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The impact of concomitant anemic syndrome on the clinical course of coronary artery disease

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

The presence of comorbid pathology negatively affects the prognosis of patients with coronary artery disease (CAD). Today it is important to clarify the features of CAD on the background of concomitant anemia and identify the main risk factors for complications to improve the tactics of this category of patients.

The aim. To investigate the influence of concomitant anemic syndrome on the clinical course of coronary artery disease, frequency and features of the main cardiovascular events.

Materials and methods. The study involved 91 patients with coronary artery disease (42 men and 49 women, age – 70 (49; 93)). All patients were divided into 2 groups: the main group (n = 46) consisted of patients with coronary artery disease with iron-deficiency anemia, the comparison group (n = 45) – patients with coronary artery disease without iron-deficiency anemia. The study of the main cardiovascular events took into account re-hospitalization due to arrhythmic disorders, progression of heart failure (HF), CAD destabilization within the observed period (1 year), as well as death from cardiovascular causes. The data analysis was performed using Statistica 13.0.

Results. During the year, 42 non-fatal cardiovascular events were noted in patients of both groups, however in the main group their total number was 30 (67 %) versus 12 (27 %) in the comparison group (χ^2 = 13.603; P < 0.05). The presence of concomitant anemia in CAD patients significantly increased the relative risk of re-hospitalizations (RR = 1.9; 95 % CI 1.230–3.112; P < 0.05). Among the reasons for hospitalization in the main group, HF decompensation prevailed – 17 (57 %) patients, unstable angina – 7 (23 %), arrhythmic disorders – 6 (20 %); in the comparison group, among the reasons for re-hospitalization, 7 (57 %) had HF decompensation, 3 (25 %) had unstable angina, and 2 (17 %) cases had arrhythmic disorders. In total, 9 (19.5 %) deaths were recorded in the main group, while in the comparison group 1 (2.2 %) death was recorded during the year (χ^2 = 6.995; P < 0.05). The presence of concomitant anemia in patients with CAD increases the risk of fatal outcome by 8.8 times (RR = 8.8; 95 % CI 1.162–66.685; P < 0.05). The presence of moderate anemia in patients with CAD significantly increases the incidence of combined critical events by 39 % during the year of follow-up compared with mild anemia (χ^2 = 12.843; P < 0.05).

Conclusions. The presence of concomitant anemia is associated with a worsened prognosis for patients having coronary artery disease due to an increased risk of non-fatal cardiovascular events that require re-hospitalization during the year of observation, and an increased incidence of death. Increasing severity of anemia is associated with an increase in the frequency of the combined critical event during 1 year of follow-up.

Key words: coronary artery disease, anemia, cardiovascular events, heart failure.

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Вплив супутнього анемічного синдрому на клінічний перебіг ішемічної хвороби серця

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Наявність коморбідної патології негативно впливає на прогноз пацієнтів з ішемічною хворобою серця (ІХС). Актуальним є уточнення особливостей перебігу ІХС на тлі супутньої анемії та визначення основних факторів ризику розвитку ускладнень для удосконалення тактики ведення таких хворих.

Мета роботи – дослідити вплив супутнього анемічного синдрому на клінічний перебіг ІХС, частоту виникнення та особливості основних кардіоваскулярних подій.

Матеріали та методи. У дослідження залучили 91 хворого на ІХС (42 чоловіки, 49 жінок віком 70 (49; 93) років), яких поділили на дві групи: основна (n = 46) – пацієнти з ІХС та супутньою залізодефіцитною анемією; група порівняння (n = 45) – ІХС без анемії. Вивчаючи основні кардіоваскулярні події, враховували повторні госпіталізації з приводу аритмічних порушень, прогресування серцевої недостатності (СН), дестабілізацію ІХС протягом року спостереження, а також летальні наслідки від серцево-судинних причин. Статистично результати опрацювали в ліцензованій програмі Statistica 13.0.

