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DESTABILIZATION OF CORONARY HEART DISEASE: ETIOPATHOGENETIC RISK FACTORS AND PERSONALIZED TREATMENT

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The monograph presents modern data on etiopathogenetic risk factors for the development of coronary heart disease, in particular hyperuricemia and anxiety-depressive syndrome. Modern literary sources from both CIS countries and foreign countries are presented. The studied literature data allowed the authors to consider some molecular genetic factors of predisposition to the development of coronary artery disease. The main etiopathogenetic factors are anxiety-depressive syndrome, asymptomatic hyperuricemia and its connection with genetic markers (genotypes of pro-inflammatory and anti-inflammatory cytokines), as well as pro- and anti-inflammatory cytokines. Based on our own clinical and laboratory studies, the molecular genetic features of the course of unstable variants of angina are described depending on etiopathogenetic risk factors.

ABBREVIATIONS

IL-	Interleukin
HADS-	hospital school
HADS-A-	Anxiety
HADS-D-	I'm depressed
e NOS -	endothelial NO – system
NO -	Nitric oxide
SNP-	Single Nucleotide Polymorphism
AB-	atherosclerotic plaque
AB-	posterior probability
AG -	arterial hypertension
BSU -	asymptomatic hyperuricemia
GGFT-	hypoxanthine guanine phosphoribosyltransferase
DBP -	diastolic blood pressure
DE -	endothelial dysfunction
IHD -	cardiac ischemia
STEMI-	ST segment elevation myocardial infarction
NSTEMI-	non-ST segment elevation myocardial infarction
KA-	atherogenic coefficient
KBZ-	coronary heart disease
KDR -	end diastolic size
KSR -	end systolic size
LP -	left atrium
LT-	personal anxiety
MK -	uric acid
NS-	unstable angina
AMI -	acute myocardial infarction
OKS-	acute coronary syndrome
PIX-	post-infarction cardiosclerosis
GARDEN -	systolic blood pressure
SS -	stable angina
CVD -	cardiovascular diseases
SSS -	the cardiovascular system
ST-	situational anxiety
ADS-	anxiety-depressive syndrome
TrT-	traditional therapy
UMK-	uric acid level
LVEF-	left ventricular ejection fraction
FC -	functional class
TNF-α-	tumor necrosis factor
CHF -	chronic heart failure
Heart rate -	heart rate
ET–1 -	endothelin – 1

PREFACE

Coronary heart disease (CHD) has recently been considered as a polyetiological disease with a pronounced psychosomatic determinant. Today, there are quite a lot of theories and models of the emergence of psychosomatic factors and methods of their classification, which show that it is impossible to separate in isolation mental and physiological constellations that could cover the entire spectrum of manifestations in this type of disease. However, all hypotheses ultimately boil down to the fact that psychological maladjustment is one of the global factors of psychosomatic pathology. In addition, one of the main points in the development of diseases of the circulatory system is the dysfunction of the vascular endothelium, the participation of systemic inflammation, immune activation in the development and progression of cardiac pathology, which determine an unfavorable prognosis and high cardiovascular risk. It is not denied that the listed disorders in the body are based on psychosomatic risk factors, which have not been sufficiently studied and require further consideration.

As IHD develops and progresses, the synthesis of pro-inflammatory cytokines, such as tumor nectosis factor (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), etc., increases, which in turn determine development of LV myocardial remodeling.

According to recent literature, the heart often becomes the organ where the damaging effects of stress are realized, as a result of which psychosomatic factors have a significant impact on the occurrence and progression of CVD. These include: depression, anxiety, individual personality traits, social isolation and stress. Numerous studies have shown that depression is most common among patients with unstable angina, hypertension, myocardial infarction and stroke. The causes of depression in patients with coronary heart disease are multifactorial and also include genetic predisposition, stress, biological and psychological negative factors.

The importance of studying the increase in the level of uric acid in the blood and its relationship with various variants of the clinical course of IHD and various polymorphic types of the URAT1, GLUT9, TNF-α genes is increasing, which in turn allows us to consider the genotypes of these genes as additional markers of an increased risk of developing the disease in the Uzbek population . The influence of polymorphism of the studied genes on the progression of unstable variants of angina was revealed. At present, it is

not completely clear what underlies the psychosomatic phenomenon in patients with coronary artery disease. Various theories are discussed that could explain the “intersection” of different aspects of pathogenesis in these nosological forms. One of the main pathogenetic aspects studied is the “cytokine” hypothesis. This hypothesis is based on the assumption that anxiety-depressive syndrome manifests itself with increased secretion of proinflammatory cytokines.

In recent decades, considerable interest has been given to various variations in genes that encode enzymes and are involved in the metabolism of homocysteine and folic acid. Polymorphisms of the methionine synthetase (MTRR) A2756G, methionine synthetase reductase (MTRR) A66G and betaine homocysteine methide transferase (BHMT) G742A genes are involved in pathogenesis and increase the risk of its development, which once again proves the influence of anxiety-depressive syndrome on the mechanisms of IHD. However, according to the literary sources of recent years, we have not seen data on the relationship between several psychosomatic factors in the progression of coronary heart disease, in particular between anxiety-depressive syndrome, hyperuricemia and cytokine imbalance.

These data make relevant research aimed at revealing the relationship between various pathogenetic links in the formation and progression of coronary artery disease for the development of new approaches to personalized therapy.

CHAPTER 1.
Literature review

Modern views on the mechanisms of progression of ischemic heart disease

Today, cardiovascular mortality is still one of the most pressing problems in global cardiological practice. In 2018, it amounted to 17.3 million people and, according to a number of forecasts, will only grow and amount to 23.6 million people by 2030 [1, 2]. Based on statistical data for 2018, acute myocardial infarction (AMI) is often a manifestation of coronary heart disease (CHD), and angina pectoris is the first symptom of the pathology in approximately 50% of patients [1].

The modern algorithm for diagnosing IHD includes both simple and well-known instrumental research methods, as well as relatively new versions of instrumental, biochemical and molecular genetic diagnostic techniques. Despite the widespread use of existing risk scales in practical cardiology, the forecast of non-fatal and fatal cardiovascular events is often given untimely.

In everyday clinical practice, the algorithm for verifying coronary artery disease, as a rule, begins with a stress test (bicycle ergometry or treadmill test) and, with an undoubted positive result, ends with coronary angiography (CAG). According to various guidelines and textbooks, the specificity and sensitivity of the screening stress test varies from 65 to 85%. When

In the event of a questionable result of primary stress testing, it is customary to use at least one of the imaging techniques: myocardial perfusion scintigraphy with stress, stress echocardiography (stress EchoCG) and multislice computed tomography with contrast of the coronary arteries (MSCT with contrast CA). However, the sensitivity and specificity of these studies are also not very high and, according to modern domestic and foreign literature, do not exceed 85%. These methods “on the way to the gold standard” (CAG) are quite expensive, which, combined with their low

specificity, makes it necessary to search for new non-invasive and affordable methods for examining patients at risk of coronary artery disease.

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Imaging techniques that are used in cardiological practice when the result of a stress test is questionable are stress myocardial perfusion scintigraphy, stress echocardiography and MSCT with contrast enhancement of the coronary artery.

Myocardial perfusion scintigraphy with stress is usually performed after myocardial scintigraphy at rest, which makes it possible to assess the dynamics of isotope distribution in the “rest” and “stress” phases. Comparison of these phases makes it possible to identify defects in isotope

accumulation, indicating either a previous AMI (a persistent accumulation defect is already present in the “rest” phase) or existing stress-induced myocardial ischemia (the accumulation defect appears only in the “stress” phase).

Similarly, in the presence of stress-induced myocardial ischemia during stress echocardiography, myocardial contractility deteriorates. By assessing the dynamics of contractility before the load and after the load test, it is possible to identify areas of decreased contractility, making the choice of a further strategy in favor of CAG. Moreover, in case of insufficient visualization during stress echocardiography, it is possible to use a contrast agent, which makes the sensitivity of the method much higher.

To verify IHD, stress echocardiography with stress is used. If coronary artery disease has already been previously verified according to coronary angiography or in the presence of a history of AMI, the question often arises about the advisability of myocardial revascularization. It is clear that revascularization is inappropriate in the absence of viable myocardium, therefore, it is the biphasic response to the dobutamine test (stress echocardiography with dobutamine) that suggests the need for a certain type of revascularization. In the absence of viable myocardium, the patient is indicated for lifelong drug therapy.

Relationship between asymptomatic hyperuricemia and cytokine imbalance in the pathogenesis of cardiovascular complications

For a long time, uric acid (UA) was considered as an inert end product of purine base catabolism, but in recent decades, conclusive evidence has accumulated that chronic asymptomatic hyperuricemia (HU) is not only associated with the deposition of monosodium urate crystals in tissues and gout, but is an independent risk factor development of arterial hypertension (AH), metabolic syndrome, chronic kidney disease (CKD) and cardiovascular diseases (CVD) [1]. The importance of asymptomatic HU for the risk of developing CVD is reflected in the inclusion of MK among the risk factors for the development of hypertension in the ESC/ESH recommendations (2018) and the recommendations of the Russian Society of Cardiology (2020) [2, 3].

It has been established that the average general population level of sUA in the blood serum is gradually increasing, which is due to changes in diets, an increase in body mass index and an increase in life expectancy both in the general population and among patients with CKD and

congestive heart failure (HF) [4]. The prevalence of pathological conditions associated with HU is increasing, which takes this problem beyond rheumatological diseases and requires a broad approach taking into account the risks of developing CVD and kidney diseases. It should be noted that despite the active study of the problem of asymptomatic HU, the most important aspects still remain the subject of debate: what level of serum uric acid is considered hyperuricemia; Whether HU is an independent predictor or just a marker of CVD risk are questions that require answers and continue to be studied [1]. Asymptomatic HU is understood as an increase in serum UA levels in the absence of symptoms of deposition of monosodium urate crystals in tissues. There are still no uniform criteria for diagnosing this condition. Statistically, GU is defined as a level of serum sUA above two standard deviations compared to the average level of a healthy population; physico-chemically - the concentration of UA in the blood serum is more than 416 μmol/l or 7 mg/dl when measured by enzymatic methods in a standard laboratory [5], pathophysiologically - the concentration of UA exceeds the solubility point at a temperature of 37 ° C when measured by enzymatic methods in a standard laboratory (6.4 or 6.8, or 7 mg/dl, according to different authors) [1, 6, 7]. The definition of HU varies widely across epidemiological and clinical studies, making comparisons of results difficult. Many studies have used a serum UA level of ≥360 μmol/L (≥6 mg/dL) in women and ≥420 μmol/L (≥7 mg/dL) in men as the cutoff value for GU [8–10]. The same values are used in the Russian recommendations for hypertension in 2020 [3]. Finally, a number of researchers propose using a single serum sUA level ≥360 μmol/L as a diagnostic criterion, based on the target sUA value for the treatment of gout [1, 6, 11]. Associations of GU with the development of hypertension have been studied for more than 100 years. At the end of the 19th century, it was suggested that increased levels of sUA may be one of the causes of increased blood pressure [31]. To date, a large amount of data has been accumulated to confirm this hypothesis. Analysis of the results of the Brisighella Heart epidemiological study (n=619) showed that the prevalence of hypertension clearly correlated with quartiles of sUA levels (56.3, 36.4 and 23% in the 4th, 3rd and 2nd quartiles, respectively; $p<0.05$) . Similarly, the incidence of metabolic syndrome and intima-media thickness increased [32]. Numerous observational studies demonstrate an increase in the relative risk of developing hypertension as serum UA concentrations increase, and this association is independent of

the presence of traditional risk factors [33, 34]. In an analysis of the EURICA study on primary prevention of CVD (5220 patients with hypertension), it was shown that the level of sUA in the blood serum was associated with resistance of hypertension to treatment with antihypertensive drugs along with some other factors (relative risk - RR 1.16 at 95% confidence level interval – CI from 1.08 to 1.14; p=0.001) [35], similar data were obtained in the analysis of the Brisighella Heart study [36]. The results of the Italian epidemiological study PAMELA are indicative, in which for the first time the measurement of sUA levels was included in the algorithm for assessing the risk of developing CVD: after full correction for prognostically significant factors, it was shown that GU was a reliable independent predictor of new cases of hypertension identified during ambulatory blood pressure measurements: RR 1 .34 with 95% CI from 1.06 to 1.7 for home blood pressure monitoring (HBP) and RR 1.29 with 95% CI from 1.05 to 1.57 for 24-hour blood pressure monitoring (ABPM), and also a predictor of death both from all causes and from CVD [37]. Large meta-analyses performed in recent years confirm independent associations of GU with new cases of hypertension: in the analysis of R.S. Grayson et al. [38] (18 studies, n=55607, initial normal blood pressure) the risk of developing hypertension in HU increased by 41%; in the analysis of J. Wang et al. [39] (25 studies, n=97824) the risk increased by 18%. Key studies demonstrating the association of GCs with the development of hypertension (adapted from [12]). It should be noted that HU is more common in essential hypertension than in white coat hypertension or secondary hypertension; in addition, it is common among individuals with high normal blood pressure or microalbuminuria [12].

