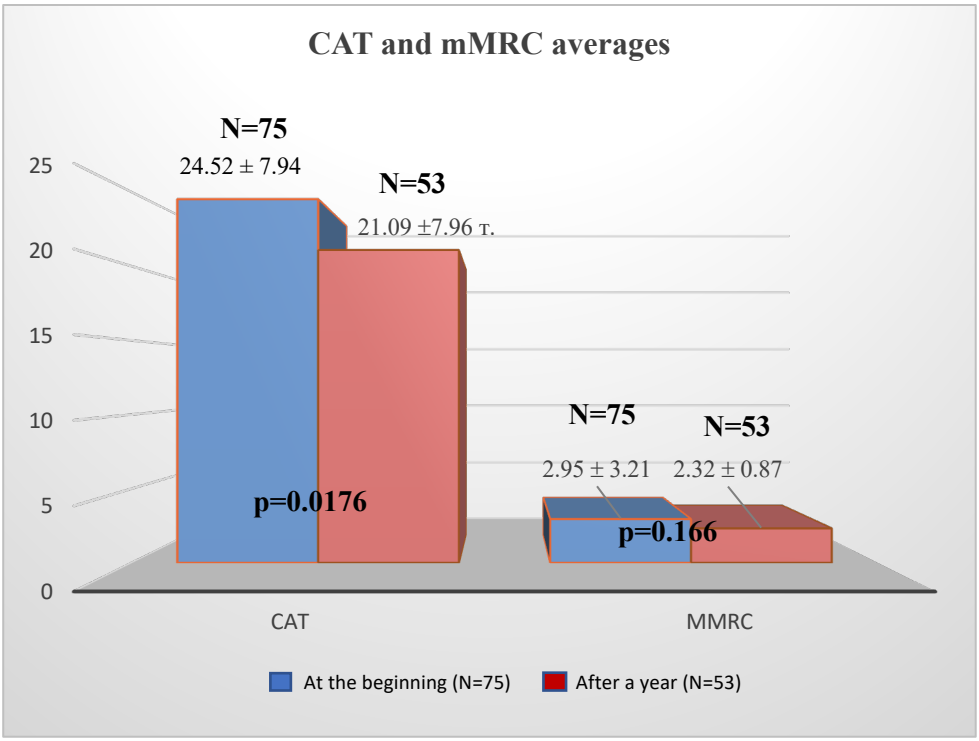

Fig 15. *Dynamics in the average values of CAT and mMRC scores for one year after the ACS*

We found a statistically significant difference in the average values of the CAT score for one year 24.52 ± 7.94 points vs 21.09 ± 7.96 points, p=0.0176). There was also a reduction in dyspnea, estimated on the mMRC scale, although statistically insignificant (2.95 ± 3.21 vs 2.32 ± 0.87, p=0.1665). The observed lower values and monitored parameters can be explained by patients progressing to the next GOLD level based on their severity. Yanev et al. found the same relationship by following COPD patients for three consecutive years. They report a decrease in the average values of the CAT score from 20.21 to 19.97 points and the mMRC scale from 1.98 to 1.13. Lin et al. also found a reduction in the average values of the CAT test within six months from the beginning, respectively from 14.5 ± 6.6 points to 12.2 ± 6.6 points. The authors also found a positive correlation between the CAT score and the incidence of exacerbations in a one-year follow-up (0.789 vs 0.609, p < .001) According to them, the change

in CAT values tracked for one year makes it possible to determine not only the risk of exacerbation, but also its severity.

7.2.4. Dynamics in exacerbations one year after ACS

As the disease progresses, the frequency of exacerbations increases. Patients with more than two exacerbations in the previous 12 months or one hospitalization are at increased risk of another one in the next year (Vestbo et al., 2013). Their frequency affects the quality of life and leads to a deterioration in lung function. For the follow-up period, we found 40 exacerbations, of which 60% required treatment in a hospital, the rest were registered as an examination in an emergency department or a follow-up pulmonologist. One exacerbation of the condition was recorded at 40% (n=18), over two moderate at 35.56% (n=16), and one severe exacerbation was recorded at 24.44% (n=6) – Figure 16.

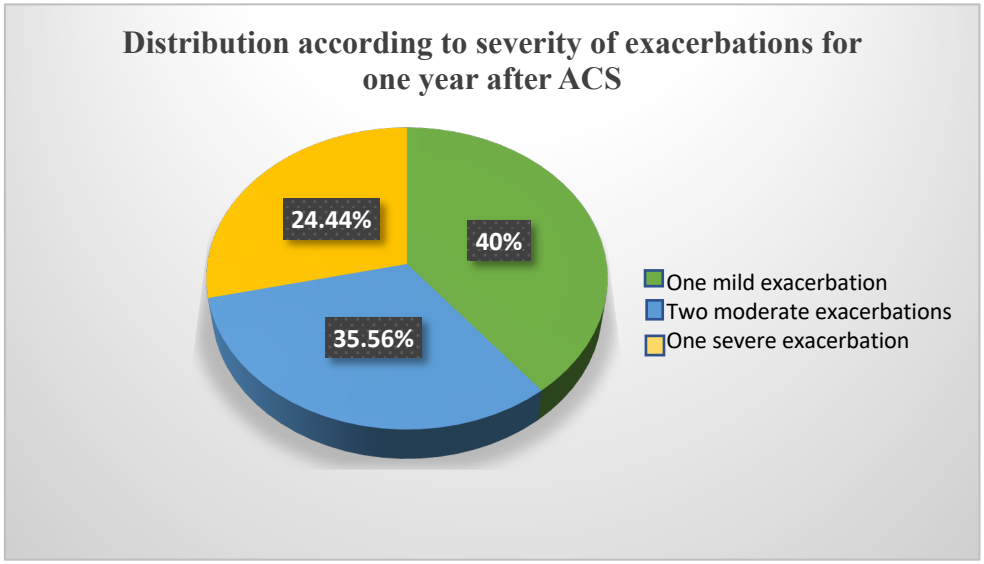

Fig. 16. *Distribution of COPD patients according to the severity of exacerbations for one year after ACS*

Studies tracking patients with COPD according to the severity of their exacerbations within a year found one mild exacerbation in 36%, over two in 16%, and one severe exacerbation in 21.8%. Using the multivariate Cox model, the authors found that patients who experienced an exacerbation in the previous year were more likely to exacerbate their condition during follow-up than those who had not recorded an exacerbation to date (Lin et al., 2022). A comparative analysis between the documentary data on exacerbations from the previous year

and the data from our follow-up found that the proportion of patients who received more than two exacerbations in the past remained the same during the follow-up period (58.67% vs 60%, p=0.156). They have a higher risk of worsening pulmonary obstruction than those who have had up to one moderate exacerbation - Figure 17.

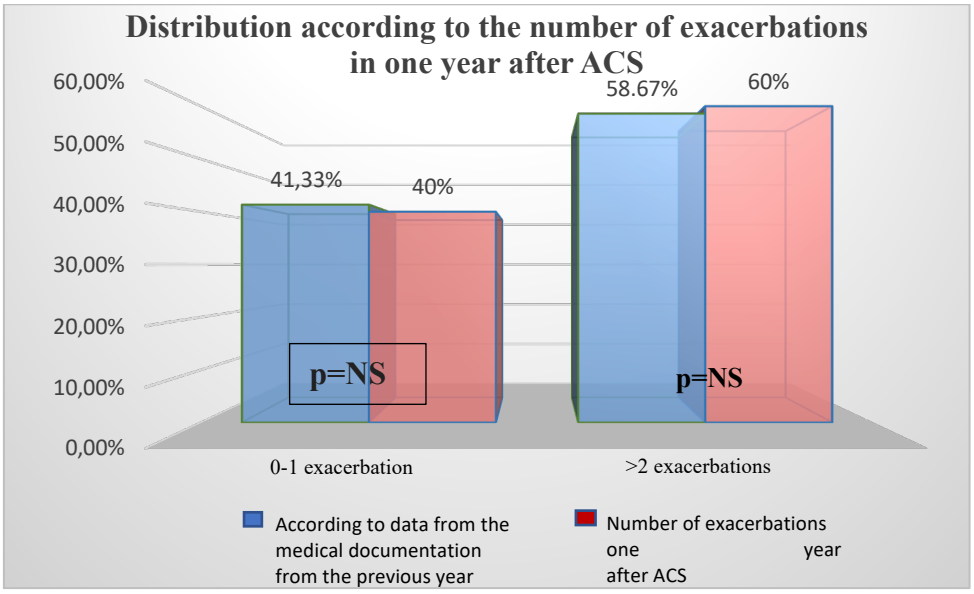

Fig. 17. *Dynamics in the number of exacerbations in one year after ACS*

7.2.5. Stability of patients according to the ABE group of GOLD one year after ACS

At the end of the 12th month, patients' stability was assessed based on the severity of their symptoms and exacerbations. According to GOLD's updated suggestion for combined ABE categorization, the highest number in our study fell into group B - 50.90%, while group E represented 39.60% of patients. – Figure 18.

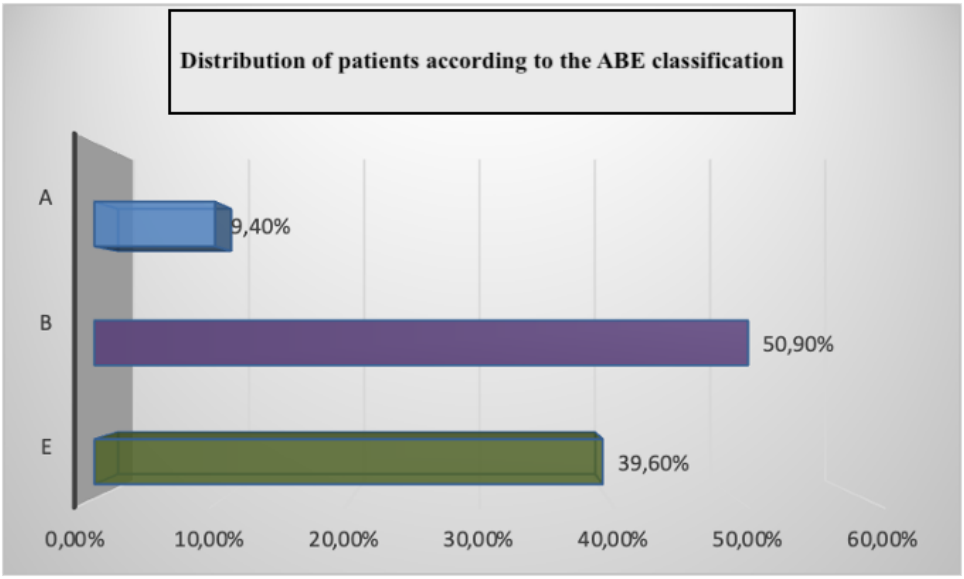

Fig. 18. *Distribution of patients according to the updated ABE group by GOLD.*

7.2.6. Developments in the BODE index for one year

The specific BODE index is a prognostic indicator of mortality in patients with COPD. In research that followed 625 patients for two years or until their death, participants were evaluated using the BODE index. The patients are divided into two groups. During the follow-up period, 25 deaths were recorded in the first group. In the second group, 162 patients died, with respiratory failure accounting for 61%, myocardial infarction for 14%, lung cancer for 12%, and other reasons for the remaining 13%. The results showed that a larger score of 7-10 points correlated with an 80% mortality rate at the 52nd month of follow-up (Celli et al., 2004).

Cote et al. track the dynamics in BODE values over 39 months among patients enrolled in a pulmonary rehabilitation program. They found adherence to daily light physical activity in 49% of patients enrolled in the program. Compared to those not enrolled, only 10% reported regular exercise. The baseline mean BODE values for patients in the program were 6.07 ± 2.01 points. In the third month, there is an average drop in the score by three points, $p<0.0001$. Eighty-three people (71%) experienced more than one point of improvement. Of these, 29 patients (25%) showed a two-point improvement, whereas 54 (47%) improved one point. In 25 patients (22%), there was no change in BODE, whereas in eight (7%), the score worsened. In parallel with these results, the persons who did not take part in the rehabilitation program showed a one-year decrease in the values of BODE of 4%, and in the second year, this percentage increased – 18%. Roberts et al. offer a modified version of the BODE index, which

assumes the mortality of patients with COPD. Data show that patients with a score between 7-10 points have an 80% risk of death in the next 52 months.

The percentage of patients with a BODE index between 3 and 4 points increased (43.30% vs. 52.30%, p=NS) while the percentage of patients who met the BODE index between 4 and 6 points decreased (47.5% vs. 40%, p=NS) after a year of population follow-up. Over the following four years, these outcomes were associated with survival rates of 67% and 57%, respectively (Roberts et al., 2013) – Figure 19.