Результати. Протягом року у хворих обох груп зафіксували 42 нефатальні кардіоваскулярні події: в основній – 30 (67 %), у групі порівняння – 12 (27 %) (χ^2 = 13,603; p < 0,05). Наявність супутньої анемії у хворих на ІХС вірогідно підвищувала відносний ризик повторних госпіталізацій (ВР = 1,9; 95 % ДІ 1,230–3,112; p < 0,05). Серед причин госпіталізації в основній групі переважали декомпенсація СН (17 (57 %) пацієнтів), нестабільна стенокардія (7 (23 %) хворих), аритмічні порушення (6 (20 %) осіб). У групі порівняння причини повторної госпіталізації: декомпенсація СН (7 (57 %) пацієнтів), нестабільна стенокардія (3 (25 %) хворих), аритмічні порушення (2 (17 %) випадки). Зафіксували 9 (19,5 %) летальних випадків в основній групі, у групі порівняння протягом року зареєстрували 1 (2,2 %) летальний випадок (χ^2 = 6,995; p < 0,05). Встановили зростання ризику летального наслідку у 8,8 раза за умов супутньої анемії у хворих

Ключові слова: ішемічна хвороба серця, анемія, кардіоваскулярні події, серцева недостатність.

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на ІХС (ВР = 8,8; 95 % ДІ 1,162–66,685; p < 0,05). Виявили, що наявність у хворих на ІХС анемії середнього ступеня тяжкості вірогідно підвищує частоту виникнення комбінованої критичної події на 39 % упродовж 1 року спостереження порівняно з анемією легкого ступеня (χ^2 = 12,843; df = 1; p < 0,05).

Висновки. Перебіг ІХС на тлі супутньої анемії характеризується гіршим прогнозом хворих на ІХС унаслідок збільшення частоти та ризику розвитку нефатальних кардіоваскулярних подій, що потребують повторних госпіталізацій протягом року спостереження, а також збільшення кількості летальних випадків. Підвищення ступеня тяжкості анемії асоціюється зі зростанням частоти виникнення комбінованої критичної події протягом 1 року спостереження.

Ключевые слова: ишемическая болезнь сердца, анемия, кардиоваскулярные события, сердечная недостаточность.

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Влияние сопутствующего анемического синдрома на клиническое течение ишемической болезни сердца

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Наличие коморбидной патологии негативно влияет на прогноз больных ишемической болезнью сердца (ИБС). Актуальным остается изучение особенностей течения ИБС на фоне сопутствующей анемии и определение основных факторов риска развития осложнений для усовершенствования тактики ведения таких больных.

Цель работы – оценить влияние сопутствующего анемического синдрома на клиническое течение ИБС, частоту возникновения и особенности основных кардиоваскулярных событий.

Материалы и методы. В исследование включили 91 больного ИБС (42 мужчины, 49 женщин в возрасте 70 (49; 93) лет), которых поделили на две группы: основную (n = 46) – пациенты с ИБС и сопутствующей железодефицитной анемией, группу сравнения (n = 45) – ИБС без анемии. При изучении основных кардиоваскулярных событий учитывали повторные госпитализации вследствие аритмических нарушений, прогрессирования сердечной недостаточности (СН), дестабилизацию ИБС в течение года наблюдения, а также летальные исходы от сердечно-сосудистых причин. Статистическая обработка данных проведена в лицензированной программе Statistica 13.0.

Результаты. В течение года у больных обеих групп зафиксировали 42 нефатальных кардиоваскулярных события: в основной – 30 (67 %), в группе сравнения – 12 (27 %) (χ^2 = 13,603; p < 0,05). Наличие сопутствующей анемии у больных ИБС достоверно повышало относительный риск повторных госпитализаций (ОР = 1,9; 95 % ДИ 1,230–3,112; p < 0,05). Среди причин госпитализации в основной группе преобладала декомпенсация СН (17 (57 %) пациентов), нестабильная стенокардия (7 (23 %) случаев), аритмические нарушения (6 (20 %) больных). В группе сравнения причины повторной госпитализации: декомпенсация СН (7 (57 %) больных), нестабильная стенокардия (3 (25 %) пациента), аритмические нарушения (2 (17 %) случая). Зафиксировали 9 (19,5 %) летальных исходов в основной группе, в группе сравнения в течение года зарегистрировали 1 (2,2 %) летальный исход (χ^2 = 6,995; p < 0,05). Отмечено увеличение риска летального исхода в 8,8 раза при сопутствующей анемии у больных ИБС (ОР = 8,8; 95 % ДИ 1,162–66,685; p < 0,05). Наличие у больных ИБС анемии средней степени тяжести достоверно повышает частоту возникновения комбинированного критического события на 39 % в течение года наблюдения по сравнению с анемией лёгкой степени тяжести (χ^2 = 12,843; p < 0,05).