Many studies demonstrate associations of HU with asymptomatic target organ damage: increased intima-media thickness of the carotid arteries [32, 46], pulse wave velocity [46, 47], decreased ankle-brachial index [48], increased size of the left atrium [49]. A long-term analysis of the PAMELA study showed that serum sUA level is a predictor of an increase in left ventricular (LV) myocardial mass index from normal to hypertrophy: the risk of developing LV hypertrophy in the highest tertile of sUA concentration was 96% higher than in the lowest [50].

The association of HU with a variety of micro- and macrovascular complications makes it an important component of the overall risk of developing CVD [51]. Many studies demonstrate the independent prognostic role of elevated UA levels in the development of adverse CVD

outcomes. In particular, independent associations of serum UA levels with total and/or CVD mortality were shown in an analysis of the NHANES database [52], the PAMELA study [37], and an analysis of the PreCIS database [53]. Two large cohort studies from Taiwan showed a J-shaped relationship between GU levels and mortality in both the general population and among patients over 65 years of age, likely reflecting the above-mentioned “uric acid paradox” [54, 55]. . A similar J-shaped relationship between sUA levels and outcomes was demonstrated in the FREED study (1070 patients over 65 years of age with HU and a high risk of developing CVD): optimal risk reduction was observed in the group with sUA concentrations in the range of 5–6 mg/dL, and excessive reduction it slightly increased the chance of adverse outcomes [56].

Analysis of the Rotterdam study (n=4,385) confirmed the independent associations of HU with the risk of MI and stroke [57]. According to a large Swedish registry (n = 417,734 patients without a history of CVD), even a moderate increase in serum UA concentrations increases the risk of myocardial infarction (MI), stroke and congestive HF [58]. The results of the large epidemiological study URRAH (n=23,467) also confirmed the independent associations between serum UA levels and the risk of fatal MI [59]. In the work of F. Crosta et al. [60] showed that the level of sUA directly correlates

with the presence and size of lacunar cerebral infarctions, including asymptomatic ones. A large retrospective analysis of patients with symptomatic HF found that HU was associated with the risk of HF hospitalization or death [61]. In a Russian study that included 172 patients with HF, HU occurred in 55.8% and correlated with the severity of HF according to NYHA and the level of natriuretic peptide [62]. The correlation between the severity of HF and HU was demonstrated in earlier Russian studies [63].

Despite the fact that many prospective studies demonstrate the association of HU with the risk of increased blood pressure, resistance to antihypertensive therapy, the development of CKD, type 2 diabetes and metabolic syndrome [10, 36, 38, 64, 65], there are studies that challenge these positions. Thus, the Framingham study did not reveal independent associations between the level of sUA and the incidence of CVD [66]. A number of studies using Mendelian randomization also do not confirm the independent effect of HU on the risk of developing CVD and diabetes [67–70]. However, most recent studies, including some other Mendelian-type studies [71, 72] and the results of recent meta-analyses [73–75],

confirm the causal relationship between HU and the risk of developing CVD, although the opposite effect of CVD and metabolic disorders an increase in sUA levels cannot be completely excluded.

The role of psychoemotional disorders on the course of unstable angina

Data from various studies show the prevalence of depression among the population of older age groups, which ranges from 9 to 30% [14, 50, 58]. In particular, depression is more common among patients with coronary heart disease (CHD) than among the general population, amounting, according to various sources, to 18–65% [88, 89]. Various studies have identified several important risk factors for the development of mood disorders in somatic diseases.

So, thanks to the results of S.L. Solovyov, the influence of biological and social factors accompanying the formation of aggression and aggressive behavior was established on models of healthy patients with endogenous mental diseases (for example, schizophrenia), patients with psychosomatic diseases (for example, coronary heart disease). The study reveals a direct link between anxiety in patients with coronary heart disease and a tendency to overcontrol emotions, which are associated with increased emotional stress. In addition, the important role of biological factors is shown, such as the presence of endogenous mental diseases that determine the formation of destructive forms of anxiety in conditions of limited ability to socialize a person. Several psychological factors in the formation of anxiety in healthy people with coronary artery disease have been identified, namely: egocentrism, emotional lability, low level of empathy, difficulties in social relationships [20, 27, 39, 42].

In the study by Bisaliev R.V. The main attention is paid to the psychological factors of the clinical dynamics of coronary heart disease, specific to each clinical form of the disease, associated with transient strokes:

✓ among patients diagnosed with coronary artery disease, painless ischemia, distinct relationships were demonstrated by tension, suppressed aggression, self-harm and low levels of ego-defensive reactions;

✓ among patients with stable clinical symptoms of coronary heart disease, myocardial infarction was more often associated with physical, indirect and verbal aggression, a decrease in the value of communication and interaction, resentment, and a decrease in the level of personal responsibility;

✓ in patients with coronary heart disease, a special relationship was demonstrated: the severity of defensive reactions of the ego, negativity, the need for love and acceptance, depression, withdrawal from reality, and feelings of guilt.

In addition, the results of recent studies do not exclude the role of immune inflammation in the occurrence and progression of affective disorders of the anxiety-depressive spectrum in coronary artery disease. The association of coronary heart disease and anxiety disorders has become more and more common in recent years and increases the mortality of such patients by 2-4 times. A striking illustration of this phenomenon was the development of the so-called "cytokine" hypothesis of depression [39, 51, 57, 58], which indicates the influence of inflammatory cytokines on the formation of depressive disorders. According to this model, the peripheral immune response induces the synthesis or appearance of cytokines and their receptors in the brain parenchyma, which can lead to a chronic local inflammatory process in brain regions responsible for symptoms of depression.

Research by Kozlov S.N. and his co-authors (2010) show that when comparing cytokine inflammatory markers in patients with coronary heart disease, depending on the presence or absence of a depressive-anxiety state, there is an increase in the level of pro-inflammatory interleukins IL-6 and TNFα in patients with concomitant pathology. Thanks to the data obtained in this study, it is possible to explain the reason for the possible high mortality in patients with coronary artery disease in the presence of mood disorders. Increased levels of the pro-inflammatory cytokine IL-6 have been reported in patients with coronary artery disease in combination with anxiety disorders. In patients with coronary artery disease combined with depressive disorders, the levels of not only IL-6, but also TNFα were significantly higher. In patients with ischemic disease associated with depression and anxiety, TNFα levels were significantly higher [39].

It should be noted that not only major depression, but also mild depression has a negative impact on the prognosis.

Heart Failure Adherence and Delay Trials (HART- Heart Failure Adherence and Retention Trial) showed that depression is a strong predictor of readmission. The longest follow-up study, conducted over 12 years at Duke University Medical Center (USA), found that depression was associated with increased all-cause mortality, independent of traditional risk factors. As a result, the survival rate of patients was inversely related to the severity of depression. Unfortunately, the relationship between symptoms

of depression and impaired left ventricular systolic function remains poorly understood [59, 88, 89].

In elderly people with isolated arterial hypertension (IAH) with symptoms of affective disorders, more pronounced structural remodeling of the myocardium is observed - its remodeling, an increase in the percentage of eccentric LV hypertrophy and latent systolic dysfunction. These structural changes depend to some extent on the duration of the disease, the degree of increase in systolic blood pressure, and the presence of depression and may have an unfavorable prognostic value. Clarification of these circumstances contributes to a deeper analysis of the pathogenetic links of this problem and optimization of treatment, which is of great practical importance [50, 59, 71, 81, 89]. In the presence of depression, patients often experience autonomic symptoms such as tachycardia, cardialgia, constipation, blood pressure, dyspeptic disorders, headaches, sleep disorders and others. The severity of emotional disorders varies. In mild cases, patients complain of low mood, depression, sadness, accompanied by a tendency to doubt, uncertainty about their future, mental and physical fatigue. In severe cases, a painful experience of severe melancholy and despair occurs, a feeling of hopelessness, meaninglessness in life ("vital melancholy") [71, 92, 128].

According to a study by F.I. Belyalov et al. [14], even in patients diagnosed with unstable angina, the decrease in quality of life is associated to a greater extent with anxiety and depression than with somatic factors (changes in the electrocardiogram, levels of troponin T, glucose and cholesterol), this explains the deterioration in the quality of life of patients with heart failure [8 , 177].

And not only in patients with heart failure, but in studies by T. Yu. Khabarova and her co-authors, the influence of anxiety and depressive disorders in patients with cerebral stroke was studied.

The following methods were chosen to identify depressive and anxiety disorders [11, 12]:

Hamilton Depression Scale - HDRS (M. Hamilton);

Zung Self-Rating Depression Scale (Zung WW Kv Durham N. C);

Hamilton Anxiety Rating Scale (HARS)

Spielberger Reactive and Personal Anxiety Scale (CD Spielberger).

Luscher color test [58].

The results of the study showed the following: - moderate depression in 35.2%, high depression in 23.3%, mild depression in 41.5%, absence of depressive disorders - 2.6%; low level of anxiety in 13.4%, moderate level

of anxiety - 51.55%, high level of anxiety - in 35.05% of patients with stroke. Before psychocorrectional measures, patients with stroke were characterized by the following characteristics: vulnerability, irritability, incontinence, anxiety, low self-esteem, self-criticism, and lack of confidence in their capabilities.

Data from modern literature show that to identify anxiety-depressive disorder, the use of the HADS scale is most appropriate, which makes it possible to identify the identified symptoms in a somatic hospital.

The relationship between hyperuricemia and psychoemotional disorders in patients with coronary artery disease

In recent decades, one of the global problems of medical, social and economic problems of modern society is the combined course of cardiovascular diseases with metabolic disorders, and the addition of psychological disorders to them greatly increases the risk of developing macrovascular atherosclerotic diseases. In patients with coronary heart disease associated with hyperuricemia and other metabolic disorders, depressive disorders are quite common. However, the relationship between hyperuricemia and depression is not fully understood. Many studies have shown that with hyperuricemia, the risk of developing depressive disorders increases with age and is more common in women than men, as well as in patients with hypertension, stroke and coronary heart disease. Nonsteroidal anti-inflammatory drugs and drugs for the treatment of hyperuricemia have shown positive dynamics in the treatment of depressive disorders. Metabolic disorders such as elevated body mass index (BMI), central obesity, hyperlipidemia, hyperglycemia and hyperuricemia are closely associated with depressive disorders and anxiety. In addition, patients with mood disorders have a higher incidence of metabolic syndrome than the general population, which has a significant impact on the quality of life of depression.