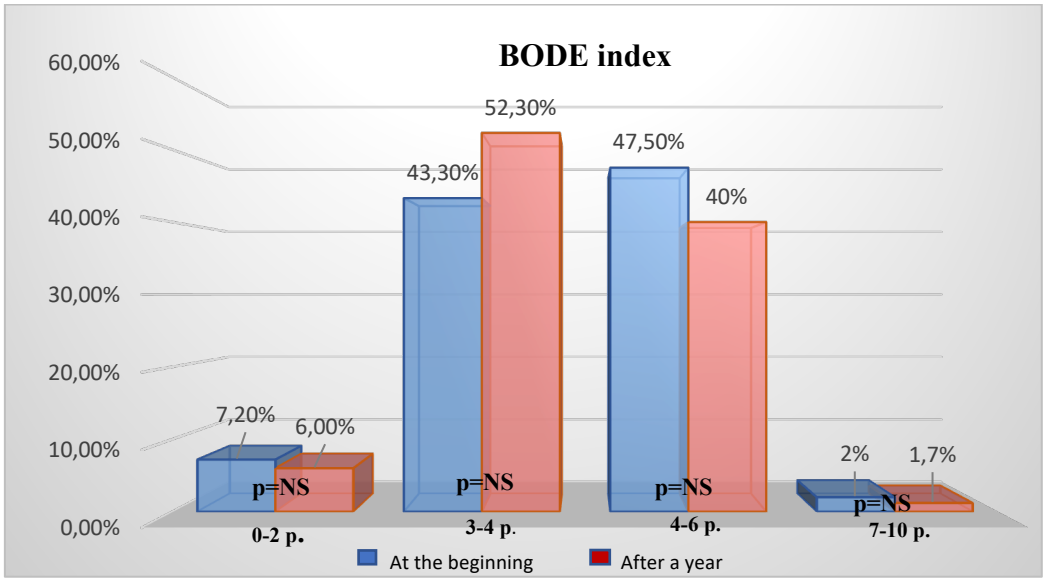

Fig. 19. *Dynamics in the score of the BODE index for one year after the ACS*

The largest part of the patients with COPD in our study were in the second stage of GOLD – 44%, which does not tolerate much dynamics within one year of ACS – 46%. This group of patients is dominant in terms of comorbidities compared to the control group. This also explains the higher average score from the CAT (24.52 ± 7.94 points) and from the mMRC (2.95 ± 3.21 points). For 12 months, the average annual number of exacerbations that we registered was 2.1 ± 1.6. These results are also consistent with the higher prevalence of patients in the updated E group (47.7%) of the ABE classification. A non-significant decrease was also reported in terms of the average values of FEO_1, respectively from 55.61±14.47 % to 52.52±15.70 % from the previous one, p=0.2596.

According to the multi-component system for assessing survival – BODE index, the subjects studied by us showed a slight improvement in the results, which correlates with the

minimal drop in the mMRC scale (from 2.95 ± 3.21 to 2.32 ± 0.87), as well as with a slight improvement in physical capacity - 6MWT (from 307±138 m to 328 ± 158 m).

Analyzing all these results, we can conclude that patients in the second stage of GOLD are a symptomatic group with a high incidence of exacerbations and worsening pulmonary obstruction. All these data point to a deteriorating quality of life and low functional capacity. However, these patients can still benefit from the timely administration of pulmonary rehabilitation, daily physical activity and drug therapy, both for COPD and for the accompanying cardiovascular pathology

8. Follow the dynamics in the results of the instrumental methods for both groups one year after the ACS

8.1. Electrocardiogram

An ECG was obtained from each patient at the time of admission and again during the follow-up period. At the beginning of the study, both groups recorded a basic sinus rhythm (85.3% vs 86.2%, p=0.762) – Table 4.

Table 4. *Output data from the electrocardiogram*

	Group A (n = 75)	**Group B (n = 65)**	**P value**
ECG % - Sinus rhythm - Atrial fibrillation - Another rhythm	85.3% 8% 6.7%	86.2% 9.2% 4.6%	0.762

8.2. Dynamics in the electrocardiogram over a period of one year after ACS

Arterial hypertension, age, stroke, COPD, and HF are some of the main predictors of rhythm-conduction disorders. They are based on fibrotic changes in the myocardium, which lead to structural remodeling (Goudis et al., 2017). Rhythm-conduction disorders are observed in 12-14% of patients with COPD. In most cases, the heart rhythm disorder is atrial fibrillation, the frequency of which increases with the progression of the severity of bronchial obstruction and with exacerbation of COPD (Sin et al., 2006).

A meta-analysis of 21 studies found a significantly increased risk of atrial fibrillation in patients with COPD compared to the healthy population RR 1.99 (95% CI: 1.46–2.70) (Liu et al., 2021). Bronchodilators, particularly short and long-acting beta-agonists, can cause atrial

fibrillation in COPD patients (Goudis et al., 2017). A single dose of inhaled Salbutamol leads to a shortening of atrial refractoriness, which induces AFib (Kallergis et al., 2005). Data from the Copenhagen City Heart Study showed that reducing FEV_1 to values between 60-80% increased the risk of AFib to RR 0.75 (95% CI: 0.59-0.94) within five years (Buch et al. 2003). Patients with a higher BODE index are at a higher risk of presenting supraventricular tachycardia, AFib, or atrial flutter (Grabicki et al., 2008).

All our patients were monitored for rhythm-conduction disorders at each visit. In approximately 85% of the cases, patients from group A remained with sinus rhythm, compared to 86% from group B. Although statistically insignificant, AFib manifested itself in a higher percentage in patients with ACS and COPD, respectively for the sixth month (16.13% vs 12.73%, p=NS) and for the twelfth month (13.21% vs 12%, p=NS) – Figure 20.

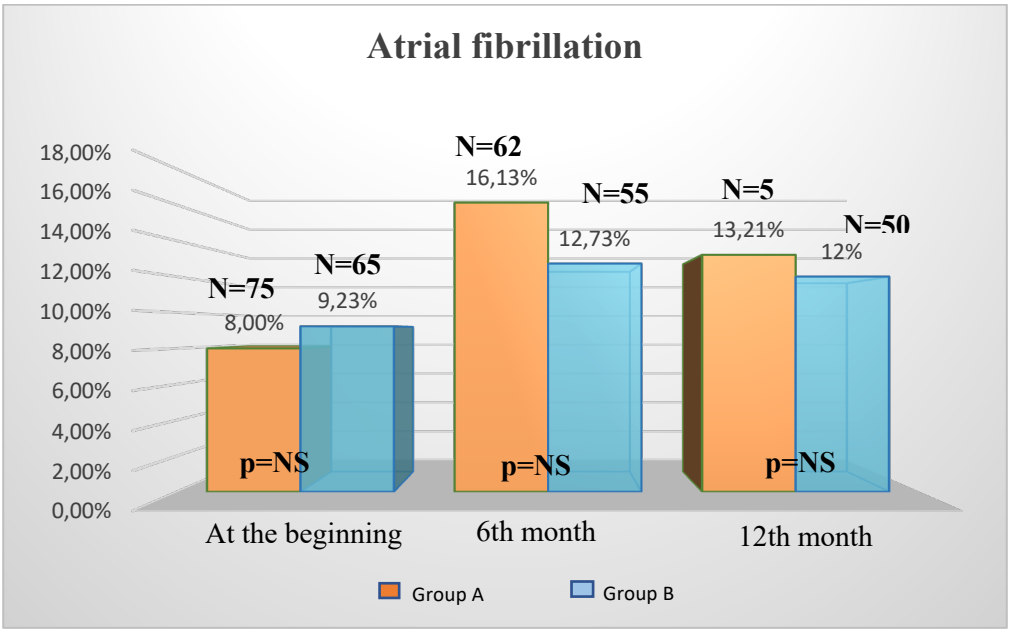

Fig. 20. *Distribution of atrial fibrillation in both groups one year after ACS*

A study following 81,191 patients after experiencing myocardial infarction during the index event found sinus rhythm in 81.4% of patients with COPD compared to 86.7% of controls, p<0.001. Follow-up in 5.2% of patients with pulmonary obstruction recorded newly emerging AFib, compared to 4.6%, p<0.001 (Andell et al. 2014). Another study found a risk of AFib in patients with ACS and COPD of RR 1.14 (95% CI 0.97-1.34, p<0.001). This group had a 24.3% incidence of newly emergent AFib, compared to 18.2%. (Stefan et al., 2021).

8.3. Transthoracic echocardiography

The recommendations for detecting and treating STEMI include a class one recommendation to assess left ventricular function by ejection fraction. The left ventricular ejection fraction predicts the likelihood of death from any cause after experiencing myocardial infarction (Ibanez et al., 2018). It is one of the main indicators of HF. A study by Macchia et al. found an incidence of it as assessed by LVEF in 17% of patients with COPD.

In all patients included in our study, transthoracic echocardiography was performed according to the recommendations of the European Society of Cardiology for the evaluation of LVEF. The mean value at the beginning of the follow-up was 50.27±8.41%, p=0.445 in both groups. According to the European consensus on HF, patients were distributed according to LVEF in three groups, respectively with LVEFs below 40%, between 40-49% and LVEFs above 50% (Ponikowski et al., 2016) – Figure 21.

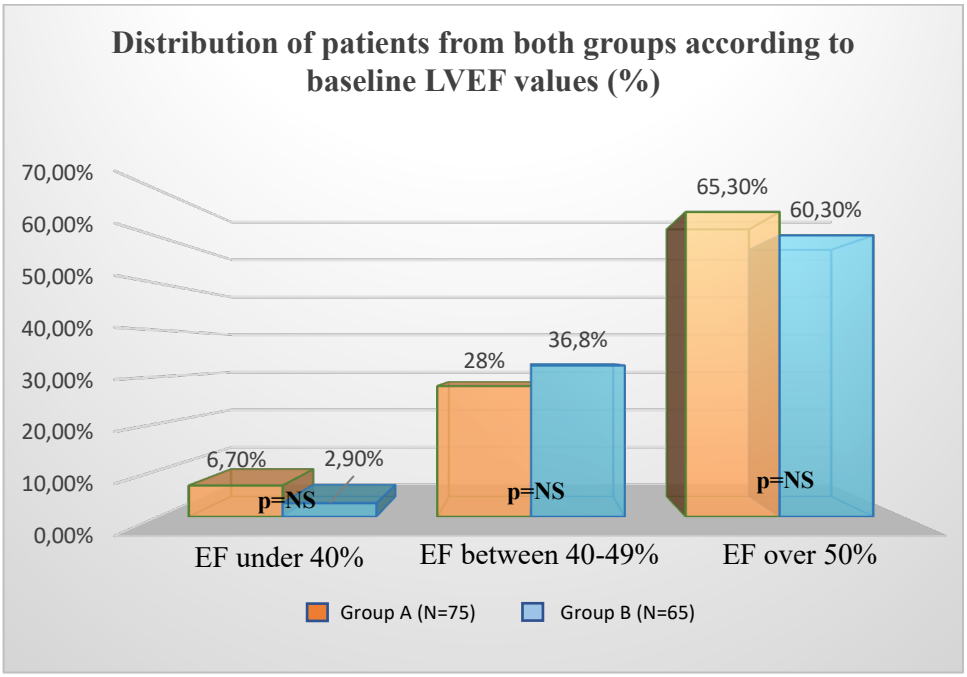

Fig. 21. *Distribution of patients from both groups according to baseline LVEF values (%).*

A few imaging investigations have tracked the dynamics in ultrasonography parameters in COPD patients after myocardial infarction. The results of whether this cohort of patients had worse LVEF compared to patients without COPD were also contradictory (Rothnie et al., 2015; Enriquez et al., 2011; Salisbury et al., 2007). The intergroup analysis revealed a prevalence of LVEF above 50% in both groups. (65.30% vs 60.30%, p=NS). Andell et al. also found a higher proportion of patients with preserved ejection fraction. In patients with ACS and COPD, the distribution according to the LVEF shows that 45% have an LVEF > 50%, 24.3% have an

LVEF between 40-49%, and 28% have a LVEF below 40%. In the control group, the percentage ratio was (53.8%, 22.9% and 21.5%). Although similar LVEF values were observed in patients with COPD compared to those without lung disease (34% vs 35.4%, p>0.05), the risk of sudden cardiac death was significantly higher in the COPD - HR 1.26 group (95% CI: 1.03–1.53, p=0.025) (Enriquez J et al. 2011).

8.4. Evolution of LVEF values one year after the ACS

COPD was an independent predictor of HF during the follow-up HR 1.19 (95% CI: 1.05–1.34)) (Hawkins et al., 2009). Data suggest that subclinical left ventricular and right ventricular systolic dysfunction can occur even in patients with mild obstruction (Macchia et al., 2007).

From the transthoracic echocardiography performed at the end of the follow-up, we found mean left ventricular EF values of 49.83 ± 8.10 in group A and 47.83 ± 11.52 in group B, p=0.987. The proportion of patients with EF below 40% was higher at the end of follow-up for both groups (15.09% vs 12%, p=0.649) - Figure 22.