Выводы. Течение ИБС на фоне сопутствующей анемии характеризуется худшим прогнозом больных ИБС за счёт роста частоты и риска развития нефатальных кардиоваскулярных событий, требующих повторных госпитализаций в течение года наблюдения, роста числа летальных исходов. Повышение степени тяжести анемии ассоциируется с увеличением частоты возникновения комбинированного критического события в течение года наблюдения.

Cardiovascular diseases are the prevailing cause of death and one of the main disabilities causing factors worldwide [1,2]. The incidence of cardiovascular diseases has almost doubled in the last 10 years, and the number of deaths caused by them continues to increase steadily. Ukraine's mortality rate due to coronary artery disease (CAD) and cardiovascular diseases in general continues to be one of the worst in the world [1].

At the same time, anemia affects about 25 % of the world's population. The prevalence of anemia increases with age, and therefore it often accompanies cardiovascular diseases. Among the potential factors leading to the development of anemia in coronary heart disease, the most important are decreased iron intake and absorption, difficulty in its release from the depot, hemodilution, chronic inflammation with hyperproduction of proinflammatory cytokines and hepcidin, decreased erythropoietin synthesis due to renal dysfunction with the development of bone marrow resistance to erythropoietin stimulation, etc. [3–5].

Concomitant anemia affects cardiovascular remodeling processes. Anemic hypoxia is compensated by a cascade of hemodynamic and hemodynamically non-associated mechanisms. Realization of the basic hemodynamic factors is achieved by an increase of myocardium contractile ability, a decrease in an afterload, and an increase in a preload, positive ino- and chronotropic effects. Increased nitric oxide production, hypoxia-induced vasodilation and decreased blood viscosity cause vascular resistance reduction, which leads to a postload reduction. In addition, chronic anemia stimulates angiogenesis and the formation of new small vessels. In its turn, the development of collaterals and the microcirculatory tract also helps to reduce postload. Increased preload and left ventricular blood supply contribute to the increase of the end-diastolic volume and the left ventricular ejection fraction. While these changes are reversible in case of short-term anemia, a chronic condition leads to remodeling, with the formation of an eccentric hypertrophy of the left ventricular myocardium [6–8].

Increased cardiac output caused by anemia facilitates the development of arterial remodeling of central vessels

of the elastic type, such as the aorta and common carotid arteries, by expanding the lumen and compensatory thickening of the intima-media complex, resulting in increased systolic pressure. Activation of the sympathetic nervous system increases left ventricular contractility and increases heart rate [3,6,7].

In turn, increasing heart rate adds to higher myocardial oxygen demand. Oxygen supply to the myocardium is determined by the coronary blood flow and hemoglobin concentration. In patients without coronary pathology, a significant decrease in oxygen concentration in the coronary bloodstream can be compensated by peripheral vasodilation, but in coronary stenosis, this mechanism has limited capabilities [9]. Severe anemia can lead to an imbalance between myocardial oxygen supply and consumption, even in the absence of hemodynamically significant coronary stenosis. The literature describes examples of the development of acute coronary syndrome with ST segment elevation in a patient with severe anemia in the absence of angiographically significant coronary stenosis, thrombosis or spasm. Therefore, a decrease in blood oxygen concentration, as well as an activation of the sympathetic nervous system, may increase myocardial oxygen demand and intensify ischemia [7,9].

These side effects mediated by anemia lead to an increase of the development of cardiovascular complications in patients with cardiovascular disease, including coronary artery disease [3,6,7].

Thus, anemia is an independent predictor of cardiovascular disease and related adverse cardiovascular events, and it is important to study further the impact of anemic syndrome on the prognosis of patients with coronary artery disease and the risk of the development of complications.

Aim

To investigate the influence of concomitant anemic syndrome on the clinical course of coronary artery disease, frequency and features of the main cardiovascular events.

Materials and methods

91 patients with coronary artery disease (stable angina pectoris II–III FC) were monitored in a monocentric one-year study in parallel groups (42 men and 49 women of average age 70 [49; 93]) hospitalized in therapeutic and cardiologic departments of the communal non-commercial enterprise "City Hospital No. 4" of Zaporizhzhia City Council (Ukraine). All patients were divided into 2 groups: the main group (n = 46) consisted of patients with coronary artery disease with iron-deficiency anemia of mild and moderate severity, the comparison group (n = 45) – patients with coronary artery disease without anemia. The groups were comparable in age, sex, risk factors, the specificity of comorbidities. Concomitant subcompensated diabetes mellitus type 2 occurred in 5 % of patients of the main group and 6 % of patients of the comparison group, arterial hypertension – in 80 % of patients of the main group and 85 % of patients of the comparison group.