Hyperuricemia is common among patients with psychosomatic disorders, and patients with hyperuricemia are 1.8 times more likely to develop psychosomatic disorders. Purinergic dysfunction plays a major role in the development of depression, including studies of genetic alterations and peripheral purinergic biomarkers and neuroimaging studies. B. Sperlag et al. (2012) reviewed the entire literature to explain the effects of the purine receptor P2rx7 and its activation on mood, which are associated with glutamate-releasing behavior and changes in neuronal plasticity in depressive disorders. Gout and nonsteroidal anti-inflammatory drugs

(NSAIDs) may have interactive effects on depression, and NSAIDs may even mediate the association between gout and depression. The inflammatory immune response is involved in the pathogenesis of hyperuricemia with high levels of C-reactive protein, the number of neutrophils in the blood and the level of cytokines such as IL-1, IL-2, IL-6, as well as TNF-α. NSAIDs are widely used in the treatment of acute gout. Depressive disorders are known to be associated with an altered and dysregulated immune system, including changes in serum protein phase and cytokines [103, 135].

The hypothesis of a role for cytokine imbalance in depression is important because it influences central serotonin levels, microglial activation, the hypothalamic-pituitary-adrenal (HPA) axis, and neuroplasticity. NSAIDs such as acetylsalicylic acid (ASA) are considered one of the oldest and best known drugs in the world, which irreversibly inhibits cyclooxygenase-1 and -2 and thereby reduces the level of the pro-inflammatory cytokine TNF-α and IL-6 [27,161].

A sufficient number of clinical studies have been conducted in which allopurinol was used as additional therapy in patients with bipolar disorder. The results of a meta-analysis demonstrated the positive efficacy of allopurinol as purinergic modulators as adjuvant therapy for bipolar mania compared with placebo [27].

Today, one of the relevant and modern concepts in medicine is the level of uric acid and the characteristics of the psycho-emotional sphere in patients with coronary heart disease. At the same time, risk stratification in these patients provides a general strategy for the prevention, treatment and prognosis of IHD, taking into account the personal, medical and social characteristics of the patient [29, 191, 202]. Research by I.V. Davydovsky confirmed that hypertension is a lifestyle disease of modern man. In this aspect, arterial hypertension should be considered as a psychosomatic problem, which essentially predetermines the solution of issues of the relationship between somatic, psychological, social unity from the point of view of modern understanding and vision of psychosomatics [55, 201]. According to 29 results of the multicenter prospective study COORDINATA (2005), depressive symptoms worsen the prognosis in patients with hypertension and coronary heart disease. A number of epidemiological studies conducted on the basis of multivariate analysis have successfully demonstrated that psychological factors, as precursors of CVD, play a greater role in the development and progression of the disease than

classical risk factors - hypercholesterolemia, smoking, physical inactivity [55, 203].

In addition, Bekezin V.V. in his studies (2012) [8, 14, 55] noted that patients with “true” hypertension and obesity, in contrast to patients with “white coat” hypertension, have higher rates of anxiety and depression. Higher levels of anxiety and depression in obese patients with “white coat” hypertension, compared with patients in the control group, require psychological correction before they develop “true” hypertension.

Unfortunately, the relationship between anxiety-depressive syndrome and other risk factors, hemodynamic state, and endothelial dysfunction in patients with coronary artery disease with hyperuricemia have not been sufficiently studied, which indicates the urgency and need for a detailed study of this problem.

Genetic predisposition to stress factors taking into account the immune response in ischemic heart disease

Among patients with coronary artery disease, the incidence of anxiety-depressive syndrome (ADS) is quite higher than other concomitant diseases, which contributes to the deterioration of the course of the underlying disease and the patient's quality of life. It is assumed that such comorbid conditions are based on common pathogenetic processes, which include the inflammatory process. According to many researchers, inflammatory processes are involved in the pathogenesis of both IHD [151, 177, 203] and depression [81], i.e. in patients with coronary artery disease in comorbidity with ADS, an increase in the immunoregulatory induction of inflammatory processes is noted.

To date, a hypothesis has been put forward about the role of cytokine imbalance in the development of depression in cardiovascular diseases, based on data from a prospective study, which showed that high levels of white cells and CRP in the blood of patients after the development or exacerbation of cardiovascular diseases are important predictors of further deterioration ADS [51, 157].

According to the results of a study by Golimbet V.E et al. [20] it is clear that the IL -4 polymorphism (C-589T) is associated with depression, as well as ischemic heart disease. But many major studies have proven that the IL -4 polymorphism (C-589T) is more likely to be associated with ischemic heart disease than with depression. For example, a study of two

independent groups of patients from different regions of Europe who suffered myocardial infarction revealed an increase in the frequency of the CC genotype compared to the control group. But in the studies of Golimbet V.E et al. [20] failed to detect an association of the TNF - α and CRP genes with depression, although data from some immunological studies indicate that such a connection may exist [57].

A.B. Smulevich et al. [70] proposed a model of depression that allows us to expand the search for the biological determinants of this condition, taking into account ideas about the complexity of its etiology and pathogenesis. According to this model, genetic predisposition makes a major contribution not only to the neurotransmission system, but also to the impact of stress factors, taking into account the immune response.

In the first W. Smith [171] established a connection between depression and cytokine imbalance (including IL -1). By injecting animals with IL -1, IL -6, TNF -α, he revealed the development of disorders such as depressive disorders. When volunteers were administered an inducer of the synthesis of pro-inflammatory cytokines, a “behavioral disorder” was also observed, in the form of disturbances in emotional-volitional and vital functions.

According to V. Valkanova et al. [193] in patients with anxiety-depressive syndrome, the level of IL-6 is slightly higher than normal levels. S. Rudolf et al . [165] consider an increased level of IL-6 to be one of the objective indicators of the presence of depressive disorder, but we are talking about atypical forms of depression. R. Haapakoski et al . [126] in their study obtained data that IL-6 is directly associated with depression, but no connection between IL-1beta and depression was found. However, E. L. Vieira et al . [195], on the contrary, found a direct relationship between IL-1beta and depression and a significant difference in indicators with a control sample without depression. In some Russian studies, depression is associated with the TNF gene polymorphism at the G238A locus: the heterozygous G/A variant is detected in a larger number of patients with depressive symptoms [83]. GWAS studies have also found an association between individual polymorphisms and depressive disorders, but the phenotypic data are extremely contradictory [48].

Thus, TNF -α plays an important role in the pathogenesis of depression, since it is this cytokine that is involved in maintaining homeostasis and regulating the blood-brain barrier in the central nervous system. Violation of the permeability of the blood-brain barrier during ADS

may be the reason for the penetration of inflammatory agents into the brain [48].

Within the framework of the above, it can be assumed that the prognosis of cardiovascular diseases in comorbidity with ADS and at the molecular genetic level is also unfavorable. It is assumed that in such cases, carriers of variations in the structure of genes for inflammatory markers associated with changes in the secretion or expression of corresponding protein products may have a higher risk of depression. But to date, the association between genes that are involved in the inflammatory process in coronary artery disease in comorbidity with ADS has not been sufficiently studied.

In conclusion, it should be noted that despite the research carried out based on the literature review of recent years, the study of pro-inflammatory cytokine genes, as well as the search for correlations between clinical (taking into account phenotypes) and genetic features, taking into account the evolution of modern ideas about the etiopathogenesis of IHD in comorbidity with depression, is relevant, an insufficiently studied problem.

§1.6. Features of treatment of patients with unstable angina with comorbid pathology

Anxiety and depressive disorders are quite often associated with coronary artery disease. Patients with this diagnosis are characterized by emotional instability, social maladjustment, and an increased risk of developing more severe somatic and psychological disorders. Therefore, it is necessary for such patients to provide both pharmacological assistance (use of antidepressants) and non-pharmacological assistance (psychotherapy, dosed physical activity). Treatment of depression with pharmacological drugs not only reduces clinical symptoms, but also significantly reduces the severity of subclinical inflammation, which can be effective in the treatment of not only anxiety-depressive disorder, but also coronary heart disease.

At the moment, there is a large selection of antidepressant drugs. In clinical practice, frequently used classes of antidepressants are as follows :

- ✓ tricyclic antidepressants (TCAs),
- ✓ selective serotonin reuptake inhibitors (SSRIs),
- ✓ serotonin and norepinephrine reuptake inhibitors (SNRIs),
- ✓ monoamine oxidase inhibitors (MAO) [58, 61].

The choice of an antidepressant is carried out taking into account the spectrum of its psychotropic activity and the predominant symptoms

(anxious or adynamic), the patient's somatic condition and contraindications to the use of the drug, concomitant drug therapy prescribed due to the presence of chronic somatic diseases, and possible undesirable drug interactions [61].

The favorable relationship between the effectiveness and safety of SSRI drugs allows them to be considered as the drugs of choice in geriatric practice.

In addition, SSRIs replaced tricyclic antidepressants and successfully entered the standard of treatment for depressive conditions. These include drugs such as citalopram, paroxetine, fluoxetine, fluvoxamine, sertraline, etc. The mechanisms of action of drugs in this group are inhibition of the reuptake of serotonin into presynaptic endings with subsequent improvement of impulse transmission to postsynaptic endings. This process occurs due to inhibition of the function of the serotonin transporter. At the same time, drugs of this group have practically no effect on other neurotransmitters, which is why they successfully received their name.

However, recent literature sources speak of the positive effect of drugs such as antibodies to protein S 100, which have an antidepressant effect, and today the drug Divaza has managed to show itself in the treatment of patients with coronary artery disease with cognitive disorders [6, 54].

Divaza is a drug that consists of release-active antibodies to protein S 100 and endothelial NO synthase and is characterized by nootropic, vasoactive, antioxidant, angioprotective and antihypoxic effects. Studies conducted in recent years have shown high effectiveness in reducing the main symptoms of cerebrovascular disorders. O.A. Shavlovskaya et al (2017). [6 , 54] conducted an observational program and assessed the effectiveness and safety of divaza, prescribed for the purpose of correcting emotional disorders. Positive dynamics in the severity of anxiety, asthenia and emotional lability were noted after 4 weeks. divase therapy ($p < 0.05$). This drug reduces the content of homocysteine in the blood, which contributes to multi-vessel stenosis of coronary atherosclerosis and lesions of peripheral arteries and increases the risk of developing coronary artery disease, heart attack, and stroke.

Thus, the prescription of divase for the treatment and prevention of ADS in NS is justified due to the pathogenetic effect on endothelial dysfunction and the high potential of the evidence base.

Thus, literary sources indicate the relevance of this work and the need for further study of the problem of anxiety-depressive syndrome in patients with coronary artery disease. In addition, it is necessary to conduct early screening of patients with coronary artery disease for the presence of depression for timely treatment. A timely approach to the treatment of patients with NS will make it possible to predict the progression of the disease, which will improve the results of treatment of IHD and improve the quality of life of patients in this category.

The results of a study of the latest data from the scientific literature show that GU contributes to the rapid development of anxiety-depressive syndrome in patients with NS and treatment of patients with GU should be aimed not only at reducing the level of sUA, but also at eliminating the main manifestations of MS, primarily hypertension, IR, GI and hyperlipedemia.