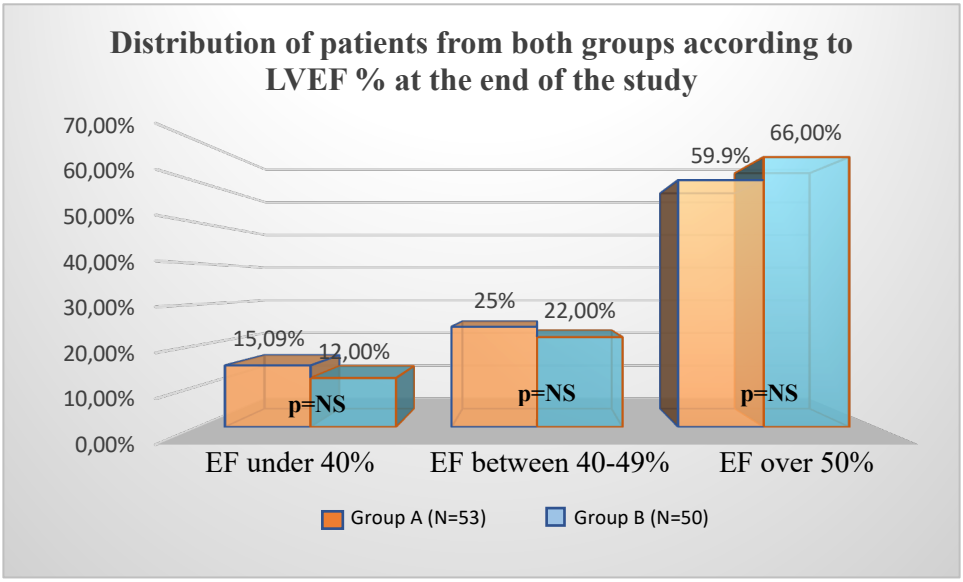

Fig. 22. *Evolution of LVEF values for one year after the ACS.*

A sub-analysis of the VALIANT study, involving 4,570 women and 10,133 men with HF or left ventricular systolic dysfunction, detected 0.5-10 days after myocardial infarction and tracked the change in LVEF and left ventricular volumes over 24.7 months. The baseline values of the LVEF for men were 39.07% and for women 39.66%, p=0.25. For one month, the change in measurements, calculated as a percentage, is -0.002% for men and 0.48% for women,

respectively (LVEF 39.08% vs LVEF 40.02%, p=0.082). For twenty months, there was a subtle improvement in LVEF by 1.73% for men and 2.55% for women, respectively (LVEF 41.18% vs LVEF 42.17%, p=0.21) (Lam et al., 2015). In the cohort of patients with ACS without COPD, an increase in patients with preserved COPD was also observed from 60.30% to 66%. In the group with ACS and COPD, this share decreases from 65.30% to 59.9% – Figures 21 and 22.

A retrospective study involving 133 patients with STEMI and COPD and 1677 patients with STEMI without COPD compared the results of conventionally measured left ventricular EF with those of the longitudinal strain. Both groups had the same ejection fraction determined by the Simpson method, but COPD patients had significantly more myocardial damage as measured by the myocardial strain (-13.7% vs. 17.3%) (Su et al., 2017). In another large registry involving 11,118 patients with STEMI, of whom 2032 had a history of COPD, the percentage of patients with COPD < 35% was significantly higher among the group with pulmonary obstruction compared to controls (15% vs 12%, p<0.01). This is of particular interest because LVEF ≤35% is the main indication for the implantation of an internal cardioverter-defibrillator (Al-Khatib et al., 2018).

9. Monitoring of the dynamics in functional capacity in both groups for one year after the ACS

The impaired functional capacity of patients is associated with a higher incidence of hospitalizations and mortality. Therefore, exercise clinical tests are an indispensable aspect of measuring functional ability and its abnormalities in individuals with COPD. (Cote et al., 2008). The participant's physical activity was assessed through a survey on their self-assessment of daily physical activity and the results of 6MWT.

9.1. Self-assessment of daily physical activity

Reduced physical activity is a factor that has a significant contribution to the deterioration of the population health status of the population in our country. It forms 4.3% of the global burden of diseases (according to DALY) and 7.7% of all deaths in Bulgaria (WHO, 2005). A national survey of risk factors for the health of the population in the country found light physical activity in 72% of the respondents, moderate in 18%, and intense in 10% (BSO, 2020).

The patients in our study gave their self-assessments according to the workload they performed. The possible responses were divided into three groups according to intensity. Light physical activity was adopted with a load of less than 30 minutes. and increasing metabolism by 2-3 MET, and moderate metabolism by increasing heart rate and metabolism to 4-5 MET. Cycling or brisk jogging was accepted as a high-intensity physical activity 6 MET (Cavill et al., 2006). The results were tracked at each visit.

At the initial completion of the self-assessment questionnaire, 37.3% of the studied patients from group A were slightly physically active compared to 30.7% from group B. A significant difference was found in terms of severe activity, with only 8% of patients with COPD coping with it compared to 20% of patients with ACS without COPD, p=0.047 – Table 5.

Table 5. *Distribution of patients according to their self-assessment of physical activity followed up for one year after ACS.*

	Group A	**Group B**	**p value**
Self-assessment questionnaire at the beginning of the study	**N=75**	**N=65**	
Low physical activity	37.33%	30.77%	0.440
Moderate physical activity	54.67%	49.23%	0.545
High physical activity	8%	20%	**0.047**
Self-assessment questionnaire at the 6th month	**N=62**	**N=55**	
Low physical activity	37.1%	23.64%	0.111
Moderate physical activity	56.45%	60%	0.698
High physical activity	6.45%	16.36%	0.092
Self-assessment questionnaire at the 12th month	**N=53**	**N=50**	
Low physical activity	37.78%	16%	**0.013**
Moderate physical activity	54.72%	68%	0.169
High physical activity	7.5%	16%	0.180

In the sixth month of follow-up, most of the patients with COPD reported moderate physical activity, respectively (56.45% vs 60%, p=0.698). At the end of the study, we noticed a slight increase in the proportion of patients with COPD performing heavy physical activity –

11.32% compared to 14% of patients without COPD, p=0.683. The percentage of patients with COPD and light physical activity remained almost the same until the end of the study (37.33%, 37.1%, and 37.78%). In group B, there is a decrease in this share of patients, and by the end, it has almost halved (30.77%, 23.64%, and 16%).

Interesting are the results of Olivera et al., which track the causes of hospitalizations in 536 patients after ACS. They compared how physical activity affected the need for hospital treatment over a period of 122±11.2 days after the acute event. Inactive patients were more likely than active patients to be re-hospitalized within one month after their discharge (20.37% vs 16.92%, p=0.6298). On the 180th day of the study, this ratio was maintained (22.55% vs 17.56%, p=0.223). Another study evaluated physical activity in adult patients with COPD and identified clinical factors associated with low levels of activity. This is the first study to analyze patterns of physical activity and predictors of its decline in adults with COPD. Patients over 65 years old are divided into three groups according to the level of physical activity (low, moderate, and high). Of all 160 people studied, 64.4% rated their physical activity as mild.

These patients also presented themselves with reduced physical capacity, measured by 6MWT - less than 250 m., increased dyspnea (mMRC>2), and reduced quality of life, measured by specific questionnaires. The authors found that the severity of dyspnea and the presence of depression were independent factors leading to decreased physical activity (Lee et al., 2018). Another study found that patients with light physical activity were at greater risk of COPD rehospitalizations compared to those with moderate to severe HR 0.72 (95% CI 0.53-0.97). Patients with moderate or heavy physical activity also showed a lower risk of all-cause death HR 0.76 (95% CI 0.65-0.90) (Garcia-Aymerich et al., 2003).

9.2. Dynamics in the results of the six-minute walking test over one year after ACS

The cardiopulmonary exercise test allows for a global assessment of the body's integrative responses, including pulmonary, cardiovascular, haematopoietic, neuro-psychological, and muscle adaption processes, which cannot be fully measured when investigating their functions individually (ATS/ACCP Statement 2003). According to a three-year international study to determine reference values for the minimum distance traveled at 6 MWT for patients with COPD, the distance of 350 m. is considered a normative achievement. Results lower than 350 m. are considered unfavorable in terms of disease prognosis and are an indicator of ineffective and inadequate therapy (Cote et al., 2008).

At enrollment in the study, patients with ACS and COPD covered a distance of 307.66 ± 138 meters compared to the group without COPD, respectively 425.52 ± 154 meters, p<0.001. All the subjects examined were followed at the sixth and twelfth months of baseline. In the sixth month, the average distance walked for group A was 326 ± 149 meters, and for group B was 456 ± 161 meters (p<0.001). A significant difference between the two groups was also found at the follow-up after one year (328 m. ± 158 m. vs 445 m. ± 168 m., p=0.004). There was an average improvement in the distance in the two groups of approximately 23.45 ± 15 meters – Figure 23.

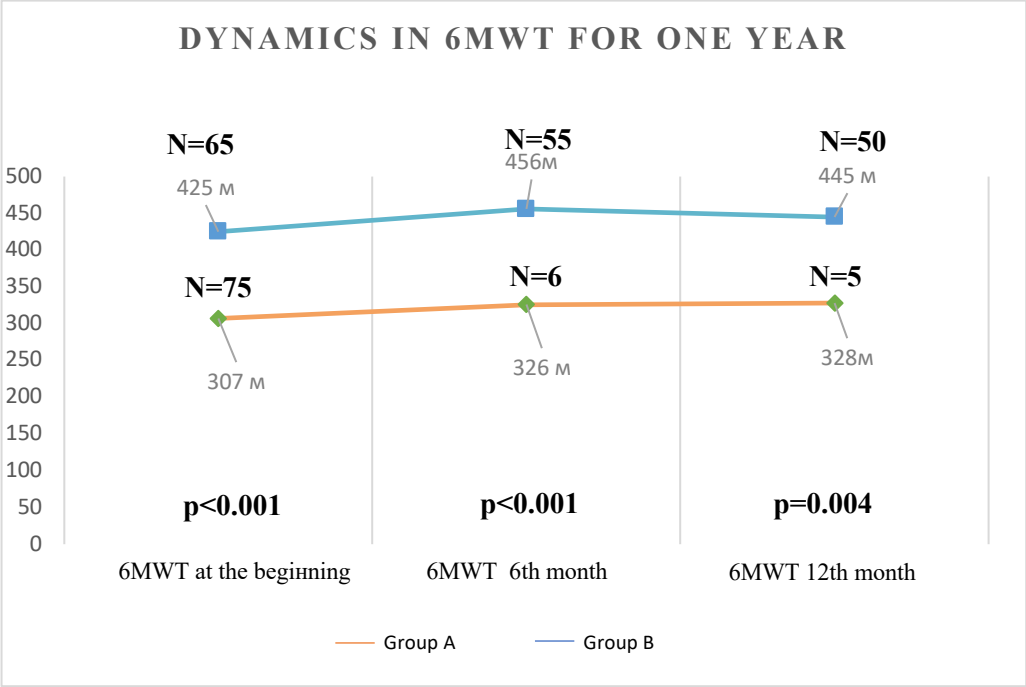

Fig. 23. *Dynamics in 6 MWT of patients from both groups followed for one year after ACS.*

A study of 295 patients with COPD over 5.3 years found an average distance walked of 446 m. at the beginning and 454 m. one year later. Nearly 23% of those surveyed have reduced their functional capacity by more than 30 meters, measured in 6MWT (Waatevik et al., 2020). A study examining patients after ACS found an average of 6MWT - 225 m. values. Following the individuals for one year, a more frequent manifestation of a recurrent cardiovascular incident was observed in persons who walked less than 290 m. compared to those over 326 m., p=0.03 (Dasari et al., 2020). Another study found a higher proportion of deceased patients with COPD who walked a shorter distance of 6MWT, respectively (269 ±

136 m. vs 348 ± 121 m.), p<0.0001. An exponential increase in all-cause mortality is observed with a shortening of the distance traveled every 100 m. (Cote et al., 2008).

Physical activity is an important aspect of the treatment of patients with COPD. The reduction of physical capacity significantly increases the risk of death. Lower physical activity is often associated with a reduced quality of life and increased levels of depression. Old age and the presence of cardiovascular pathology in patients with COPD further disrupt their functional capacity. Regular physical activity and rehabilitation would improve their prognosis and quality of life.

10. Dynamics in health status as measured by questionnaire LVD-36

We assessed our patients' quality of life using the LVD-36 questionnaire. Its results are very similar to those of the SF-36, another non-specific quality-of-life questionnaire. The responses to LVD-36 during six months correlate with overall health status. (F = 5.7; p <0.001) (O'Leary et al., 2000). The mean result of the questionnaire for left ventricular dysfunction in patients with COPD at enrollment in the study was 19.13 ± 11.36 points, which indicates a reduced quality of life compared to patients without COPD, respectively 12.20 ± 7.69 points, p=1.000.

To assess the dynamics in the results of the LVD-36 questionnaire, we used the Paired t-test. The cross-group study revealed a small improvement in the findings for both groups. At the end of the follow-up for patients from group A it was approximately 3.28 points compared to 2.29 points for group B, p=0.012 – Table 6.