Coronary artery disease diagnosis was verified according to clinical, laboratory and instrumental criteria of the 2019 European Society of Cardiology (ESC) Guidelines for the diagnosis and management of chronic coronary syndromes. Concomitant anemic syndrome was detected by determining the level of hemoglobin and counting the number of erythrocytes. The etiology of anemia was established through biochemical and enzyme-linked immunosorbent assay in accordance with the Ministry of Health of Ukraine orders No. 709 of 02.11.2015 and No. 647 of 30.07.2010 as amended on July 29.07.2016.

The vast majority of anemia cases (95 %) was iron deficiency, diagnosed according to the 2020 recommendations of the American Gastroenterological Association (AGA), other patients had anemia of mixed etiology (anemia of chronic disease and iron deficiency anemia).

Inclusion criterion for the study were: providing informed consent; age over 18; the presence of anemia of mild (Hb 100–120 g/L in women, and 100–135 g/L in men) and moderate (Hb 80–99 g/L) severity; verified coronary artery disease. Exclusion criterion were: absence of informed consent, acute bleeding diagnosed in hospital; acute coronary syndrome; CKD III–V stages; severe anemia requiring blood transfusion; hemolytic anemia; hypo-aplastic anemia; malignant tumors, including those of hematopoietic organs; B12-folate deficiency anemia.

The work follows the moral and ethical principles of bioethics in accordance with the rules of the ICH/GCP, the Declaration of Human Rights of Helsinki (1964), the Council of Europe Convention on Human Rights and Biomedicine (1997), as well as current legislation of Ukraine.

All patients received basic therapy for coronary heart disease, which included antiplatelet drugs, statins, β-blockers, long-acting nitrates and in the case of concomitant hypertension, diabetes, heart failure or left ventricular systolic dysfunction – ACE inhibitors. Patients with coronary heart disease with concomitant anemia received iron supplements. Patients with concomitant anemia of mild severity received oral iron – iron sulfate 247.25 mg, which is equivalent to 80 mg of iron (II), 1 tablet once a day. Patients with concomitant anemia of moderate severity received intravenous drip in 100 ml of 0.9 % sodium solution, 5 ml of iron (III) hydroxide-sucrose complex with a concentration of 20 mg/ml (100 mg of iron), 3 times a week.

The study of the main cardiovascular events took into account re-hospitalizations due to arrhythmic disorders, progression of heart failure (HF), CAD destabilization during the observed year, as well as the incidence of death from cardiovascular causes. Studies of adverse cardiovascular events were conducted via in-person or telephone interviews with patients and analysis of medical documentation.

Statistical data processing was performed using the software package Statistica 13.0 (StatSoft Inc., USA, No. license JPZ8041382130ARCN10-J). Pearson's χ^2 test was used to compare the clinical features of cardiovascular complaints and to assess the frequency of cardiovascular events depending on the presence of anemic syndrome. To assess the impact of anemic syndrome on the clinical course of coronary heart disease,

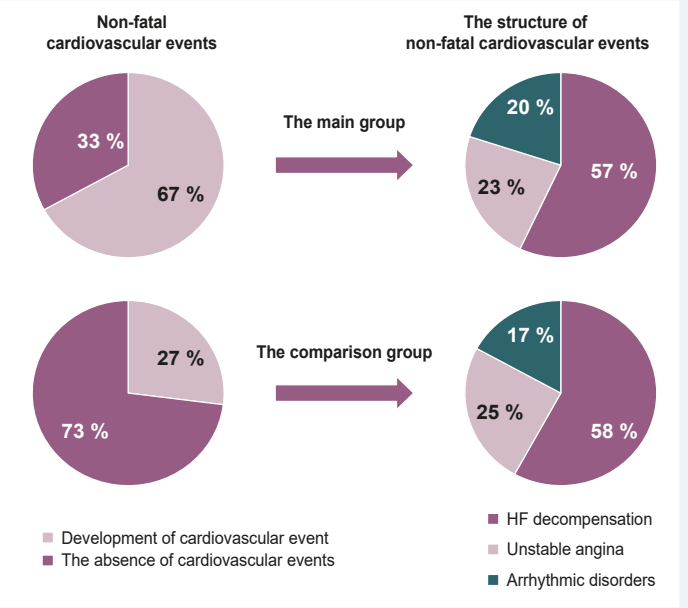

Fig. 1. The structure of non-fatal cardiovascular complications in patients with coronary artery disease depending on the presence of anemia.