Until now, there is no clearly formulated and generally accepted classification of metabolic drugs that would be effective when included in complex therapy of patients with HU combined with MS, IR, HI and CVD. In this regard, the search and study of effective metabolic drugs and their rational combinations with basic drugs for the treatment of CVD continues [77, 187, 188].

The importance of using specific uricosuric drugs in patients with cardiovascular pathologies and asymptomatic hyperuricemia requires an evidence base in randomized trials [7].

However, scientists insist that correction of the level of uric acid in the blood must begin with alkalizing the body, namely with potassium citrate or potassium bicarbonate, vitamin C, but not with allopurinol [34, 55, 100].

In recent years, febuxostat has been frequently used. This drug is a non-purine drug that has a dual way of inhibiting xanthine oxidase, namely inhibition of oxidized xanthine oxidase and reduced xanthine oxidase, which leaves no bypass for the formation of xanthine from hypoxanthine, unlike allopurinol. The drug was approved in 2009 for the treatment of gout. The drug is metabolized primarily in the liver, with allopurinol being excreted primarily by the kidneys. Therefore, febusostat can also be prescribed to patients with impaired renal function [7, 34].

The APEX study, which included 1067 patients with gout with serum UA levels greater than 480 μmol/L, showed a statistically significant advantage of febuxostat at a dose of 120 mg once daily compared with allopurinol at a dose of 300 mg. Since 76-94% of patients receiving febuxostat achieved target values, and only 41% of patients taking allopurinol.

EXCEL, CONFIRMS, and FOCUS studies also confirmed both the effectiveness of the drug febuxostat in relation to the clinical manifestations of gout, in contrast to allopurinol, and the beneficial effect on indicators of kidney function. There are no data on fertility disorders or teratogenic effects on the fetus. The effect of the drug occurs quite quickly, which makes it possible to re-determine the concentration of uric acid after 2 weeks. The goal of treatment is to reduce uric acid concentrations and maintain them at <6 mg/dL (357 μmol/L) [75, 79].

Thus, the use of febuxostat is important in the prevention and treatment of cardiovascular disorders. The results of the studies indicate the effectiveness of febuxostat in conditions such as angina pectoris, atherosclerosis, ischemic heart disease, ischemic heart disease in combination with hyperuricemia, heart failure, intermittent claudication. In addition, it is possible that febuxotate also has a beneficial effect on the level of cytokines, which will lead to a reduction in the inflammatory process and an improvement in the prognosis of CVD.

CHAPTER 2.
Modern concepts of coronary artery disease, risk stratification and genetic architecture

Modern ideas about coronary heart disease

Ischemia is defined as insufficient blood supply to a specific area due to blockage of the blood vessels supplying that area. Ischemia means that an organ (such as the heart) is not receiving enough blood and oxygen. Coronary heart disease is myocardial damage caused by impaired coronary circulation as a result of an imbalance between coronary blood flow and the metabolic needs of the heart muscle. In other words, the myocardium needs more oxygen than the blood supplies it with. IHD can occur acutely (in the form of myocardial infarction), as well as chronically (recurrent attacks of angina). Although the narrowing can be caused by a blood clot or narrowing of a blood vessel, it is most often caused by the accumulation of atherosclerotic plaques in the lumen of the vessel, which is called atherosclerosis. When blood flow to the heart muscle is completely blocked,

heart muscle cells die, which is called a heart attack or myocardial infarction (MI). Most people with early (less than 50%) CAD do not experience symptoms or blood flow restriction. However, as atherosclerosis progresses, especially if left untreated, symptoms may occur. They most often occur during exercise or emotional stress, when the demand for oxygen carried by the blood increases [196].

The discomfort that occurs when there is a lack of oxygen in the heart muscle is called angina. This is a clinical syndrome characterized by discomfort in the chest, jaw, shoulder, back or arms, which is usually worsened by exercise or emotional stress and quickly resolves with rest or nitroglycerin. Angina usually occurs in patients with coronary artery disease, but can also occur in people with valvular heart disease, hypertrophic cardiomyopathy, and uncontrolled hypertension. Infrequently, patients with normal coronary arteries may experience angina associated with coronary spasm or endothelial dysfunction (Gibbons et al., 2002).

Angina is classified using the Canadian Cardiovascular Society (CCS) scheme, which classifies angina or its equivalent (eg, dyspnea on exertion) based on a description of the level of activity that causes symptoms. Class I is defined as angina that occurs with heavy, rapid, or prolonged exertion at work or leisure, but not with normal physical activity. Angina develops with significant, accelerated or particularly prolonged stress (effort). Class II is defined by angina that slightly limits normal activity, such as angina that occurs when walking or quickly climbing stairs, walking uphill, walking or climbing stairs after eating; in the cold or wind; with emotional stress; only during the first few hours after waking up; or walking more than two blocks on level ground and climbing more than one flight of ordinary stairs at a normal pace and under normal conditions. Class III is defined by significant limitation of usual physical activity, for example, angina occurs when walking one or two blocks on a level surface, climbing one flight of stairs under normal conditions and at a normal pace. Class IV is defined by the inability to perform any physical activity without discomfort; angina syndrome may be present at rest (Campeau, 1976, 2002; Goldman et al., 1981). Between 3 and 4 million Americans may have silent ischemia, or ischemia without pain, or a heart attack without warning. People with angina may also have undiagnosed episodes of silent ischemia. In addition, people who have had heart attacks or have diabetes are at risk of developing ischemia.

Table 2.1.

Functional classification of angina proposed by the Canadian Cardiovascular Society

Class	Definition	Restrictions
I	There are no restrictions for normal activities. Angina occurs during intense, rapid or prolonged exercise at work or leisure.	The usual level of physical activity does not cause an attack of angina: for example, it does not occur when walking or climbing stairs. Angina develops with significant, accelerated or particularly prolonged stress (effort).
II	Slight limitation of usual activities.	Angina occurs when walking quickly or quickly climbing stairs : walking uphill; walking or climbing stairs after eating; in cold or windy weather; with emotional stress; or only in the first hours after waking up. Angina occurs when walking > 2 blocks (> 500 m) on level ground, climbing > 1 flight of normal steps, at a normal pace, under normal conditions.
III	Significant limitation of usual physical activity.	"Significant limitation of usual physical activity." Angina occurs when walking 1-2 blocks (<500 m) on level ground, when climbing 1 flight of ordinary steps, at a normal pace, under normal conditions.
IV	Inability to perform any physical activity without discomfort.	Anginal symptoms may be present at rest.

SOURCE : Adapted from Goldman et al.2005 2.2 **.**

Stratification of risk factors for ischemic heart disease

When we refer to risk factors for cardiovascular disease, we are actually expecting treatment from the disease (event) to the disease-free phase. It is essential to be confident in the evidence for the effectiveness of the intervention. For example, between 40 and 69 years of age, the difference in systolic blood pressure is 20 mmHg. Art. is associated with a more than twofold increase in the risk of death from stroke and approximately twofold increase in the risk of death from coronary heart disease [10]. On the other hand, a decrease of 5 mmHg. is associated with a 14% reduction in deaths from stroke, 9% in coronary heart disease, and 7% in all-cause mortality [11].

We know how difficult it is to adjust for different risk factors and their relative importance for an individual patient. This difficulty has necessitated the identification of algorithms capable of predicting the likelihood of an event occurring and assisting in decision-making regarding medical intervention to effectively modify the natural history of the atherosclerotic process to prevent cardiovascular disease.

Table 2.2.

Risk factors for cardiovascular disease (adapted from Mendis et al.)

Unmodifiable	Other modifiable risk factors	Changeable	New risk factors
Floor	Poverty	Arterial hypertension	Inflammation
Family history	Psychological factors	Excess homocysteine	Blood clotting disorders
Genetic predisposition	Psychosocial stress	Lipid disorders (LDL cholesterol)	
	Alcohol abuse	Overweight and Obesity	
	Some medications	Smoking	
	Lipoprotein	Unhealthy diet	
	Left ventricular hypertrophy	Passive lifestyle	
		Diabetes	
		Hyperuricemia	

Following the shock of the premature death of President Franklin D. Roosevelt in 1945, a study was designed to identify common factors and characteristics contributing to cardiovascular disease following its development in a cohort of healthy individuals over a long period of time [13].

The Framingham Study, begun in 1948, included 5,209 men and women from Framingham, a small town in Massachusetts, USA. He presented much of the current knowledge about risk factors for cardiovascular disease: tobacco, lipid disorders, high blood pressure, electrocardiographic abnormalities, menopause, atrial fibrillation, overweight and obesity, among many others associated with increased cardiovascular events, and protective factors, physical activity and HDL cholesterol were also identified. The original cohort was expanded in 1971 to include the descendants (5,124 sons and daughters) of the original participants, and in 2002 to also include their 4,095 grandchildren. Research is now expanding into genetics and epigenetics, describing hundreds of new genes associated with major cardiovascular diseases and their precursors or risk factors [176, 182].

In 1994, the first non-Caucasian cohort was added, which included 507 African Americans, Hispanics, Asians, Indians, Native Americans, and Pacific Islanders, with an additional 410 participants later included (2003) [182]. Risk calculators are one of the results of the Framingham study. The best known is the risk rating for predicting cardiovascular diseases [36]. It estimates the 10-year risk of cardiovascular disease or death (coronary death, acute myocardial infarction, coronary ischemia, angina, ischemic or hemorrhagic stroke, transient ischemic attack, peripheral arterial disease, and congestive heart failure) in people 30 to 74 years of age. age in primary prevention using age, sex, smoking habits, systolic blood pressure, diabetes mellitus, total cholesterol, and HDL cholesterol in the general model or body mass index in the simplified model.

There are many other risk assessment algorithms:

1) **Globorisk** is a continuation of the Framingham calculator and 7 other promising studies. It estimates the 10-year risk of fatal cardiovascular disease in people aged 20 to 80 years.

1) The American College of Cardiology/American Heart Association Task Force proposed a new **pooled cohort ASCVD** (Atherosclerotic Cardiovascular Disease Risk Assessment) risk equation [194] to estimate cardiovascular disease between 40 and 79 year olds, adjusting for sex and race. (Caucasians and African Americans). The

variables in the model are age, total cholesterol, LDL cholesterol, systolic blood pressure (including treated and untreated patients), diabetes mellitus, and smoking.

2) **The Reynolds Estimator** adapts the calculation formula for women by entering age, systolic blood pressure, high-sensitivity C-reactive protein, total cholesterol, HDL cholesterol, hemoglobin (%), current smoker, and family history of premature cardiovascular disease.

3) The International Coronary Disease Prevention Task Force guidelines suggest the **PROCAM calculator**. It estimates the 10-year risk of major coronary artery disease or stroke between ages 20 and 75 for both sexes.

4) In the United Kingdom, the National Institute for Health and Care Excellence (NICE) recommends the use of QRISK2 to assess cardiovascular risk.

5) The United British Society Consensus offers the **JBS3 risk calculator**, based on QRISK Lifetime. It controls for a number of variables that provide the probability of being alive and free of cardiovascular disease at each age, as well as the cumulative risk of cardiovascular disease.

6) The Scottish Intercollegiate Guidelines Network recommends using **the ASSIGN-SCORE** to assess the risk of cardiovascular events in people aged 30–74 years.

7) In Italy, the **CUORE project** provides another risk estimate for the first major event in the next 10 years, based on sex, age, systolic blood pressure, serum total cholesterol, smoking status and diabetes, applicable in primary prevention from 35 to 69 years of age (Source: ©2019 Healsens Inc.) .