Table 6. *Dynamics in quality of life measured by the LVD-36 questionnaire in patients in both groups over one year.*

Group A						
		Mean	**N**	**Std. deviation**	**Paired t-test**	**95% confidence interval**
Pair 1	LVD-36 % at the beginning	19.1356	59	11.36003	t=2.16, **p=0.035**	0.11; 2.83
	LVD-36 % 6th month	17.6610	59	10.22271		
Pair 2	LVD-36 % 6th month	17.3269	52	9.58496	t=1.60, p=0.116	-0.21; 1.90
	LVD-36 % 12th month	16.4808	52	8.71215		

Pair 3	LVD-36 % at the beginning	18.7885	52	11.05483	t=4.07, **p=0.012**	0.53;4.07
	LVD-36 % 12th month	16.4808	52	8.71215		
Group B						
		Mean	**N**	**Std. deviation**	**Paired t-test**	**95% confidence interval**
Pair 1	LVD-36 % at the beginning	12.2000	55	7.69415	t=4.37, **p=0.001**	1.09; 2.94
	LVD-36 % 6th month	10.1818	55	6.89093		
Pair 2	LVD-36 % 6th month	10.5833	36	7.43111	t=0.34, p=0.973	-1.65; 1.70;
	LVD-36 % 12th month	10.5556	36	8.29611		
Pair 3	LVD-36 % at the beginning	12.4595	37	8.81159	t=2.11, **p=0.041**	0.09; 4.23
	LVD-36 % 12th month	10.2973	37	8.32955		

A meta-analysis involving 29 studies on patients after ACS found a significant improvement in quality of life depending on the treatment undertaken. A few months after PCI, improvement was found by an average of 30.22 (95% CI 29.9-30.53, $p<0.005$) and up to one year after aortic-coronary bypass surgery by 34.01 (95% CI 33.66-34.37, $p<0.005$) (Kaambwa et al., 2020). On the other hand, patients with COPD and concomitant CVD have a poor quality of life in all aspects of life compared to the general population (De-Miguel et al., 2010). The reasons for this include the disease's progressive nature, the patient's advanced age, and their socioeconomic status (Ferrer et al., 2002). Motivating patients to change their behavior and engage in more physical exercise improves final results.

A large meta-analysis of data from several studies tracked the change in the quality of life of patients with COPD after their inclusion in self-help programs. These recommendations encourage patients to change their behavioral habits to improve the social, emotional, and physical aspects of their lives. The results showed an improvement in all aspects of the quality of life of the studied patients 3.32 (95% CI −4.60−2.04, $p < 0.001$), including an improvement in 6MWT 30.50 (95% CI 3.32 - 57.68, $p = 0.028$) (Cannon et al., 2016).

The LVD-36 questionnaire we have attached makes it possible to assess the quality of life in all its aspects. Likely, more frequent visits and guidelines for the control of risk factors

had a positive impact on the results in both groups. However, patients with COPD continued to have a worse quality of life compared to controls one year after ACS.

11. Drug therapy

11.1. Comparison between the prescribed therapy before and after dehospitalization for ACS

Treatment of ACS consists of revascularization in the acute phase and subsequent drug therapy with prevention of individual risk factors as secondary prevention. Current guidelines for secondary prevention in these patients are based on randomized clinical trials and include BB, lipid-lowering medications, and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). These include dual antiplatelet therapy (aspirin for an indefinite period and a P2Y12 receptor antagonist), usually prescribed for one year. In patients with increased hemorrhagic risk or in elderly patients with multiple comorbidities, a shortened intake of dual antiplatelet therapy may be considered within three to six months after the acute event (Quint et al., 2013). Patients with COPD were discharged more often for treatment with ACE inhibitors and diuretics and significantly less often with BB (Bursi et al., 2010). Another study found that patients with ACS and COPD were less likely to be prescribed medications that reduce mortality, such as antiplatelet agents, statins, and ACE inhibitors. On the other hand, these patients receive more frequent therapy with calcium antagonists, digitalis, and nitrate (Stefan et al., 2012). The distribution of the main classes of medicines before and after dehospitalization of the following patients in the two groups is presented in Table 7.

Table 7. *Distribution of the main classes of medications before and after dehospitalization*

	Therapy before hospitalization			**Therapy after dehospitalization**			
	Group A (n=75)	**Group B (n=65)**	**P value**	**Group A (n=75)**	**Group B (n=65)**	**P value**	**Chi-square**
Beta blocker %	48%	43.1%	NS	79%	72.3%	NS	0.788
ACE/ ARBs %	31.1%	26.2%	NS	86%	80%	NS	0.410
Lipid-lowering drugs %	30.7%	29.2%	NS	100%	98.5%	NS	1.18

Antiplatelet treatment %: - mono therapy with Aspirin; - dual antiplatelet антиагрегантна therapy with P2Y12 receptor antagonist;	23% 5%	12.4% 3%	NS NS	13.65% 82.35%	16.67% 83.33%	NS NS	3.37
Therapy for COPD %	62.7 %			87%			

Using the nonparametric chi-square test, we found that a higher proportion of patients with COPD received an ACE inhibitor or ARBs before (31.1% vs 26.2%, p = 0.522) and after their dehospitalization (86% vs 80%, p = 0.422). This result corresponded with other studies. For example, in the study of Bursi et al., 37% of patients with COPD received an ACE inhibitor as a home therapy compared to 29% of controls, p<0.001. Another study tracking the change in treatment before and after dishospitalization after myocardial infarction found a significant difference in the prescription of this class of drugs in patients with pulmonary obstruction (19.9% vs 50.6%, p=0.001) (Stefan et al., 2012). The intergroup study also revealed a lower number of patients with ACS and COPD released for dual antiplatelet treatment (82.35% vs 83.33%, p=0.066). This group of patients are older, with more comorbidities and a higher percentage of anemic syndrome.

11.2. Adherence to the prescribed therapy

Adherence to therapy is important and key to achieving clinical outcomes. The low intake rate of certain classes of medications can lead to a worsening or exacerbation of the condition, which lowers the quality of life and increases the risk of a fatal event. The results of TORCH (Towards a Revolution in COPD Health) show that better adherence to therapy is associated with lower mortality in patients with COPD (Calverley et al., 2007). A study conducted in 2017 in the territory of Bulgaria shows that only 40% of patients with COPD regularly take therapy for their CVD. The reasons for this are varied. On the one hand, they are determined by the patient's socioeconomic status and physical condition, and on the other, by the health system and drug therapy itself (Mitkova, 2017).

11.2.1 Beta-blockers

Although one of the main classes of medications for the treatment of ICD is beta-blockers, they are still considered to be contraindicated due to their broncho-obstructive effect

in people with COPD. In 2017, a large prospective study involving patients from the COPD Gene cohort showed that regardless of the severity of airway obstruction, the use of BB was associated with a significant reduction in COPD exacerbations (Li et al., 2020). In 2016, the European Society of Cardiology established guidelines recommending the use of these drugs in COPD and CVD patients. A meta-analysis conducted in 2020 found that BBs are safe and reduce overall mortality (including nosocomial mortality) in patients with COPD, while selective BBs may even reduce acute cases of COPD exacerbations (Yang et al., 2020). Also, these medications control the increased heart rate due to the use of bronchodilators without interfering with their effectiveness (Yang et al., 2020). Despite this evidence, BB continues to be underused in patients with ACS and COPD (Salpeter et al., 2004).

The intergroup analysis of our patients' sixth month of follow-up revealed a substantial difference in adherence to beta-blocker therapy. In patients with COPD and ACS, only 70.7% accepted their therapy compared to 100% of group B, p=0.003, and this trend persisted until the end of follow-up – Figure 24.

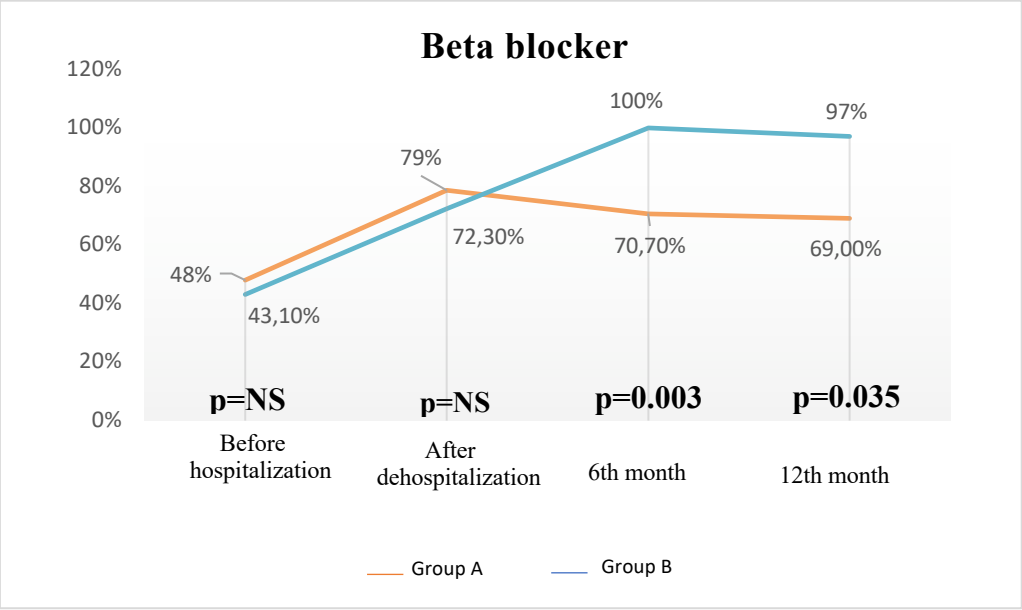

Fig. 24. *Adherence to beta-blocker therapy for one year after ACS.*

A multivariate analysis of the SWEADHEART study among patients with ACS found more frequent non-adherence to the prescribed therapy with BB in the elderly, low socio-economic status, and those with dementia, cancer, or COPD (Andell et al., 2014). The risk of non-adherence to the prescribed BB in patients with ACS and COPD was higher OR 0.71 (95%

CI 0.58-0.87, p=0.001) compared to controls (Di Martino et al., 2016). According to the analysis of Dhame et al. the proportion of patients with COPD and CVD who do not adhere to therapy with BB increases over time. They found an OR of 1.39 (95% CI 1.21-1.61, p<0.001) at a follow-up of 24 months (Dhamane et al., 2016). Another study followed persons with ACS with no known comorbidity within one year and found adherence to prescribed BB in 68.9% of them (Andell et al., 2014). Another research that followed patients after myocardial infarction for eight years found that of the prescribed BB 91% at the end of the study, only 71.3% accepted it (Jaakko et al., 2020). The results of a large-scale national study in New Zealand, involving 83,435 patients with ACS and COPD are also interesting. Of these, 28.4% received BB prior to the acute incident, whereas 56.6% were discharged to one. According to the authors, patients who have previously received antiischemic therapy are more likely to obtain BB after discharge (45.3% vs 18.3%, p < 0.001). The severity of the pulmonary obstruction is another key factor in the choice of therapy. Patients with moderate or severe COPD or with a history of frequent exacerbations are less likely to receive BB therapy compared to individuals with mild obstruction (Hawkins et al., 2022).

11.2.2. ACE/ARBs/ARNI

Renin-angiotensin aldosterone (RAAS) system inhibitors have proven benefits in patients after ACS. These medications have cardioprotective, antihypertensive, and antithrombotic effects by inhibiting the angiotensin-converting enzyme, which leads to a reduction in mortality and an improvement in survival in patients with ACS. Numerous large randomized trials (HOPE, SAVE, TRACE) investigating the role of ACE inhibitors in more than 110 thousand patients with myocardial infarction confirm these beneficial effects (Nikolov et al., 2002). However, data on the use of these medications are limited in the COPD population. The results of a large population-based study, the Multi-Ethnic Study of Atherosclerosis Lung Study, revealed that both ACE inhibitors and ARBs were associated with slower progression of emphysema, especially among former smokers. Even without CVD, the use of RAAS inhibitors has a protective role. The authors explain the effect of these drugs by inhibiting transforming growth factor-β signals in the lung, thereby reducing the progression of emphysema (Parikh et al., 2017). According to the American Heart Association's program for the follow-up of patients with IHD, 60,847 of the patients evaluated showed strong evidence of benefits from the use of ACE inhibitors. However, only 70% have been prescribed these medications. In 19,394 of the participants, ACE was appropriate and should be initiated, however, the frequency of administration was much lower, at 69% (Bainey et al., 2014). In

our population in group A - 86% received therapy with a RAAS inhibitor after hospitalization compared to 80% of group B - Figure 25.