Table 1. The main complaints in patients with coronary artery disease

Symptom	The main group, n = 46		The comparison group, n = 45		χ^2
	Absolute amount	%	Absolute amount	%	
Chest pain	41	89	30	65	8.073; P < 0.05
Exertional breathlessness	42	91	36	80	2.374; P > 0.05
Chest discomfort	38	83	32	71	1.694; P > 0.05
Rapid heart rate	35	77	26	57	3.451; P > 0.05
Cardiac rhythm disturbances	6	17	5	11	0.080; P > 0.05

Table 2. Relative risk of adverse cardiovascular events in patients with coronary artery disease with concomitant anemia

Cardiovascular events	RR	95 % CI
HF decompensation	2.376*	1.091–5.174
Unstable angina	2.283	0.629–8.281
Arrhythmic disorders	2.935	0.625–13.781
Fatal outcome	8.804*	1.162–66.685

*: P < 0.05.

Table 3. The frequency of cardiovascular events in patients with coronary artery disease depending on the severity of anemia

Cardiovascular event	Anemia of mild severity, n = 18		Anemia of moderate severity, n = 28		χ^2
	Absolute amount	%	Absolute amount	%	
Non-fatal cardiovascular event	9	50	21	75	3.019; P > 0.05
Fatal outcome	2	11	7	25	1.343; P > 0.05
Combined critical event	11	61	28	100	12.843; P < 0.05

the relative risk was determined with a 95 % confidence interval (CI). The obtained results were considered statistically significant at P < 0.05.

Results

In the main group, the dominant complaints were exertional breathlessness and chest pain – 91 % and 89 %, respectively (*Table 1*). 83 % of patients in the main group noted the appearance of chest discomfort, 77 % – a feeling of rapid heart rate, 17 % – cardiac rhythm disturbances. 80 % of patients in the comparison group complained of exertional breathlessness, and attacks of chest pain or chest discomfort occurred in 65 % and 71 %, respectively. In addition, 57 % of patients in the comparison group complained of a feeling of rapid heart rate, and 11 % – cardiac rhythm disturbances.

Therefore, chest pain attacks occurred significantly more often in patients with coronary heart disease with concomitant anemia compared with patients without anemia (χ^2= 8.073; P < 0.05).

During the year, 42 non-fatal cardiovascular events were noted in patients of both groups, including 24 (57 %) cases of heart failure (HF) decompensation, 10 (24 %) cases of unstable angina and 8 (19 %) cases of arrhythmic disorders. In the main group, the total number of cardiovascular events that required hospitalization of patients was 30 (67 %) against 12 (27 %) of the comparison group (χ^2 = 13.603; P < 0.05). Among the main group patients, 17 (57 %) were hospitalized due to HF decompensation, 7 (23 %) – unstable angina, and 6 (20 %) – arrhythmic disorders. In the comparison group, 7 (58 %) had HF decompensation, 3 (25 %) – unstable angina, and arrhythmic disorders were recorded in 2 (17 %) cases. The development of myocardial infarction in both observation groups was not registered during the year. The structure of non-fatal cardiovascular complications depending on the presence of anemic syndrome is shown in *Fig. 1*.

Fatal outcome was observed in 9 patients of the main group, which was 19.5 % of the total number of patients in the main group, while in the comparison group was recorded for 1 (2.2 %) death during the year (χ^2 = 6.995; P < 0.05). As follows, the presence of concomitant anemia in patients with CAD increases the risk of fatal outcome by 8.8 times (RR = 8.804; 95 % CI 1.162–66.685; P < 0.05).