All models are valid, although they present several differences in what they actually assess and how the outcome can be integrated into clinical practice. These calculators often highlight two problems: underestimation of risk in younger people and difficulty managing residual risk. Aging is a major factor influencing the risk of cardiovascular disease. Age assessment of cardiovascular risk [24] is a way to overcome this difficulty. This concept is easy to explain and easy to visualize in a diagram. This may be useful for younger people, especially if the relative risk is high and even when the absolute risk is low. Long-term risk prediction algorithms also attempt to overcome this difficulty, but they have not been fully implemented in clinical practice [25]. The sensitivity of the Framingham Risk Score for top quintile coronary disease is 45.9 in men and 57.5 in women, and for stroke

it is 71.6 in men and 61.6 in women. The specificity is 83.2 and 81.9 for coronary disease and 81.3 and 80.8 for stroke, respectively [15]. In prevention/screening we need tests with high sensitivity to find true negatives, and in diagnosis we need tests with high specificity to find true positives.

In an attempt to address some of these issues, the European Society of Cardiology developed *the Systematic Coronary Risk Assessment* (SCORE) based on a large number of European participants. The outcome variable is death from cardiovascular disease, chosen because it is a strong and reproducible variable. This makes it possible to separate mortality from coronary heart disease and stroke. Countries are classified into low- and high-risk categories based on mortality rates in the 45–74 age group using a threshold of 225/100,000 in men and 175/100,000 in women based on CVD mortality data for 2012 in the WHO report [26]. The model allows for calibration for each country according to local mortality rates. Data were obtained from 12 European cohort studies involving more than 250,000 patients and 3 million people per year followed, resulting in a total of approximately 7,000 deaths from cardiovascular disease [203]. However, modern technology allows a significant proportion of patients with cardiovascular disease to survive, limiting the interpretation of the final result of this calculation since it only counts deaths.

Although the model may present some variations, such as using the cholesterol/HDL ratio, the variables included in the algorithm are age, gender, and 3 major risk factors (systolic blood pressure, total cholesterol, and current smoker) [203]. It also includes several other modifiers of cardiovascular disease risk to reduce estimation error: sedentary lifestyle, central obesity, poor socioeconomic conditions, low HDL cholesterol, high triglycerides, fibrinogen, apo-B, and elevated lipoprotein(a), evidence of preclinical asymptomatic atherosclerosis (eg, carotid plaques), presence of chronic kidney disease (glomerular filtration rate - GFR <60 ml/min/1.73 m ^{2}) and family history of premature cardiovascular death. One interesting aspect of SCORE is its translation into risk categories rather than the absolute value of the calculation. This categorization makes it possible to simplify and personalize the characteristics of each patient and select the best intervention for each case [201]. The European Society of Cardiology recommends that all persons with a family history of premature cardiovascular disease, those with underlying risk factors and those with significant comorbidities be assessed for cardiovascular risk at a maximum interval of 5 years. The remaining asymptomatic population with no known

risk factors could be offered risk estimates from 40 years for men and 50 years for women, although the evidence is less reliable [201].

Genetic architecture of signs of development of ischemic heart disease

The genetic architecture of a phenotypic trait (a quantifiable biological trait) refers to the genes and their variants that determine or are associated with the trait of interest.

Before examining the genetic architecture of a trait, it is important to first determine whether the genetic component is important? Several cohort studies have shown that a family history of CAD is associated with an increased risk of developing the disease, suggesting that genetic factors are important; however, it is also important to consider that family background conveys not only genetic information, but also attitudes and lifestyles. The heritability of a trait is an indicator of its percentage variability associated with the genetic variability of the population [161]. Published estimates of the heritability of CAD range from 35% to 55% [150,161] .

Once the importance of the genetic component is established, studies can be designed to identify genes and genetic variants associated with CAD. With regard to genetic transmission, two broad groups of phenotypes or diseases can be distinguished [175]:

- ✓ Monogenic (or oligogenic), in which the risk of developing a disease is associated with the presence of variants in one gene or a small number of genes. A good example is familial hypercholesterolemia, the occurrence of which is determined by sequence variants in a discrete group of genes (*LDLR, APOB, PCSK9* and *LDLRAP1*).
- ✓ Polygenic or complex, in which the risk of disease is determined by many genes, many variants of these genes and their interaction with environmental factors. CAD is a prime example of a polygenic or complex trait [175] .

The genetic architecture of a phenotypic trait can be studied using 4 approaches:

1. *Analysis of connections* . This type of analysis has proven useful in the study of monogenic and oligogenic diseases. Linkage studies are conducted in families in which the disease is initially diagnosed in at least 1 member (proband) and other family members with the disease are also found in more than 1 generation. Family members are analyzed for several hundred genetic markers distributed throughout the genome, and the intergenerational transmission of these markers is analyzed to identify any association with disease occurrence (segregation). The goal is to locate the

region of the genome in which the gene is located and identify the disease-causing genetic variant. Once a region of the genome has been identified, further studies, including genotyping and usually sequencing, are performed to more accurately identify the gene and variant causing the disease. This type of analysis has proven to be very useful in the study of monogenic and oligogenic diseases. For example, in familial hypercholesterolemia, linkage analysis identified a region on chromosome 1 containing the *PCSK9 gene* , and subsequent sequencing analysis identified disease-causing *PCSK9 sequence variants* . Although linkage analysis is less useful in the study of complex diseases, sequence variants associated with CAD have been identified in *the ALOX5AP* and *MEF2A genes [175, 187]*.

2. *Candidate gene association studies* . This type of analysis usually uses a case-control design to determine whether one or more variants of a particular gene are more or less common in patients with the disease than in healthy controls. In this hypothesis testing approach, a candidate gene is selected according to knowledge of disease pathophysiology, and the genetic variants analyzed are typically common (allele frequency >5%). Candidate gene association studies have provided little insight into the genetic architecture of CAD or other complex phenotypes [175 , 189]. The main problem with this approach is poor reproducibility, usually associated with the small sample size in these studies, resulting in insufficient statistical power to detect weakly associated variants.

3. *Genome-wide association studies (GWAS).* Over the past 20 years, new technologies for genome sequencing and the generation of multiple sequence variants in a single sample have expanded our knowledge of the genetic basis of complex diseases. Moreover, the publication of the HapMap study revealed that many common sequence variants are associated at the population level (they are in linkage disequilibrium) [137, 175]. Together with technological advances, knowledge of the pattern of linkage disequilibrium in the human genome has led to the development of laboratory kits capable of detecting between 100,000 and 500,000 sequence variants. This type of analysis captures much of the total genetic variation in the human genome and has enabled the development of GWAS approaches, which are used to examine hundreds of thousands of genetic features and their relationship to a phenotypic trait in a hypothesis-free manner. The lack of a guiding hypothesis has two main consequences for the design and interpretation of GWAS:

a) a number of sequence variants are identified in the discovery sample that show potential association with the trait of interest, and the results from this initial sample are confirmed by replication in an independent sample;

b) Simultaneous analysis of hundreds of thousands of sequence variants generates a huge number of multiple comparisons, and the *P value* for assigning statistical significance tends to be $<1\times10^{-8}$.

Early work with GWAS showed that common genetic variants showed only weak associations with complex traits of interest, with odds ratios (OR) ranging from 1.1 to 1.4. The need to identify weakly associated variants with such small *P values* and to replicate the results in independent samples generated an international collaboration that resulted in the collection of samples involving thousands of individuals [175].

The first 2 GWAS of CAD produced consistent results, identifying sequence variants on chromosome 9 associated with increased disease risk. Since then, several GWAS have been published, and in 2015, a meta-analysis of the accumulated results identified 55 loci associated with CAD, each with 1 or more sequence variants (Table 2.3.1) [175] . These variants explain approximately 15% of the heritability of CAD; moreover, some of them are also associated with lipid metabolism, blood pressure and inflammation, confirming the importance of these risk factors in the etiology and pathogenesis of CAD. More recent systems biology approaches have identified the overrepresentation of CAD-associated genes in several processes and metabolic pathways, including lipid metabolism, sulfur-containing amino acid metabolism, polyamine metabolism, innate immunity, extracellular matrix degradation, and the collapsesin response mediator protein family [174]. Moreover, the majority of these variants are located in intergenic regions close to gene promoters, indicating possible effects on expression and highlighting the importance of gene expression and epigenetics in determining CAD risk. All GWAS results related to CAD, its risk factors and other complex characteristics were cataloged to provide easy access to researchers and clinicians [175, 189].

Table 2.3.

*Summary of key findings from a recent meta-analysis of genome-wide association studies examining DNA sequence variants associated with coronary heart disease **

SNP	Closest gene	Chromosome	Risk/non-risk allele	Risk allele frequency	*P*	OR (95% CI)

rs11206510	PCSK9	1	T/S	0.848	2.34 E-08	1.08 (1.05–1.11)
rs9970807	PPAP2B	1	C/T	0.915	5.00 E-14	1.13 (1.10–1.17)
rs7528419	*SORT1*	1	A/G	0.786	1.97 E-23	1.12 (1.10–1.15)
rs6689306	*IL6R*	1	A/G	0.448	2.60 E-09	1.06 (1.04–1.08)
rs67180937	*MIA3*	1	G/T	0.663	1.01 E-12	1.08 (1.06–1.11)
rs16986953	*AK097927*	2	A/G	0.105	1.45 E-08	1.09 (1.06–1.12)
chr2:21378433:D	*APOB*	2	D/ I	0.746	2.89 E-08	1.07 (1.04–1.10)
chr2: 44074126: D	*ABCG5-ABCG8*	2	I /D	0.745	2.60 E-08	1.06 (1.04–1.09)
rs7568458	*VAMP5-VAMP8-GGCX*	2	IN	0.449	3.62 E-10	1.06 (1.04–1.08)
rs17678683	*ZEB2-ACO74093.1*	2	G/T	0.088	3.00 E-09	1.10 (1.07–1.14)
chr2:203828796: I	*WDR12*	2	I /D	0.108	2.15 E-18	1.15 (1.11–1.18)
chr3: 138099161: I	*MRAS*	3	I /D	0.163	2.89 E-09	1.08 (1.05–1.10)
rs4593108	*EDNRA*	4	C/G	0.795	8.82 E-10	1.07 (1.05–1.10)
rs72689147	*GUCY1A3*	4	G/T	0.817	6.07 E-09	1.07 (1.05–1.10)
rs17087335	*REST-NOA1*	4	T/ C	0.210	4.60 E-08	1.06 (1.04–1.09)
rs273909	*SLC22A4-SLC22A5*	5	G/A	0.117	1.24 E-04	1.06 (1.03–1.09)
rs6903956	*ADTRP-C6orf105*	6	A/G	0.354	0.96	1.00 (0.98–1.02)

rs9349379	*PHACTR1*	6	G/A	0.432	1.81 E-42	1.14 (1.12–1.16)
rs17609940	*ANKS1A*	6	G/C	0.824	0.03	1.03 (1.00–1.05)
rs56336142	*KCNK5*	6	T/S	0.807	1.85 E-08	1.07 (1.04–1.09)
rs12202017	*TCF21*	6	A/G	0.700	1.98 E-11	1.07 (1.05–1.09)
rs55730499	*SLC22A3-LPAL2-LPA*	6	T/S	0.056	5.39 E-39	1.37 (1.31–1.44)
rs4252185	*PLG*	6	C/T	0.060	1.64 E-32	1.34 (1.28–1.41)
rs2107595	*HDAC9*	7	A/G	0.200	8.05 E-11	1.08 (1.05–1.10)
rs10953541	*7q22*	7	C/T	0.783	1.02 E-05	1.05 (1.03–1.08)
rs11556924	*ZC3HC1*	7	C/T	0.687	5.34 E-11	1.08 (1.05–1.10)
rs17087335	*NOS3*	7	T/S	0.060	1.70 E-09	1.14 (1.09–1.19)
rs264	*LPL*	8	G/A	0.853	1.06 E-05	1.06 (1.03–1.09)
rs2954029	*TRIB1*	8	A/ T	0.551	2.61E-06	1.04 (1.03–1.06)
rs2891168	*9p21*	9	G/A	0.489	2.29 E-98	1.21 (1.19–1.24)
rs2891168	*9p21*	9	G/A	0.489	2.29 E-98	1.21 (1.19–1.24)
rs2519093	*ABO*	9	T/S	0.191	1.19 E-11	1.08 (1.06–1.11)
rs2487928	*KIAA1462*	10	A/G	0.418	4.41 E-11	1.06 (1.04–1.08)
rs1870634	*CXCL12*	10	G/T	0.637	5.55 E-15	1.08 (1.06–1.10)