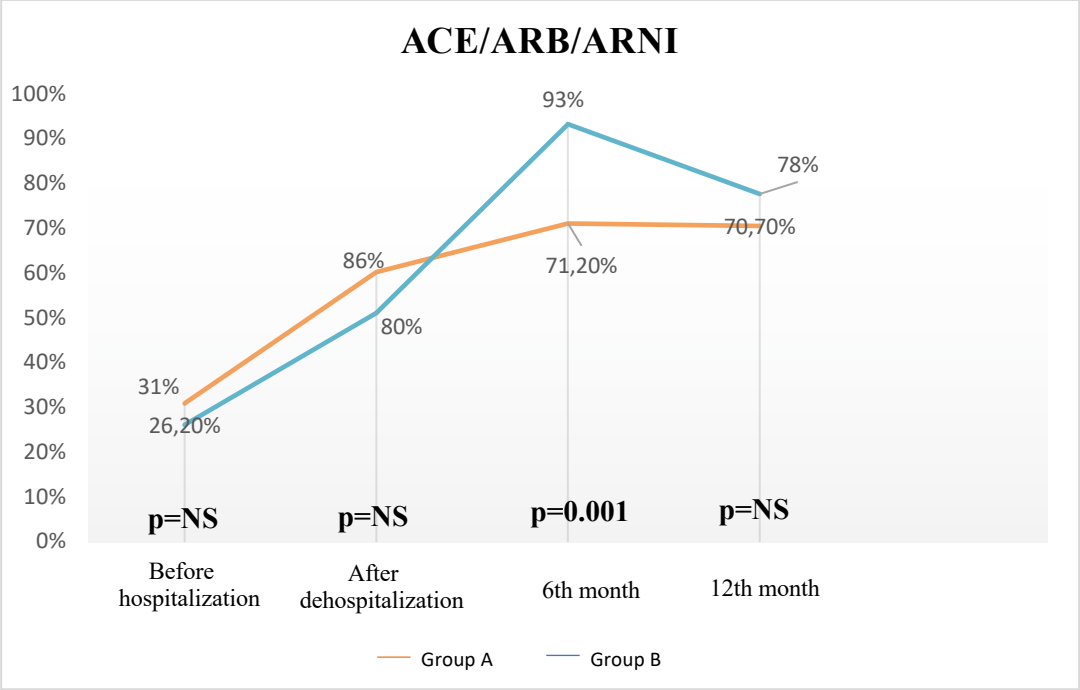

Fig. 25. *Adherence to ACE/ARB/ARNI therapy for one year after ACS.*

Unfortunately, the most common side effect of ACE inhibitor therapy is coughing. It occurs in 5-20% of cases and can be a reason for discontinuation of treatment, especially in patients with COPD. The low probability of worsening pulmonary obstruction leads to the use of ACE inhibitors with caution or even their exclusion from therapy in patients with ACS and COPD (Chandy et al., 2013).

Analyzing the results of the sixth month of our study, we found significant non-adherence to RAAS inhibitors, and it was more pronounced in the ACS and COPD groups, respectively (71.2% vs 93%, p = 0.001). At the end of the first year, this result was almost equal for both groups (78% vs 70.7%, p=NS). The results of EUROASPIRE I, II and III also showed adherence to the ACE inhibitor in only 67% (Kotseva et al., 2009). A population-based study of patients with COPD reported a high rate of non-adherence to prescribed antihypertensive therapy, including both ACE and ARBs OR 1.55 (95% CI 1.38 – 1.74) (Dhamane et al., 2016).

On the other hand, the PARADIGM-HF study (Prospective comparison of Angiotensin Receptor-neprilysin inhibitor (ARNI) with Angiotensin converting enzyme inhibitor to Determine Impact on Global Mortality and morbidity in Heart Failure) demonstrated that the use of ACE inhibitors and ARNI in individuals with HF and COPD was similar to those without lung disease, indicating that these drugs did not cause any more side effects in patients with pulmonary obstruction (Ehteshami-Afshar et al., 2021).

Data from an observational cohort study among COPD patients who used RAAS inhibitors showed that ARBs were associated with fewer side effects in patients with COPD (Candy et al., 2013). A study following patients with COPD and CVD found a reduction in the risk of fatal events with ARBs RR 0.63 (95% CI: 0.44 to 0.89, p = 0.0010) (Mancini et al., 2006). Similar results have been observed in including ARNI in patients with COPD (Ehteshami et al., 2021). Due to the reduction of LVEF in three patients from group A and one from group B, it was necessary to initiate therapy with ARNI in the sixth month of follow-up.

An analysis of 1885 patients who survived myocardial infarction tracked the effect of adherence to drug therapy and mortality for several years. Patients who received a RAAS inhibitor at the beginning were 72%, and by the end of the first year – 82%, but at the end of follow-up only 72% remained on the prescribed therapy. These results also significantly increased the mortality risk RR 4.06 (95% CI 3.31 – 4.98, p<0.001) (Jaakko et al., 2020).

11.2.3. Lipid-lowering therapy

Statins are recommended as a first-line pharmacological treatment, as in patients with established CVD or RF present for its development. If LDL-C targets cannot be achieved with the use of high doses of statin, combination therapy with the addition of an intestinal cholesterol resorption inhibitor should be discussed as monotherapy (Mach et al., 2020). NHANES data indicate that despite improved knowledge, drug treatment, and control of LDL-cholesterol, the presence of elevated LDL-cholesterol levels in the general population is approximately 26% (Wei et al., 1994). A more recent publication analyzing NHANES data for the period 2003-2004 reported up to 40% control for LDL-cholesterol and non-HDL-C in patients with established cardiovascular disease compared to 85-89% in patients in primary prevention settings (Ghandehari et al., 2008). For Bulgaria, data from EUROASPIRE III indicate approximately 62% of hospital prescriptions of statins in patients with established coronary artery disease. Within 6 months, 59.1% of patients continued to take the prescribed medication (Georgiev et al., 2012).

A lipid-lowering medication prevalent in our therapy is Rosuvastatin at a dose titrated according to the LDL values of the individual visits. In 15% of patients in group A and 20% of those in group B, ezetimibe was required. In another trial of a similar cohort of patients, statin medication was used in 63%, and it was later essential to add ezetimibe in 5% and fibrate in 3% (Hawkins et al., 2022).

We found no significant variation in periods between the two populations we studied. After the 12th month, only 69% of patients with ACS without lung disease who had been prescribed lipid-lowering treatment were still motivated to take it. Patients with ACS without COPD have a comparable rate (61.30%) - see Figure 26.

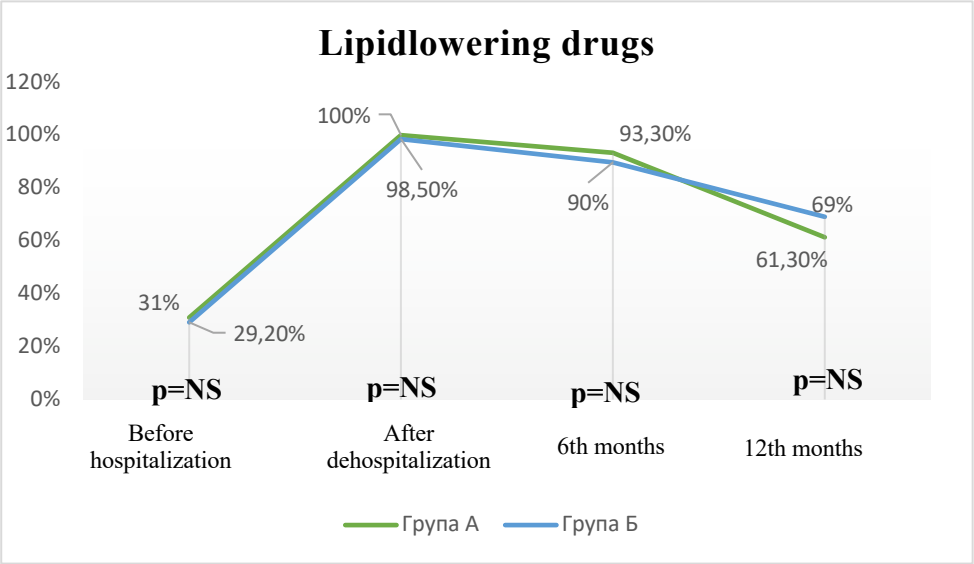

Fig 26. *Adherence to lipid-lowering therapy for one year after ACS.*

This negative trend increases the risk of recurrent cardiovascular accidents and increases mortality (Mach et al., 2020). Non-adherence to lipid-lowering therapy in patients with pulmonary obstruction was OR 1.54% (1.37-1.74, p<0.0001) (Dhamane et al., 2016). Reduced survival has been documented in patients with COPD who have discontinued statin (Soyseth et al., 2007). A study conducted in Germany in 542 patients with ACS found a reduced adherence to lipid-lowering therapy by 15.7% at the end of the first year (Phan et al., 2012). Hawkins et al. monitored the dynamics of risk factors for IHD in patients with COPD for five years. At the end of the study, they noticed a decrease in adherence to statin therapy from 63.5% to 62.2%, p = 0.023. Another observational study found repeated ACS in 66.4% of patients who stopped taking a statin one month after the index event. The mortality rate in this group is over 15.2% (Sulzgruber et al., 2020).

11.2.4. Antiplatelet agent

Dual antiplatelet therapy is the basis for the treatment of patients with ACS even after coronary interventions. The results of the PLATO and TRITON-TIMI 38 studies (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38) confirm the efficacy of dual antiplatelet therapy involving aspirin and a P2Y12 receptor inhibitor (Wallentin et al., 2009). Antiplatelet therapy also contributes significantly to the reduction of overall mortality in patients with COPD (Pavasini et al., 2016). Data from a prospective national study indicate that these drugs increase the survival rate of patients with COPD (Ekstrom et al., 2013). A post hoc analysis of the PLATO trial showed that without increasing the overall incidence of major hemorrhagic incidents, antiplatelet treatment significantly reduced the absolute risk of ischemic events in patients with COPD (Wallentin et al., 2009). Despite the proven positive properties of antiaggregation for subsequent treatment of ACS and COPD, in our population, by the end of follow-up, only 86% of patients in group A and only 81.4% in group B accepted their dual antiplatelet therapy. The curves are divided as early as the sixth month, p=0.001 – Figure 27.

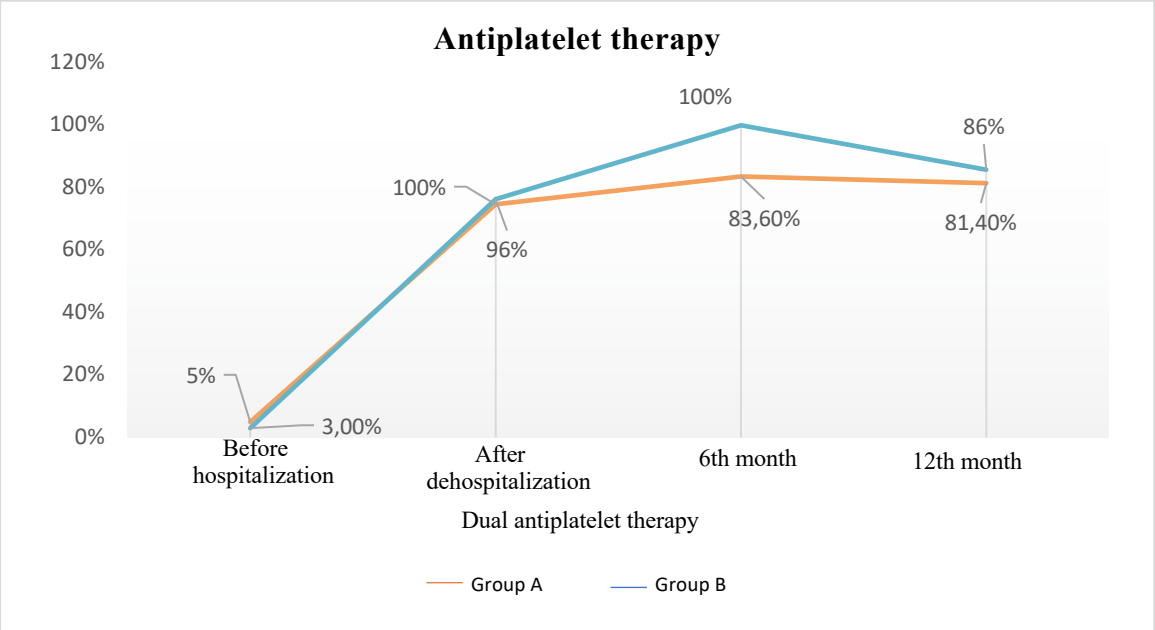

Fig. 27. *Adherence to double antiplatelet therapy for one year after ACS.*

Amann et al. analyzed the results of adherence to therapy in 1667 patients with AMI six years after their discharge. The proportion of patients discharged with BB, statin, ACE inhibitor, or antiplatelet agent decreased from 83.6% to 79.3% at the end of the study. Mangiapane et al. monitored the therapy of 30,028 patients after myocardial infarction in

Germany. They found that treatment adherence decreased within five years, respectively for BB from 82% to 36%, statin from 73% to 17%, for ACE inhibitor from 69% to 31%, and for dual antiplatelet therapy from 66% to 10%. Another study tracking patients with ACS and COPD found that the possibility of discharging BB in them was 56% lower compared to controls, for statins, it was 30%, and for antiplatelet therapy, this possibility was 44% lower. This group of patients is less likely to reach PCI (OR, 0.64; 95% CI, 0.54-0.77) or aortocoronary bypass surgery (OR, 0.46; 95% CI, 0.32-0.66) (Stefan et al., 2012). Similar are the results of the national study in Taiwan, conducted in the period 2004-2013 in 6770 patients with myocardial infarction. In 28.3% of the examined, COPD was detected. After dehospitalization, it became clear that this group of patients received less often BB OR 0.66 (95% CI 0.59–0.74), ACE inhibitor OR 0.83 (95% CI 0.73–0.93), lipid-lowering medication or dual antiplatelet therapy. Patients with ACS and COPD are less likely to be referred for SCAG, which also corresponds to a higher mortality HR 0.83 (95% CI 0.73–0.93), one year after dehospitalization (Su et al., 2017).