Therefore, the concomitant anemic syndrome (*Table 2*) is significantly more often associated with the need for re-hospitalization of patients with coronary heart disease and increases its relative risk by 1.96 times (RR = 1.957; 95 % CI 1.230–3.112; P < 0.05). The leading cause of repeated hospitalizations is decompensation of heart failure (χ^2 = 5.365; P < 0.05), the risk of which increases by 2.4 times in the presence of concomitant anemia in patients (RR = 2.376; 95 % CI 1.091–5.174; P < 0.05).

The frequency of cardiovascular events depending on the severity of anemia was analyzed (*Table 3*). It was found, that the presence of anemia of moderate severity in patients with CAD significantly increases the incidence of combined critical events (death or hospitalization for cardiovascular reasons) within the observed period (1

year) (χ^2 = 12.843; P < 0.05). However, there was no statistically significant difference between the incidence of certain types of non-fatal and fatal cardiovascular events depending on the severity of anemia.

Therefore, the concomitant anemia is an independent factor in the worsening of the prognosis in CAD due to clinical symptoms intensification and increasing the frequency of complications.

Discussion

In our study, we found that patients having CAD with concomitant anemia are more likely to have chest pain attacks compared with patients without anemia (χ^2 = 8.073; P < 0.05). This conclusion agrees with other known sources [5]. According to the literature, concomitant anemia in CAD patients affects their life quality, reduces tolerance to physical load, and is an independent negative predictor of prognosis [10–12]. This can be explained by increased myocardial ischemia due to a decrease in blood oxygen concentration at low hemoglobin levels [9].

We established a negative effect of concomitant anemia on the prognosis of CAD patients: the presence of anemia in this category of patients significantly increased the frequency of re-hospitalizations due to decompensation of heart failure. Obtained data agree with the results of the study ATTEMPT-CVD [13], which found that the frequency of cardiovascular and renal events was significantly higher in the group of patients with concomitant anemia than in the comparison group (RR = 1.945; 95 % CI 1.208–3.130; P < 0.05). The MAGGIC study, which included 13 295 patients with heart failure, recognized anemia as an independent prognostic predictor in HF with reduced left ventricular ejection fraction and heart failure with preserved ejection fraction [14].

Also, the study [15] showed that the relative risk of hospitalization for heart failure in groups with iron deficiency was higher compared to the reference group (low iron content: RR = 1.29; 95 % CI 1.19–1.41; functional iron deficiency: RR = 1.25; 95 % CI 1.13–1.37).

In our work, the frequency of arrhythmic disorders in patients with coronary heart disease with concomitant anemia did not differ significantly. However, in the study by Woo-Hyun Lim et al. [16] the risk of developing AF increased by 6 % in patients with anemia and low Hb levels (Hb levels <13 and 13.0–13.9 g/dl in men and <12 and 12.0–12.9 g/dl in women).

In our work, a significant increase in the number of deaths among patients with coronary heart disease with concomitant anemia was recorded (χ^2 = 6.284; df = 1; P < 0.05). According to the study [17], it was shown that low hemoglobin level is an independent predictor of mortality from cardiovascular causes, and anemia is independently associated with overall mortality (RR = 1.90; 95 % CI 1.55–2.33).

In addition, according to the literature, among patients with CAD and concomitant anemia there is an increase in mortality compared with patients with isolated CAD, with anemia being an independent predictor of acute ischemic myocardial damage [6].

A study [18] demonstrated that during 8–36 months of observation, 21.94 % of deaths were recorded in patients with HF with anemia and 9.78 % in patients without anemia. According to Line Davidsen et al. [19], anemia in patients with stable angina is significantly associated with bleeding, the development of acute coronary syndrome and all-cause mortality, even after percutaneous coronary intervention.

Conclusions

1. The features of the clinical course of coronary artery disease with concomitant anemia include a higher frequency of attacks of typical chest pain and a higher frequency of fatal (17.3 %) and non-fatal (40.0 %) cardiovascular events during the year of follow-up compared with patients without concomitant anemia.

2. The presence of concomitant anemia in patients with coronary artery disease increases the risk of fatal outcome by 8.8 times, re-hospitalization by 1.96 times, decompensation of pre-existing heart failure by 2.4 times.

3. The presence of anemia of moderate severity in patients with coronary artery disease is associated with an increase in the incidence of combined critical events by 39 % (death or hospitalization for cardiovascular reasons) during the year of follow-up compared with mild anemia.

Further work. Selecting predictors of adverse cardiovascular events and establishing further criteria for predicting the course of coronary artery disease on the background of concomitant anemia is promising.

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