rs1412444	*LIPA*	10	T/S	0.369	5.15 E-12	1.07 (1.05–1.09)
rs11191416	*CYP17A1-CNNM2-NT5C2*	10	T/ G	0.873	4.65 E-09	1.08 (1.05–1.11)
rs2128739	*PDGFD*	eleven	A/C	0.324	7.05 E-11	1.07 (1.05–1.09)
rs964184	*ZNF259-APOA5-APOA1*	eleven	G/C	0.185	5.60 E-05	1.05 (1.03–1.08)
rs10840293	*SWAP70*	eleven	A/G	0.550	1.38 E-08	1.06 (1.04–1.08)
rs2681472	*ATP2B1*	12	G/A	0.201	6.17 E-11	1.08 (1.05–1.10)
rs3184504	*SH2B3*	12	T/S	0.422	1.03 E-09	1.07 (1.04–1.09)
rs1180803	*KSR2*	12	G/T	0.360	3.12 E-09	1.12 (1.08–1.16)
rs9319428	*FLT1*	13	A/G	0.314	7.13 E-05	1.04 (1.02–1.06)
rs11838776	*COL4A1/A2*	13	A/G	0.263	1.83 E-10	1.07 (1.05–1.09)
rs10139550	*HHIPL1*	14	G/C	0.423	1.38 E-08	1.06 (1.04–1.08)
rs4468572	*ADAMTS7*	15	C/T	0.586	4.44 E-16	1.08 (1.06–1.10)
rs17514846	*FURIN-FES*	15	Air conditioner	0.440	3.10 E-07	1.05 (1.03–1.07)
rs56062135	*SMAD3*	15	C/T	0.790	4.50 E-09	1.07 (1.05–1.10)
rs8042271	*MFGE8-ABHD2*	15	G/A	0.900	3.70 E-08	1.10 (1.06–1.14)
rs216172	*SMG6*	17	C/G	0.350	5.07 E-07	1.05 (1.03–1.07)
rs12936587	*RAI1-PEMT-RASD1*	17	G/A	0.611	8.24 E-04	1.03 (1.01–1.05)

rs46522	*UBE2Z*	17	T/S	0.513	1.84 E-05	1.04 (1.02–1.06)
rs7212798	*BCAS3*	17	C/T	0.150	1.90 E-08	1.08 (1.05–1.11)
rs663129	*PMAIP1-MC4R*	18	A/G	0.260	3.20 E-08	1.06 (1.04–1.08)
rs56289821	*LDLR*	19	G/A	0.900	4.44 E-15	1.14 (1.11–1.18)
rs4420638	*APOE-APOC1*	19	G/A	0.166	7.07 E-11	1.10 (1.07–1.13)
rs12976411 *	*ZNF507-LOC400684*	19	T/A	0.090	1.18 E-14	1.49 (1.35–1.67)
rs28451064	*KCNE2*	21 years old	A/G	0.121	1.33 E-15	1.14 (1.10–1.17)
rs180803	*POM121L9P-ADORA2A*	22	G/T	0.970	1.60 E-10	1.20 (1.13–1.27)

A, adenine; C, cytosine; D, removal; G, guanine; I , firmware; OR - odds ratio; SNP - single nucleotide polymorphism; T, thymine; 95% CI, 95% confidence interval *

The table shows the most informative SNP at each identified locus, the closest gene, the chromosome on which it is located, the risk allele and its frequency, *P value* and magnitude of association [175].

The main benefits of GWAS are the consistency of findings, the creation of cross-group collaborations, and the provision of data to the scientific community. Available GWAS databases include the European Genome-Phenome Archive, the American Database of Genotypes and Phenotypes (dbGaP), and the cumulative database of genetic variants associated with CAD from the CARDIoGRAMplusC4D consortium, which includes data from more than 60,000 patients and more than 123,000 controls [175].

The main limitations of GWAS are that the identified sequence variants do not necessarily have to be causally related to the phenotype in question (they may be in linkage disequilibrium with the causative variant) and that they do not provide information about the associated pathophysiological mechanism, which therefore must be determined with using specific functional studies. Moreover, these studies are mainly aimed

at identifying common sequence variants with small effects and are less suitable for identifying rare variants with large effects [175].

The characterization of a yet undiscovered hereditary component is one of the main problems in the genetics of complex diseases. This heritability may be due to as yet undiscovered variants in gene sequences associated with the disease. Alternatively, it may be due to changes elsewhere that do not affect the base sequence of the gene of interest, but instead modulate its DNA structure, influencing its expression through epigenetic changes [187].

4. *Genome sequencing studies* . Sequencing methodology has traditionally been used to study monogenic and oligogenic diseases that exhibit clear familial segregation. Sequencing studies can focus on a single gene, a group of genes, an exome (the part of the genome that encodes proteins), or the entire genome. The human genome contains about 3,100 million nucleotides, while the exome contains only 30 million nucleotides and about 23,000 genes. Large-scale sequencing studies of CAD may identify rare genetic variants that would theoretically have a greater effect than more common variants. In a recent study, discovery of exome sequencing was followed by targeted exon sequencing in approximately 6,700 patients and 6,700 controls; analysis identified rare *variants in the LDLR* and *APOA5* sequences associated with a higher risk of acute myocardial infarction (OR 1.5 to 4.5), again confirming the important influence of lipid metabolites (low-density lipoprotein cholesterol and triglycerides on cardiovascular risk) . Other studies have focused on specific genes and also identified rare CAD-associated variants in genes involved in lipid metabolism: *APOC3* , *NPC1L1* , *SCARB1* and *ANGPTL4* , *LPL* and *SVEP1* [175, 182, 193] .

Association Studies

To date, GWAS approaches have identified 55 gene loci associated with CAD . Of these, only one third are associated with classical risk factors, suggesting that new mechanisms and therapeutic targets may be identified. In a recent meta-analysis of 361 GWAS published up to February 2001, 991 trait-associated genes were identified as potential drug targets. The same study found that in 63 patients, the identified gene was the target of a drug that was already being used to treat or prevent the disease in question. Moreover, in the other 92 patients, the gene associated with the trait was the target of a drug or drugs used to treat another disease, suggesting the possibility of drug repositioning.

Despite these encouraging results, the identification of a disease-associated sequence variant does not confirm that the gene is a therapeutic target. An example of an identified gene that has become a drug target is *PCSK9* . Linkage analysis showed that the gene was associated with familial hypercholesterolemia, and subsequent studies showed that the encoded enzyme PCSK9 increases HDL levels by triggering degradation of the LDL receptor. Tailored anti-PCSK9 antibodies have been shown to reduce LDL levels, and these PCSK9 inhibitors are currently being evaluated in phase III clinical trials for their effectiveness in preventing clinical events.

More often, the identified association with a disease does not lead to new treatment, which indicates the need to determine the mechanism of association between the sequence variant and the disease trait. An example is the 9p21 region, which was shown to be associated with CAD in the first GWAS reports published in 2007 [93]. Sequence variants associated with CAD are located in an intergenic region close to a gene cluster that encodes cell -*cycle regulators* (*CDKN2A* and *CDKN2B*) and the non-coding RNA *CDKN2BAS* (also called *ANRIL*). Several explanations for the association with CAD have been proposed, but the underlying mechanism remains unclear, hindering the development of new drugs to prevent cardiovascular disease.

Mendelian randomization studies

This study uses genetic variants as tools to determine the association between a biomarker and a disease, which is a prerequisite for candidacy of the biomarker as a therapeutic target. Mendelian randomization studies are based on two fundamental biological principles: *a)* sequence variants decay randomly during meiosis and *b)* alleles of one gene are transmitted from one generation to the next independently of the alleles of other genes, according to Mendel's law of independent assortment. In practice, these principles imply that the sequence variant in question is the only factor discriminating between carriers and non-carriers of the associated biomarker.

In this type of study, a biomarker associated with a disease is examined along with one or more sequence variants associated with that biomarker to determine whether these variants are associated with the disease. The presence of such an association suggests that the biomarker is causally related to the disease phenotype. On the contrary, its absence indicates that the association between the biomarker and the disease is not causal, and may instead represent an example of reverse causation or mediation by another biomarker (Figure 2.3.1).

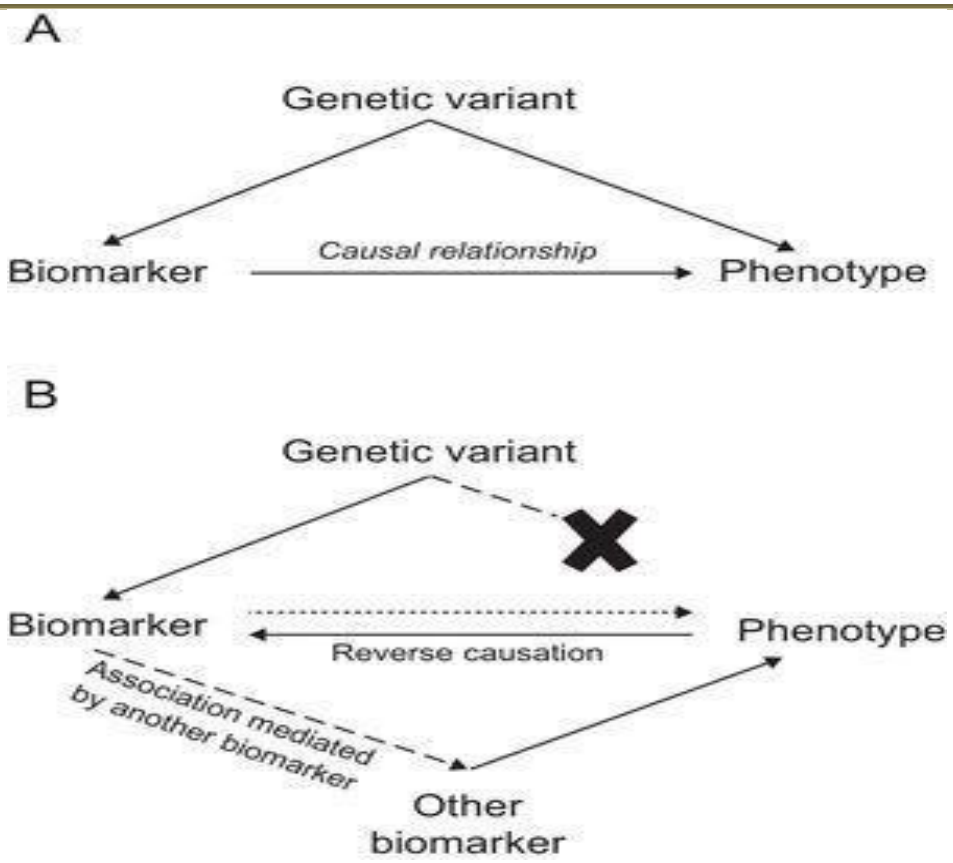

Figure 2.1. *The theory underlying Mendelian randomization studies. A: Causality. B : non-causal connection [166].*

Mendelian randomization studies of CAD biomarkers support causation for LDL, triglycerides, interleukin 6, obesity, and diabetes; In contrast, this type of analysis questioned the causal relationship with high-density lipoprotein cholesterol, C-reactive protein, uric acid, cystatin C, adiponectin, phospholipase A2, bilirubin, and vitamin D (Table 2.3.2). A mendelian randomization analysis also showed that *PCSK9 sequence variants* associated with lower LDL concentrations are also associated with increased blood glucose, waist circumference, and diabetes risk, highlighting the need to monitor possible side effects of anti-PCSK9 therapy [175].