11.2.5. Therapy for the treatment of COPD

The updated GOLD recommendations aim to improve the choice of therapy for patients in group E. Initial treatment for these patients is suitable triple therapy (inhaled corticosteroids in addition (ICS) with long-acting muscarinic antagonist (LAMA) and long-acting β_2 agonist (LABA)). Patients receiving ICS + LABA who continue to have flare-ups are also recommended to switch to triple therapy. This is essential as switching to triple therapy has been shown to reduce future exacerbations, health resource utilization, and mortality (GOLD, 2023). Bronchodilators are classes of drugs that increase FEV_1 and improve other spirometry parameters, reducing dynamic hyperinflation at rest and during exercise, thereby improving exercise performance and reducing the number of exacerbations (GOLD, 2023). The extent of these changes suggests that these drugs may have a beneficial effect on CVD outcomes. An extensive network meta-analysis involving 23 studies found that LAMA/LABA combination therapy had comparable effects with both monotherapies on safety outcomes (Obai et al., 2016).

Despite the many positive effects, the treatment regimens used in patients with COPD are particularly vulnerable to adherence problems due to the chronic nature of the disease, polypharmacy, and periods of remission. In our study, compliance with the prescribed outpatient bronchodilator therapy in patients with ACS and COPD was 62.7%. This low rate

has been maintained for half a year since the start of the tracking. Despite intensive and frequent monitoring of patients in the course of the study, at the end of the study, we achieved 87% compliance with the therapeutic plan, p=0.0038 – Figure 28.

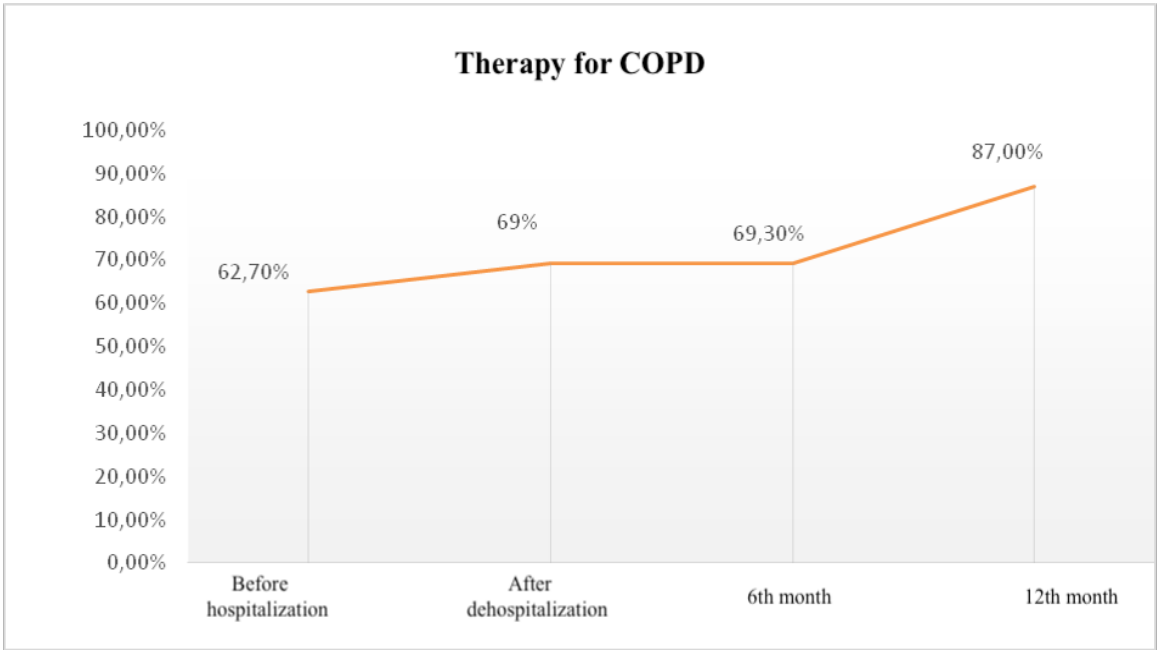

Fig. 28. *Adherence to COPD therapy for one year after ACS.*

Patients with COPD have significantly lower adherence to therapy compared to patients with asthma (Haupt et al., 2008). One of the possible reasons is the symptoms of the patients. According to research, individuals who have more symptoms are more likely to persist with their inhalation therapy (Dhamane et al., 2016). Numerous studies have shown that 60% of patients with COPD do not adhere to the prescribed treatment for their lung disease, and 85% use their inhalers ineffectively (Krigsman et al., 2007).

Based on the facts presented thus far about prescription pharmacological therapy, we can conclude that patients with ACS and COPD are less likely to adhere to the treatment regimen over time. This could be due to older age, poorer social status, lesser income, or to comorbidities. Patients with COPD are forced to take more and different classes of medications needed to treat their accompanying diseases. This feature leads to a more frequent change in therapy, such as excluding BB due to unjustified side effects or not taking into account different drug interactions. Despite the different factors that can influence long-term compliance with the treatment regimen, all scientific studies agree on the danger of rehospitalization and death in the event of non-compliance with the prescribed therapy.

12. Re-hospitalizations one year after ACS

12.1. Re-hospitalizations for cardiovascular disease for one year after ACS

Chronic obstructive pulmonary disease is an independent predictor of cardiovascular hospitalizations. The VALIANT study found that the combined risk of hospitalization for myocardial infarction and HF significantly increased in patients with obstructive pulmonary disease RR 1.14 (95% CI, 1.04 -1.25). Sidney et al. found a relative risk of 2.09 (95% CI, 1.99 - 2.20) for cardiovascular hospitalizations in patients with COPD. This is confirmed by the results of another study following the same cohort of patients with RR 2.2 (95% CI, 2.0-2.3) (Curkendall et al., 2006). The incidence of cardiovascular events was 45% in individuals with ACS and COPD compared to 30% in the control group (Hawkins et al., 2009). The team of authors of Oliveira found re-hospitalization in 21.46% of patients after myocardial infarction within one year of the acute accident. In our study, 35 (46.7%) hospitalizations for CVD were recorded in patients in group A over one year compared to 19 (29.3%) in group B, p=0.036 – Figure 29.

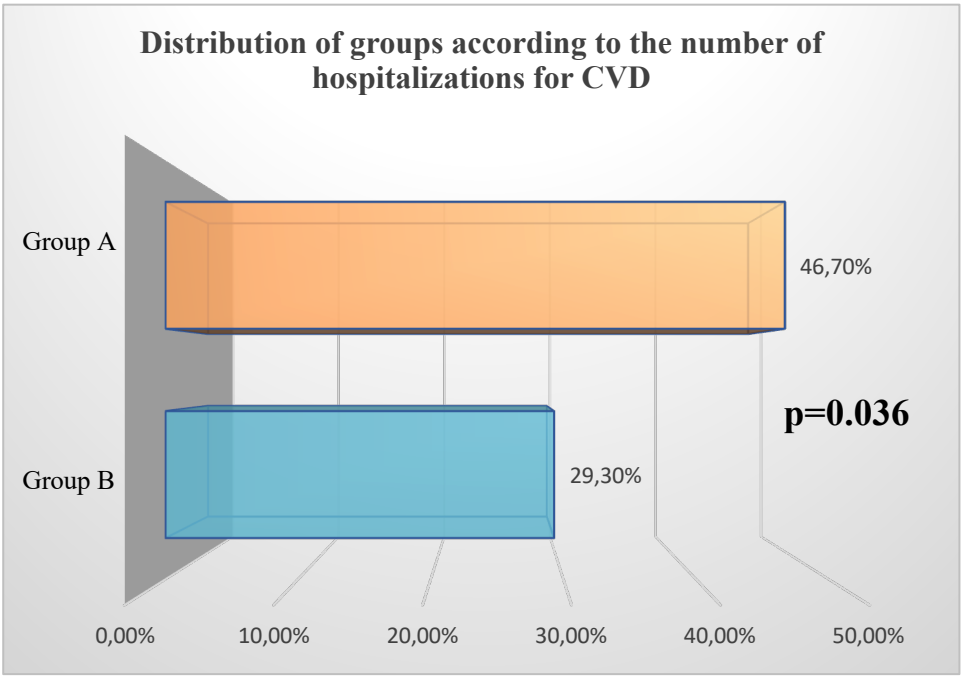

Fig. 29. *Distribution of groups according to the total number of hospitalizations for CVD over a period of one year after ACS.*

12.1.1 Distribution of CVD hospitalizations by cause

Sach et al. observed the most common causes of rehospitalization in patients with ACS within 30 days after the index event. They found cardiovascular morbidity in 42% of cases (HF

in 20.6% and ACS in 11.6%) According to them, 27.6% of COPD hospitalizations are related to the diagnosis of the index event, emphasizing the importance of concomitant diseases.

A study among people with ACS found non-cardiogenic reasons for re-hospitalization in 38.4%. They are distributed accordingly: 11.4% for respiratory diseases, 9.4% for infectious diseases, 6.5% for gastrointestinal, 4.8% for renal problems, and in 6.3% of cases, surgical intervention was required (Shah et al., 2018). Another team of authors found an extracardiac cause in 36.52% of the following individuals (Oliveira et al., 2019). A study by Sidney et al. found a twofold increased risk of cardiovascular rehospitalization in patients with COPD compared to those without lung disease (Sorel et al., 2005). Another six-year study found a higher incidence of hospitalizations for CVD in patients with COPD compared to controls (52.3% vs 11%, p<0.001 (Ferreira и сътр., 2023). A meta-analysis based on the causes of IHD found that patients with COPD had an increased risk for ACS (OR 186, 95% CI 151-230 p<0.0001), OMI (OR 271, 95% CI 169-435, p<0.0001), and NRA (OR 816, 95% CI 308-215, p<0.0001) (Chen et al., 2015).

The most common cardiovascular cause of hospitalization in the subjects we examined is heart failure, followed by IHD – Figure 30.

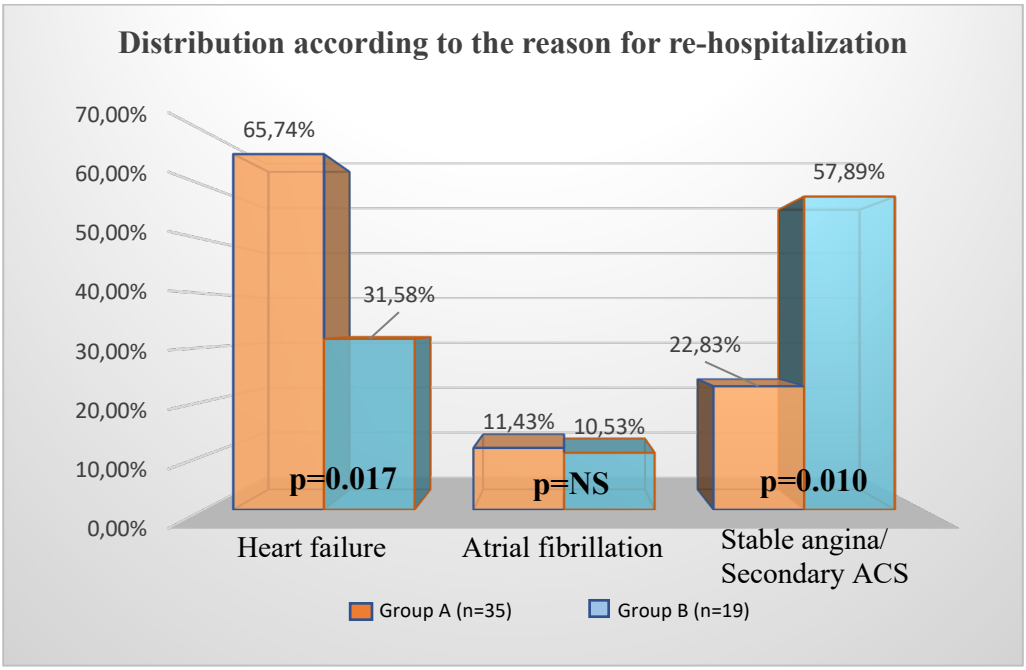

Fig. 30. *Distribution of hospitalizations for CVD by reasons for one year after ACS.*

A study tracking long-term complications after AMI found a higher risk of HF development in COPD patients with HR 1.35 (95% CI 1.24–1.47) in the first year (Andell et al., 2014). The research of Stefan et al. also confirms these results (OR 1.59, 95% CI 1.37 –

1.83). Santibanez et al. report a significantly higher risk of HF hospitalizations in people with COPD. Another study involving patients with pulmonary obstruction found a higher incidence of hospitalizations for HF or left ventricular systolic dysfunction in the first three years after AMI with an HR of 1.19 (95% CI 1.05 – 1.34) (Hawkins et al., 2009). In the population we studied, we also found a statistically significant difference in hospitalizations for HF, and this reason prevailed in the COPD group (65.74% vs 31.58%, p=0.017). We also used the one-factor analysis of variance ANOVA (F= 6.17, df=3, p=0.001) for confirmation. These results are close to what Stefan et al., reported cardiac decompensation in 52.5% of patients with COPD compared to 34.8% of controls (Stefan et al., 2012).

Ferreira et al. found a higher incidence of repeated ACS - 27.3% in people with lung disease compared to 5.5% in those without. Another team of authors found a 42.6% incidence of repeated myocardial infarction within the first year (Oliveira et al., 2019). In our study, patients with ACS without COPD had statistically more frequent hospitalization for recurrent ACS and stable angina pectoris (22.83% vs 57.89%, p=0.010).

A study reported a significantly increased risk of arrhythmia comparable to the GOLD stage and the degree of respiratory obstruction OR 0.4 (95% CI, 0.2-1.1) for stage one and OR 1.7 (95% CI, 0.8-3.8) for stage three and fourth (Lange et al., 2010). Another study found a greater manifestation of AFib after ACS in patients with COPD compared to controls (24.3% vs 18.2%) (Stefan et al., 2012). Observational analysis found that the frequency of rhythm disturbances in patients with COPD was between 0.3% and 29% (Mullerova et al., 2013). The incidence of AFib in the COPD group we studied one year after ACS was 11.43%.

12.2. Hospitalizations for COPD according to the GOLD stage

The number of hospitalizations per year is positively correlated with the severity of pulmonary obstruction according to GOLD, with 85% of hospitalizations for patients in stage 3 or 4 (Wong et al., 2008). A prospective study found a higher frequency of repeated hospital admissions for COPD in patients in the third stage of GOLD - 35.6% and in the fourth GOLD stage - 27.9% (Luth et al., 2023). The HUNT study (The Trøndelag Health Study) followed 1,300 participants with COPD for twenty years. In the course of the study, repeated hospitalization was recorded in a total of 522 patients. According to the GOLD classification, 31.9% of them were in the first stage, 54.2% in the second, 12.5% in the third, and 1.4% in the fourth (Krokstad et al., 2013). Another study, tracking re-administration due to exacerbation of lung disease, found the highest incidence in patients in the first stage of GOLD - 56% and in

the second stage respectively at 37.6% and in total for stages three and four - 6.4% (Lundberg и сътр., 2011).

We used chi-square analysis to determine the number of hospitalizations according to the GOLD stage in the group we studied, we used chi-square analysis. According to the findings, the second stage of COPD accounts for the highest percentage of hospitalizations (45.3%), followed by the third stage (32.1%). 5.7% of persons, including those who have more than two hospital stays a year, are in the fourth stage – Table 8.

Table 8. *Distribution of re-hospitalizations for COPD according to GOLD one year after ACS.*

X^2=11.49, p=0.487			GOLD 12-th month				Total
			I stage	II stage	III stage	IV stage	
COPD hospitalization, one year after ACS	none	number	6	14	9	0	29
		%	11.3%	26.4%	17%	0%	54.7%
	1.00	number	2	6	2	2	12
		%	3.8%	11.3%	3.8%	3.8%	22.6%
	2.00	number	1	1	4	0	6
		%	1.9%	1.9%	7.5%	0.0%	11.3%
	3.00	number	0	3	2	0	5
		%	0.0%	5.7%	3.8%	0.0%	9.4%
	6.00	number	0	0	0	1	1
		%	0.0%	0.0%	0%%	2%	2%
Total		number	9	24	17	3	53
		%	17.0%	45.3%	32.1%	5.7%	100.0%

12.2.1. Repeated ACS according to the GOLD stage in one year

A study found a strong correlation between acute exacerbation of COPD and the severity of GOLD with the incidence of AMI. The team of authors found a risk for ACS RR 1.69 (95% CI: 1.45–1.98) in the first and second stages of GOLD and for the third and fourth RR 1.98 (95% CI: 1.61–2.05, p = 0.007) (Molina et al., 2018). Fahad et al. report that patients who experience AMI during acute exacerbation of COPD have a 100% increased risk of imminent rehospitalizations for CVD and a 50% longer hospital stay compared to persons without AMI (Alqahtani et al., 2020).

In the population we studied, we found that the highest incidence of repeated ACS occurs in the second stage of GOLD (F= 0.001, df=1, p=0.971) – Table 9.

Table 9. *Distribution of re-hospitalization for ACS by GOLD stage for one year.*

X^2=1.99, p=0.574			GOLD 12-th month				Total
			I stage	II stage	III stage	IV stage	
Rehospitalization for ACS	none	number	8	23	16	3	50
		%	14.8%	42.6%	31.5%	5.6%	94.4%
	one	number	1	2	0	0	3
		%	1.9%	3.7%	0.0%	0.0%	5.6%
Total		number	9	25	16	3	53
		%	16.7%	46.3%	31.5%	5.6%	100.0%

13.Death

Patients with COPD are at greater risk of a fatal cardiovascular event compared to those without lung disease (86% vs 40%, p<0.001) (Ferreira et al., 2023). In the prospective PREMIER study involving 2481 patients with myocardial infarction, patients with COPD had a higher mortality rate, a higher rate of rehospitalization, and poorer health one year after the acute event. The presence of COPD was assessed as an age-independent RF for death HR 1.30 (95% CI 1.10-1.54, p < 0.01) (Bursi et al., 2010).

A comparison of individuals with COPD and CVD and those without pulmonary disease indicated that people with pulmonary obstruction died more commonly during hospitalization (13.5% vs 10.1%) and within 30 days after release (18.7% vs 13.2%). (Stefan et al., 2012). Another study tracking cardiovascular morbidity found an increased mortality rate in individuals with COPD HR 1.42 (95%CI, 1.09–1.86) (203). Bursi et al. also found reduced survival in patients with pulmonary obstruction and myocardial infarction compared to those without pulmonary disease, respectively (46% [95% CI 41%-52%] vs 68% [95% CI 66%-70%], p < 0.01).

Over one year, we recorded a total of 32 deaths. The incidence of fatal events was higher in the COPD group - 25.3% compared to those without lung disease 20%, p=0.457 – Figure 31.

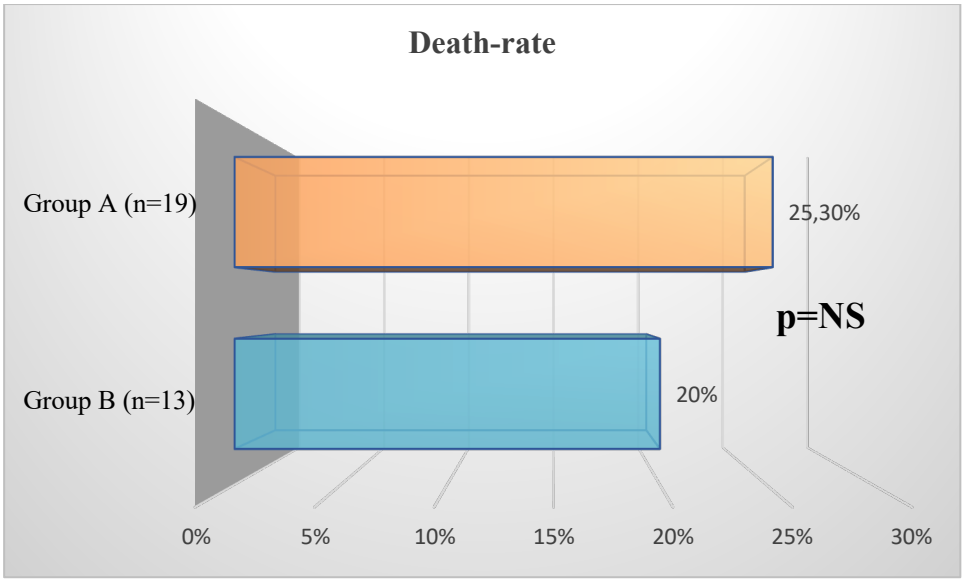

Fig. 31. *Distribution according to the number of deceased patients in both groups, one year after ACS.*

13.1. Mortality by period

The negative link between COPD and mortality has grown greater in recent years (p=0.005 for the interaction of COPD and year). Compared to patients without COPD, those with pulmonary obstruction had a 16% risk of death caused by AMI that occurred in 1979-1985 (HR 1.16, 95% CI, 0.82-1.64), which more than doubled in the same cohort of patients in 2000-2007 (HR 2.37, 95% CI, 1.85-3.04) (Bursi et al., 2010).

Stefan et al. found a higher incidence of deaths in the ACS and COPD group at the time of hospitalization (13.5% vs 10.1%) and within 30 days after discharge (18.7% vs 13.2%). Another study followed individuals with COPD and CVD for 287±121 days and observed a decrease in survival. It was 95.2% for the first month, 88.2% for the third, 80.9% for the sixth and 68.2% at the end of the year, respectively (Macchia Bursi et al., 2005). Andell et al. found a higher mortality rate in the ACS and COPD group after a one-year follow-up compared to those without COPD (24.6% vs 13.8%). The PREMIER study also reported greater mortality after AMI in the COPD group within one year (Bursi et al., 2010).

In our study, the change in mortality in the two groups, tracked by periods, is impressive. While in the first 90 days of follow-up, mortality was higher in the group with ACS without COPD, respectively (26.30% vs 61.60%, p<0.0001), at the end of the first year, this ratio statistically changed in favor of patients with COPD (52.60% vs 15.40%, p=0.035) – Figure 32.

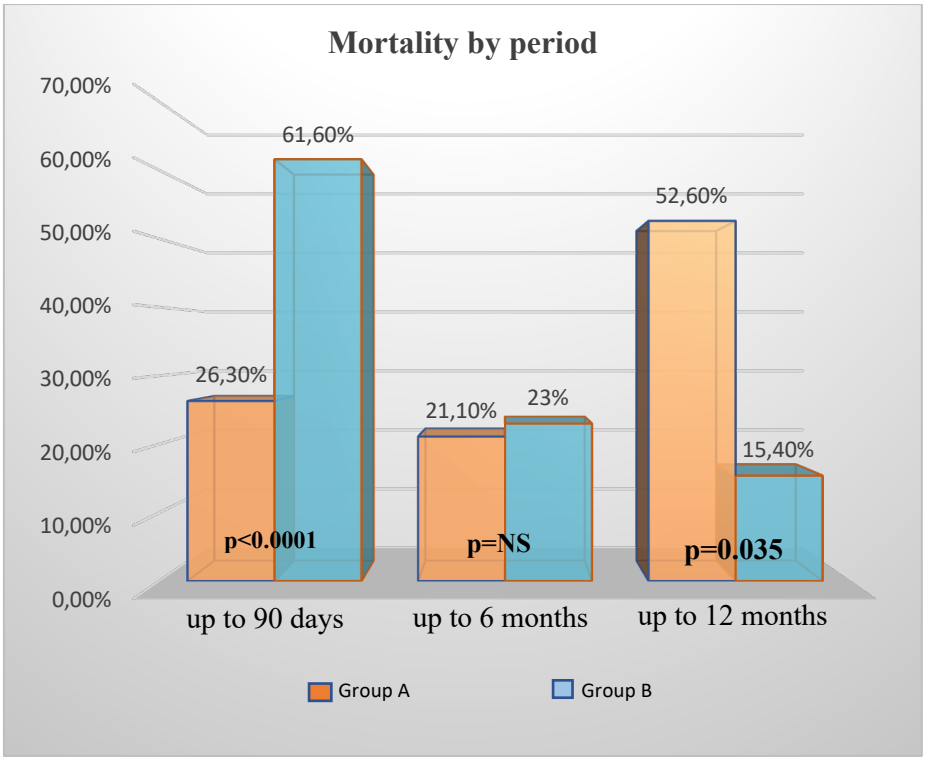

Fig. 32. *Distribution of mortality by periods one year after the ACS.*

A probable reason for these results is the predominance of ACS without ST-elevation in group A (74.67% vs 36.92%, p<0.0001) and of ACS with ST-elevation in group B (25.33% vs 63.08%, p<0.0001). Studies have shown that higher early mortality in STEMI is a result of mechanical complications and cardiogenic shock, which are less common in patients with NSTEMI (Aissaoui et al., 2020). A study following 1822 patients with ACS found early mortality in 6.7% of individuals presenting with ST-segment ACS, compared to 4.7% of patients without ST-segment elevation, p=0.09. A ten-year follow-up showed a worse long-term prognosis for patients with NSTEMI. The mortality rate in this group was 22.8% compared to the controls - 19.6%, p=0.11 (Bouisset et al., 2021). The unadjusted risk of death in patients with COPD compared to patients without COPD increases over time, mostly due to the effect of age and emphasizing that due to population aging, the burden of COPD after ACD is likely to increase (Bursi et al., 2010).

13.2. Demographic and clinical characteristics of deceased patients

Gulf RACE is the largest international registry for acute coronary events in the Middle East (The Gulf Registry of Acute Coronary Events). According to him, the main predictors of hospital mortality in patients with myocardial infarction are age, female sex, and cardiogenic

shock (Hadi et al., 2010). Data from a registry of 150 hospitals in the UK shows that age is the main factor in 30-day deaths after hospitalization for COPD (OR, 8.5, 95% CI, 7.7-9.4). (Raposeiras et al., 2012). Another study corroborated age and gender but identified smoking as an independent risk factor for death in individuals with ACS and COPD (HR 1.54, 95% CI, 1.34-1.77) (Bursi et al., 2010). An analysis of the Swedish registry SWEDEHEART found that the average age of deceased patients with concomitant COPD was 75 years, with a prevalence of male sex – 54% and smoking in 32.9% (Andell et al., 2014). Another study among patients with COPD and acute myocardial infarction also confirmed these results, finding that the average age of the deceased was 73 years, 59% were men, and 35% of the deceased were active smokers (Bursi et al., 2010). In our study, we found that deceased patients in the ACS and COPD groups were older compared to those without COPD, respectively (69.10±7.94 years vs 64.61±15.31 years, p=0.284). The ratio in the distribution by sex is the same for both groups. A statistically significant difference was reported regarding the share of current smokers in group A compared to group B (89.47% vs 53.8%, p=0.024) – Table 10.