Table 2.4.

Results of Mendelian randomization studies examining the relationship between selected biomarkers and coronary heart disease

Maintaining a cause-and-effect relationship with IHD	**Doubt about the cause-and-effect relationship with IHD**
LDL	HDL
Triglycerides	C-reactive protein

IL -6	Uric acid
Obesity	Cystatin C
Diabetes	Adiponectin
	Phospholipase A2
	Bilirubin
	Vitamin D

Improved cardiovascular risk assessment

The European Society of Cardiology recommends that preventive strategies be individualized according to estimated cardiovascular risk calculated using a validated risk scoring system [145]. Several risk scales have been developed and adapted for use in Spain, including the calibrated risk chart SCORE, REGICOR, FRESCO, and ERICE; however, validation data is only available for two of them. These scores calculate an individual's 10-year risk of a cardiovascular or coronary event based on exposure to classical risk factors. A limitation of these risk scores is their low sensitivity, with a significant proportion of events occurring in individuals at low or moderate risk. This limitation forces the evaluation of new biomarkers to improve the sensitivity of the risk score (especially for people currently classified as moderate risk) according to specific guidelines [145, 175].

Genetic variants associated with coronary artery disease are candidate parameters to improve the predictive ability of existing risk scores. Advantages include one-time determination, low cost, and high accuracy of genotyping methodologies. The main disadvantage is the low magnitude of association of individual sequence variants (OR 1.1 to 1.4), which limits their predictive ability; however, by combining several variants together in a genetic risk score, the magnitude of the association increases to that of classical risk factors. Several studies have assessed the added value of including genetic information in classic risk scores. Almost all of these studies report an association between genetic variants and CHD risk that is independent of established CVD risk factors and family history of CHD. In most studies, including genetic information in the risk score did not improve discriminatory power; however, improvements in risk classification were found, especially among those classified as moderate risk on conventional scales. Moreover, a recent meta-analysis showed that a high genetic risk score was associated with a poor prognosis among survivors, as well as with higher efficacy of statins in both primary and secondary prevention [130, 175].

Pharmacogenomics of Cardiovascular Diseases

Genetic variation may also underlie individual differences in drug response. When it comes to cardiovascular disease, two prominent examples are statins and clopidogrel. About 5% of individual variations decrease LDL

cholesterol from statin use can be explained by genetic variations *SORT1/CELSR2/PSRC1*, *SLCO1B1*, *APOE*; in addition, *SLCO1B1* sequence *variants* show a consistent association with an increased risk of simvastatin-induced myopathy. Clopidogrel is metabolized by the cytochrome P450 (CYP) system in the liver, releasing an active metabolite that has an anticoagulant effect by binding to the platelet receptor P2Y. One of the CYPs involved in the metabolism of clopidogrel is CYP2C19, and several sequence variants *of CYP2C19 have been identified* , some of which increase and others decrease the activity of the enzyme. These variants may be associated with clinical events such as stent thrombosis, bleeding risk, and cardiovascular mortality. In 2010, the US Food and Drug Administration added a warning to the clopidogrel patient information leaflet, stating that, depending on their genetic characteristics, some patients may not experience the expected benefit from the drug [175, 190].

CHAPTER 3.
Results of our own and foreign studies of the occurrence of psycho-emotional risk factors in patients with NS

Negative psychological states are commonly experienced by patients with cardiovascular disease. To date, depression has received the most attention among patients with cardiovascular events, especially in patients who have suffered a major cardiac event such as acute coronary syndrome (ACS). Recently, however, anxiety has emerged as another important psychological construct that is highly prevalent, often co-occurs with depression, and interferes with response to treatment for depression, and may ultimately influence the course of cardiovascular disease independent of depression. In this chapter, we aim to review the recent literature on anxiety and related disorders in cardiovascular disease.

Anxiety is common in patients with cardiovascular diseases such as coronary heart disease (CHD). After an ACS, 20-30% of patients experience an increased level of anxiety [1, 20]. Although anxiety after heart failure may be transient in some patients, in half of cases anxiety persists for up to 1 year after the event [1], suggesting that anxiety is a chronic condition for many patients with heart disease. Studies have shown similar prevalence rates in patients with CAD awaiting coronary artery bypass grafting (CABG) surgery. In this population, 25% of patients experience increased levels of anxiety before the procedure, with many experiencing a reduction in symptoms for several months after surgery [37].

Anxiety is also common in patients with other forms of heart disease. In a recent meta-analysis of 38 studies, Easton and all estimated that 32% of patients with heart failure (HF) experience elevated levels of anxiety, and 13% meet criteria for an anxiety disorder [177]. Concern also affects approximately 20% of patients with more advanced heart failure who require implantation of a left ventricular assist device to maintain cardiac function [166]. Finally, among patients implanted with an implantable cardioverter defibrillator to prevent the development of fatal arrhythmias, increased anxiety is present in approximately 20–40% [163].

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The relationship between anxiety and cardiovascular health is complex. Anxiety can be a normal reaction to a stressful situation such as an acute cardiac event, and if anxiety motivates a person to engage more in treatment (eg, exercise regularly, adhere to medications), this may be helpful. However, when anxiety is present in excess or for extended periods of time, it is considered detrimental to psychiatric and general health. Anxiety is associated with the incidence and, in some cases, progression of cardiovascular disease. In patients without heart disease, anxiety is associated with subsequent development of coronary artery disease. In a 2010 meta-analysis including 20 studies and approximately 250,000 patients, Roest and colleagues found that anxiety, when adjusted for other medical variables when possible, resulted in a 26% increased risk of incident CHD [165]. Although the overall results were significant, it is noteworthy that only 10 of the 20 studies found a significant relationship between anxiety and incident CHD in multivariate analyses, suggesting that there is mixed evidence in the literature regarding this relationship. In patients with established CAD, the literature on the relationship between anxiety and cardiac outcomes is also mixed. In a recent meta-analysis of 44 studies, anxiety was significantly associated with poor cardiac outcomes, including recurrent cardiac events and mortality, in an unadjusted analysis [165]. However, when adjusting for medical and psychological covariates, almost all of these relationships became nonsignificant, suggesting that although anxiety may be a good marker of poor heart health, other medical and psychological factors may in fact explain most of the relationship between anxiety and outcomes. Ultimately, it may be that anxiety following an ACS is more likely to be transient than anxiety measured during a period of clinical stability.

The association between anxiety and cardiac outcomes in patients with heart failure is relatively weak. To date, four prospective studies have examined the association between anxiety and CVD [195]. In a prospective

study of 153 adult outpatients with heart failure, anxiety was not significantly associated with mortality in unadjusted analyses; however, when controlling for relevant covariates, this relationship became nonsignificant. In the second study, 643 patients with chronic heart failure were followed for an average of 3 years to examine the proposed association between psychological distress (a combination of depression and anxiety) and mortality. In unadjusted analyses, depression/anxiety was not significantly associated with mortality; however, this relationship again became nonsignificant when controlling for demographic and health factors [195]. Two other studies found no significant associations between anxiety and CVD in adjusted or unadjusted analyses. Consistent with studies in patients with CAD, it appears that although anxiety may be a good marker of adverse outcomes in patients with heart disease, the actual association between anxiety and outcomes in some cases may be explained by other factors.

Finally, anxiety disorders are also common in patients who present to cardiac care but do not have heart disease, such as those with so-called noncardiac chest pain. This is an important public health issue because these patients have higher functional impairment and quality of life than patients with a confirmed diagnosis. Moreover, the repeated use of medical care by patients with noncardiac chest pain results in a significant financial burden on an annual basis.

Generalized anxiety disorder (GAD) is highly prevalent in patients with heart disease. A recent meta-analysis found an 11% point and 26% lifetime prevalence of GAD in patients with CAD, and a similar meta-analysis found the prevalence of GAD to be 14%. These rates are significantly higher than the lifetime prevalence of GAD of 3–7% in the general US population [177].

GAD is independently associated with poor outcomes in patients with established heart disease, particularly CAD. Although one study found that GAD was protective in the post-ACS period [21], most studies show that GAD is associated with CAD [177]. After myocardial infarction (MI), GAD has been associated with a nearly twofold increase in the risk of mortality over the subsequent ten years [23], and in patients with stable CAD, GAD is associated with a twofold increase in the risk of major cardiac adverse events over the next two years. In a prospective study of 158 patients undergoing CABG surgery, GAD was associated with major adverse cardiac events over the subsequent 5 years. The relationship between GAD and heart failure outcomes has not yet been studied.

Panic disorder (PD) is also common in patients with heart disease. Among patients with CAD, studies have varied: one review estimates the prevalence of CR to be 10–50% [1], although another analysis and a recent cross-sectional study estimated the prevalence of CR to be 5–8% in patients with established CAD [92]. These latter studies are likely closer to the true estimate, as a study of patients who had an ACS found that PD was significantly less common than GAD or depression. Although less common than GAD, PR significantly increases the risk of developing and progressing heart disease. In a cohort study of almost 80,000 people without previously established CAD, CR was associated with an almost twofold increase in the risk of incident CAD [92]. In another cohort study of 57,615 patients with CR and nearly 350,000 age- and sex-matched controls, patients with CR had a significantly higher risk of developing CAD but a lower risk of CAD-related death. Finally, a systematic review and meta-regression analysis of over 1 million patients found that CR was significantly associated with CAD, major adverse cardiac events, and MI [1].

There are several mechanisms that may explain the underlying link between anxiety disorders and heart disease. Although no definitive model exists, these hypotheses include both behavioral and physiological factors.

Inflammatory pathways play a key role in both the development and progression of heart disease [176]. Inflammatory pathways involving interleukin-1 (IL-1), interleukin-4 (IL-4), tumor necrosis factor alpha (TNF-α) and C-reactive protein (CRP) have been implicated in the development of atherosclerosis and heart disease, including CAD. heart failure and unstable angina. In patients with unstable CAD, inflammatory markers such as CRP have been associated with increased long-term mortality. Similarly, inflammatory pathways have been associated with worse function, increased hospitalization, and poor survival in patients with heart failure. Anxiety disorders are associated with increased markers of inflammation. One large study of healthy adults with increased anxiety found that they had higher levels of CRP, TNF-α, IL-6, homocysteine, and fibrinogen [176]. In addition, anxiety disorders, including GAD and PD, are associated with increased inflammation, primarily CRP. Thus, the link between anxiety disorders and inflammation may be the process by which anxiety disorders are associated with the development of heart disease. In addition to all of the above, the vascular endothelium plays a key role in the health and

maintenance of the circulatory system through the regulation of platelet activity, thrombosis, vascular tone and leukocyte adhesion. Its dysfunction leads to the development of atherosclerosis [31,33] and has been shown to increase the incidence of hospitalization, heart transplantation, and death in patients with heart failure. Anxiety disorders are associated with changes in the vascular endothelium. Patients with anxiety have impaired flow-mediated vascular dilation, indicating greater endothelial dysfunction. Patients with GAD, PD, and obsessive-compulsive disorder have decreased levels of circulating endothelial progenitor cells, which are vital for healthy endothelial function and prevent the progression of CAD [40,42].