Table 10. *Demographic characteristics of deceased patients in both groups*

	Group A (n=19)	**Group B (n=13)**	**p value**
Sex %			
Male %	47.37%	46.15%	0.946
Female %	52.63%	53.85%	0.946
Age	69.10±7.94 г.	64.61±15.31 г.	0.284
Presence of obesity according to BMI (%)	84.21%	46.2%	**0.025**
Smokers:			
Current smokers %	89.47%	53.8%	**0.024**
Ex-smokers %	10.5%	7.7%	0.792
Presence of diabetes mellitus	68.4%	46.2%	0.216
6MWT	257.37±166.48 м.	470±176.77 м.	**0.016**
CRP mg/l	33.11± 40.70	5.25 ±12.23	**0.023**

Obesity is associated with a 20–30% increase in all-cause mortality in patients with moderate COPD compared to others of normal weight and the same degree of obstruction (Aguib et al., 2015). Corrected all-cause mortality was higher in moderate (HR 1.39, 95% CI: 1.10-1.75) and severely obese (2.06, 95% CI: 1.57-2.70) compared to mildly obese patients with ACS. The main causes of death in patients with obesity and COPD are both cardiovascular (HR 2.36, 95% CI: 1.67-3.32) and non-cardiovascular diseases (HR 1.67, 95% CI: 1.07-2.61) (Williams Bursi et al., 2010). We found a higher proportion of deceased patients with COPD and the presence of obesity compared to that of people with ACS without COPD (84.21% vs 46.2%, p=0.025).

Physical activity, along with obesity, is a significant predictor of mortality. Celli et al. establish a correlation between the shorter distance traveled during 6MWT and the higher mortality in patients with COPD. Another study, following 282 patients undergoing pulmonary rehabilitation, found a worse survival rate in the group with an average distance traveled of 6MWT less than 150 meters (Dajczman et al., 2015). In our study, deceased patients with ACS and COPD had a worse result of 6MWT compared to the controls (257.37±166.48 m. vs 470±176.77 m., p=0.016). Individuals with systemic inflammation are known to be more obese, have lower physical tolerance, and have poor quality of life (Rutten et al., 2012).

We also reported a significant difference according to the CRP parameter (33.11 ± 40.70 mg/l vs 5.25 ±12.23 mg/l, p=0.023). Multivariate analysis proves that elevated baseline CRP levels in patients with COPD are significantly associated with higher mortality (HR 1.53, 95% CI 1.32-1.77, p<0.001) (Leuzzi et al., 2017). Using bivariate analysis, Sharma et al. found a positive correlation between high CRP values and atherogenic risk in patients with COPD (r=0.4265, p<0.006) (Sharma et al., 2019).

Due to the small number of participants in both groups, the regression analysis did not register predictiveness in the studied demographic parameters.

13.3. Correlation

According to European recommendations, BB is one of the main classes of drugs for secondary prevention of ACS in patients with COPD (Hamm et al., 2011). Numerous studies have proven that these drugs not only improve symptoms but also reduce mortality in this cohort of patients (Salpeter et al., 2003; Andell et al., 2014). We use the Spearmen rank correlation coefficient to investigate the association between BB therapy adherence and mortality. In patients with ACS and COPD who took BB before hospitalization and during follow-up, we found (rho (75) = 0.268, p=0.002) and (rho (62) = 0.228, p=0.052, respectively.

The correlation sign is positive, which means that mortality decreases with regular intake of BB and compliance with the therapeutic regimen until the sixth month.

Lee et al. found that mortality in patients with COPD who took BB was lower compared to those without such therapy (25.2% vs 35%, p=0.002). These results are close to the population without known pulmonary obstruction, respectively 15% in patients with BB and 27.9% in those without (Hawkins et al., 2009). Another team of investigators found that individuals with ACS and COPD who were followed up for three years had a higher survival rate (HR 0.50 (95% CI: 0.36-0.69) (Quint et al., 2013). Lower mortality in COPD patients taking BB was seen even during hospitalization due to disease exacerbation (McAllister et al., 2012).

The presence of COPD significantly worsens the quality of life in patients with ACS. For many patients, a lifestyle change is unpleasant and results in a loss of social status, necessitating a change of job and increasing feelings of despair and sadness (De Miguel et al., 2010). According to a study following patients with COPD for 53 months, reduced quality of life was a better predictor of death even than FEV_1 HR 1.13 (95% CI 1.06–1.22) (Antonelli-Incalzi et al., 2009). We used the Pearson correlation coefficient to investigate the linear relationship between quality of life through the LVD-36 questionnaires and mortality. In the sixth month of follow-up for patients with ACS and COPD, we discovered ($r(62) = 0.888$, p=0.005), indicating a statistically significant linear correlation. According to the Cohen scale of 1988, the magnitude of the effect was strong or greater than average, indicating that patients in group A had a lower quality of life in the sixth month of follow-up, which was associated with an increase in mortality.

14. Sample algorithm for tracking patients with ACS and COPD

Currently, more than 90% of the total risk of developing IHD, and in particular ACS, worldwide is due to modifiable risk factors, including smoking, hypertension, obesity, unhealthy diet, dyslipidemia, and reduced physical activity. All these RFs are also characteristic of patients with COPD (Kotseva et al., 2009). Unfortunately, the modernization of developing countries also leads to unhealthy lifestyles. Despite the improvement of therapy for primary and secondary prevention of CVD, the data remain alarming.

All European cardiology societies believe that efforts should be directed toward risk factor management, adherence to prescribed medicine, and IHD preventive programs. On the other hand, the specifics of patients with ACS and COPD remain underestimated. Advanced age, deteriorating lung function, debilitating symptoms, and lower socioeconomic status lead

to a deterioration in the quality of life of these patients. Chronic obstructive pulmonary disease is a disease that, although slowly progressing, is incurable, and the improvement in lung function is minimal. This is why it is critical to develop more effective treatment techniques that will improve the quality of life and reduce medical costs for this high-risk group.

Developing and implementing an algorithm for the follow-up of patients with ACS and COPD requires careful analysis of the data from the current study. As a result, several exemplary recommendations for behavior emerged:

1. Individualizing the strategy for each patient based on his or her socioeconomic background.
2. Educating the patient and his family about the characteristics of the two diseases, ACS and COPD, including symptoms, progression, and prognosis.
3. Motivating the patient to quit smoking. Informing on the Regional Health Inspectorates' active consultative offices. National Smoking Cessation Hotline: **0 700 10 323.**
4. Promoting yearly influenza vaccinations.
5. Cardiac rehabilitation is based on low-to-moderate-intensity exercise 8-12 weeks after the cardiac accident. Inclusion in structured exercise programs for 3-6 months to achieve an appropriate level of activity. They are performing regular physical activity five times a week for 30 minutes (Pelliccia et al. 2021).
6. Patients with COPD in categories B and E should participate in specialized respiratory rehabilitation programs offered by Specialised Rehabilitation Hospitals throughout the country (GOLD, 2023). Telerehabilitation programs for patients with limited mobility or living in remote places will be developed using platforms and mobile applications.
7. Maintaining a balanced diet with adequate protein, vitamins, antioxidants, and water (GOLD, 2023).
8. Encourages weight loss. A moderate dose of 5-10% can help with hypertension, dyslipidemia, and glycaemic management (Ghandehari H et al., 2008).
9. Using quality-of-life questionnaires in daily practice could give us a clear picture of our patient’s mental health and refer them to a psychotherapy and support group.
10. Educating patients and their relatives on the method of administration, the effects of the prescribed drug therapy, and the risks of non-adherence
11. Conducting large-scale training campaigns aimed at general practitioners and those from other specialties for the complex treatment of patients with ACS and COPD. Bringing attention to the need for beta-blocker use, as well as the option of a personalized therapy strategy adapted to the specific needs of this patient group.

12. Begin BB therapy with a moderate dose titration over 1-2 weeks, with parallel HB, BP, and potentially spirometry measurements.
13. Early follow-up of patients with ACS and COPD – one month after their dishospitalization for cardiovascular status, performing a functional breathing test and tracking the values of the BODE-index. After 3-6 months, a follow-up visit to check the stability of the lung condition. We also offer regular follow-up of patients with COPD even at the 12th month of the acute event (currently under the NHIF these patients are entitled to one spirometry and two follow-up examinations per year).
14. Monitoring the achievement of targets for LDL-cholesterol in patients with ACS < 1.4 mmol/l or reduction by 50% of its basal values, offering follow-up at the first, sixth, and twelfth month after the acute event.
15. Monitoring of glycemic control at least once a year in persons without data on DM and adherence to glycated hemoglobin values HbA1C<7% in persons with established DM.

IMPLICATIONS

Based on the results obtained, we can draw the following implications:

1. Patients with ACS and COPD have a more pronounced risk profile for IHD compared to patients with ACS without COPD.

2. The incidence of anemia, CKD, and stroke is higher in the COPD group.

3. Patients with ACS and COPD have poorer lipid profile control and are slower to achieve the target blood sugar values in the presence of DM. They are less motivated to quit smoking in the long term and are less physically active.

4. Patients with COPD are more likely to present with a clinical sign of ACS without ST elevation. Because of their high-risk profile, they are less frequently referred for invasive diagnosis and subsequent treatment. According to their coronary pathology, people with ACS and COPD have a dominating single-vessel CAD, with RCA being the most typically impacted.

5. The population with ACS and COPD studied by us shows weaker adherence to the prescribed main classes of medications – BB, ACE/ARBs/ARNI, lipid-lowering agents, and antiplatelet therapy.

6. ACS, in combination with COPD, has a multifactorial effect on all aspects of patients' lives, with health status remaining permanently reduced within one year after ACS compared to the control group.

7. Patients with concomitant COPD are at greater risk of hospitalization for CVD up to twelve months after the acute coronary event. The most common cause is HF, followed by IHD.

8. Higher BMI, smoking, lower physical activity, and higher baseline CRP values are associated with higher mortality in COPD patients one year after ACS.

CONTRIBUTIONS

Contributions of an original nature

1. For the first time in Bulgaria, a study has been conducted on the risk and clinical characteristics of patients with ACS and COPD. The merit of the study is the monitoring of the spirometric parameters of pulmonary obstruction.

2. For the first time in Bulgaria, the quality of life of patients with ACS and COPD is being studied.

3. For the first time in Bulgaria, adherence to the prescribed drug therapy for the region of Northeastern Bulgaria is objectively monitored.

4. For the first time in Bulgaria, the causes of hospitalizations in patients with ACS and COPD for one year after the acute coronary event are being tracked.

5. For the first time in Bulgaria, mortality in patients with ACS and COPD is monitored.

Confirmatory contributions

1. The risk characteristic for CAD in patients with COPD is confirmed.

2. The need for patients with COPD to be treated as a high-risk population for the manifestation of ACS is confirmed.

3. The need for functional testing after ACS in patients with established COPD is confirmed.

4. The poorer quality of life in patients with ACS and COPD is confirmed;

5. The more frequent occurrence of ACS without ST elevation in patients with COPD is confirmed.

6. The less frequent referral for SCA in patients with ACS and COPD is confirmed.

7. The thesis, defended by an increasing number of authors, about the lack of contraindications to the use of cardioselective BB and the need for control for adherence to therapy is confirmed.

8. The role of CVD as a cause of more frequent hospitalizations in patients with COPD has been confirmed.

PUBLICATIONS AND PARTICIPATION IN SCIENTIFIC FORUMS RELATED TO THE DISSERTATION

Publications:

1. S. Nikolaeva, A. Angelov. Petkova D. Clinical characteristics and comorbidities in patients with chronic obstructive pulmonary disease and acute coronary syndrome. Science Pulmonology 2024; 70: 4-14;

2. S. Nikolaeva. Acute coronary syndrome in chronic obstructive pulmonary disease patients – epidemiology, pathophysiology and treatment. Heart-Lung 2021; 27: 17-27;

Scientific Communications:

1. **S. Nikolaeva**, D. Petkova, A. Angelov. Assessment of quality of life in patients with acute coronary syndrome and chronic obstructive pulmonary disease. The Autumn Scientific Meeting of the Bulgarian Society of Lung Diseases, Albena 20 - 22.10.2023

2. **S. Nikolaeva,** A. Angelov, D. Petkova. Adherence to therapy for patients with acute coronary syndrome and chronic obstructive pulmonary disease. XXVII Scientific Conference of the Heart-Lung Association, Albena 10.11 - 11.11. Oct. 2023

3. S. Nikolaeva, A. Angelov, D. Petkova. Clinical characteristics and adherence to beta-blocker therapy in patients with acute coronary syndrome and chronic obstructive pulmonary disease. IX Varna Cardiology Days, Golden Sands 02. 02. – 04. 02. 2024

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