Among patients with cardiovascular diseases, anxiety and formal anxiety disorders are common and are associated with CVD, including the development and progression of coronary artery disease and heart failure. The association between anxiety disorders and cardiac outcomes is likely mediated by both behavioral and physiological mechanisms, including autonomic dysfunction, inflammation, and platelet aggregation. Given their association with poor outcomes, diagnosis and treatment of anxiety disorders are critical. With careful diagnosis and appropriate treatment of anxiety disorders among patients with CVD, quality of life can be improved and the development of cardiovascular complications can be reduced.

Clinical characteristics of patients

On the basis of the Samarkand branch of the Republican Scientific Center for Emergency Medical Care (SRNTsEMP) from 2018 to 2020. 202 patients diagnosed with coronary heart disease (CHD) were examined. The average age of patients with coronary artery disease was 63.75±11.08 years. Of these, 155 patients with unstable angina (UA) and 47 patients with stable angina (SS), who made up a comparable group. In addition, 40 healthy people formed the control group. The study protocol was approved by the US National Institutes of Health (trial registration (https://register.clinicaltrials.gov) # NCT04599621). All patients gave their written informed consent for inclusion in the study. The purpose and objectives of the study, the potential clinical benefits of prophylactic medication, and possible side effects associated with non-compliance with medical recommendations were explained to all patients.

The study included 83 women and 72 men with NS, as well as 20 women and 27 men with SS (Fig. 3.1.).

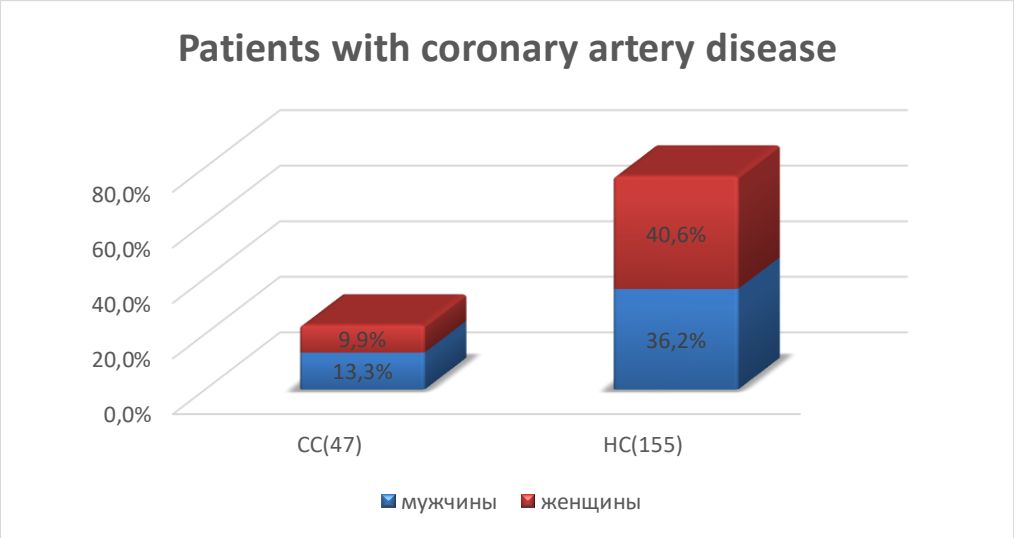


Fig.3.1. *Distribution of patients with NS and SS depending on gender.*

Table 3.1.

Clinical and anamnestic data of examination of patients

Indicators	NS patients , n=155	Patients with SS , n=47
Age	63.75 ± 2.14	59.6±2.45
Gender(m/f)	73/82	27/20
IHD experience, years	18.24± 0.82	12.45±0.45
History of PICS	47 (30.3%)	5 (10.6%)
History of stroke	9 (5.8%)	1 (2.1%)
Type 2 diabetes	39 (25.2%)	5 (10.6%)
HSNFC (NYHA): I II III IV	 17(11.56%) 38 (24.5%) 79 (50.9%)	 14 (29.8%) 11 (23.4%)
BMI, kg/ m^2	30.48±1.7	29.14±1.63
Obesity	76 (49.0%)	21 (44.6%)
Burdened heredity	89 (57.4%)	17 (36.17%)
Smoking	52 (33.5%)	11 (23.4%)
Presence of hypertension	108 (69.6%)	32 (68.1%)

Inclusion criteria were as follows:

- presence of an established diagnosis in patients with coronary artery disease

-n unstable angina (UA). When making a diagnosis, the recommendations of ESH / ESC (2015) and RKO / WHO (2014) were used.

- stable angina pectoris (SES) FC I - III . When making a diagnosis, the classification of IHD was used, adopted at the IV Congress of Cardiologists of the Republic of Uzbekistan (2000), as well as in accordance with the recommendations of ESH / ESC (2019) and RSC / WHO (2017).

The exclusion criteria were as follows:

-Refusal of the patient to participate in the study;

-Pregnancy and lactation;

-Severe and unstable condition of the patient, making it difficult to conduct a survey (for ethical reasons);

-Acute cerebrovascular accident

-Acute or chronic psychosis in history;

- The presence of concomitant acute diseases or chronic diseases in the acute stage.

All patients throughout the study had the right to voluntarily withdraw from the study at their own request by notifying the researcher in writing or orally.

During the study, special attention was paid to the clinical examination of patients, which in turn included the collection of complaints, medical history, and physical examination.

When collecting anamnesis in patients with unstable angina, the presence of coronary artery disease (previous myocardial infarction, angina pectoris of exertion or rest), and the presence of risk factors for coronary artery disease and myocardial infarction (atherosclerosis of other vascular areas, hypertension, smoking, diabetes, obesity) were determined. When questioning the patient, attention was paid to the period preceding the development of myocardial infarction, as well as to the factors that provoked the development of the present disease (excessive physical activity, infections, psycho-emotional stress), and information about the early manifestation of CVD in close relatives was found out.

The leading complaint in people with unstable angina is chest pain. For a more detailed characterization of anginal pain, the following criteria were used:

- features of the pain syndrome (localization, irradiation, connection of the attack with physical activity, psycho-emotional stress, increased blood pressure);
- intensity of a pain attack (assessed in points by the patient on a ten-point scale)

- frequency of pain attacks (per day, per week);
- duration of a painful attack (in minutes, in hours);
- exercise tolerance (in meters);
- the effect of nitroglycerin, non-narcotic or narcotic analgesics;
- vegetative manifestations (weakness, pale skin, sweating, nausea, vomiting);
- hemodynamic disorders (increased or decreased blood pressure).

The following clinical groups are typical for the diagnosis of NS:

- patients after a prolonged anginal attack at rest, lasting more than 15 minutes, not relieved by taking nitroglycerin;
- patients with severe angina for the first time in the last 28-30 days,
- persons who have experienced destabilization of a pre-existing CV with the appearance of characteristics inherent in at least FC III according to the classification of the Canadian Heart Association or attacks of pain at rest.

The diagnosis of post-infarction cardiosclerosis was made on the basis of anamnestic data, ECG and EchoCG data.

The purpose of the physical examination was to exclude extracardiac causes of pain, heart diseases of non-coronary origin, as well as non-cardiac causes that increase ischemia (for example, anemia), and to identify cardiac causes that increase or cause myocardial ischemia.

Table 3.2.

Frequency of prescription of drugs for NS depending on the general condition

Drug groups	Frequency of application (%)
Nitrates	91.61
β-blockers	50.3
$^{+2}$ channel blockers	41.29
ACE inhibitors	30.3
AII receptor antagonists	57.41
Antiplatelet agents	92.2
Statins	69.7
Diuretics	46.4
Febuxostat	48.01
Divaza	48.01

At the initial stage of the study, an analysis of the frequency of occurrence of comorbid conditions was carried out. In the course of which it was established that among patients with coronary artery disease such comorbid conditions as anxiety-depressive syndrome (ADS) and

asymptomatic hyperuricemia (ASH) are often found. These data served to divide patients with NS into 2 groups: group 1 - patients with NS and ADS and group 2 - patients with NS and without ADS.

At the time of the examination, there were no statistically significant differences between these groups in gender, age, duration of IHD, as well as the incidence of concomitant pathologies and complications of IHD (p ≥0.05).

Patients with NS of both groups in the hospital were prescribed standard basic therapy, following the "Recommendations of the RSC from 201 4 and the European Society of Cardiology (revision 2015) for the diagnosis and treatment of NS", as well as the "ESH/ESC Recommendations for the treatment of arterial hypertension from 2018." In addition to standard basic therapy, patients with ADS were prescribed the drug Divaza. This drug consists of release-active antibodies to protein S - 100 and endothelial NO synthase and is characterized by nootropic, vasoactive, antioxidant, angioprotective and antihypoxic effects . Patients with BGU were prescribed the drug febuxostat at a dose of 0.02-0.04 g/day per day.

Assessment of the frequency of occurrence of psychoemotional risk factors in patients with NS

When examining patients with unstable angina, the following were used: Hospital HADS scale [Kozlova S.N. 2013]. And also the Spielberger-Khanin scale [Psychiatry - Goffman A.G. 2010], developed by Spielberger C.D. and adapted by Khanin Yu.L. [Psychiatry - Goffman A.G. 2010].

Description of the hospital scale (HADS)

This questionnaire is intended for the patient to fill out independently [Kozlova S.N. 2013]. The questionnaire consists of 14 statements, "serving" 2 subscales: the "anxiety" subscale, marked in red, consists of odd points - 1, 3, 5, 7, 9, 11, 13 and the "depression" subscale, marked in blue, consists of even points - 2, 4, 6, 8, 10, 12, 14 (Fig. 2) [54, 131].

Hospital Anxiety and Depression Scale

FULL NAME.:	Case history no.:
Age:	Survey date:
Address:	Phone number:

Read each of the sentences below carefully and cross out the number in the appropriate box depending on how you feel at the moment.

D	A		D	A	

		I feel tense or excited:			**It seems to me that I began to do everything more slowly:**
	3	Most part of time.	3		Almost constantly.
	2	Often enough.	2		Often.
	1	Sometimes, from time to time.	1		Sometimes.
	0	Very rarely.	0		Not at all.
		What brought me pleasure before also brings me pleasure now:			**I am very excited or scared:**
0		Yes, that's right.		0	Not at all.
1		Almost, but not quite.		1	Sometimes, from time to time.
2		Only partially, to a small extent.		2	Often enough.
3		Not at all.		3	Often.
		I feel uneasy, it feels like something terrible is about to happen:			I don't take care of my appearance:
	3	Most likely, and I am very afraid of this.	3		Yes, I don't follow.
	2	Yes, but it's not that bad.	2		I don't take care of my appearance as much as I should.
	1	Partly, and it's not that it bothers me that much.	1		Perhaps I take less care of myself than I should.
	0	Not at all.	0		I take care of myself the same way as before.
D	A	**I am able to laugh and notice funny things around me:**	D	A	**I feel restless, as if I needed to run somewhere:**
0		Just like I've always been able to do.		3	Absolutely right.
1		Yes, but not quite the same as before.		2	To a large extent.
2		Definitely not the same as before.		1	Only to some extent.
3		Now I am not capable of this at all.		0	It's not like that at all.
		Restless thoughts are spinning in my head:			**I'm looking forward to doing something enjoyable:**
	3	Constantly.	0		The same as always.
	2	Most part of time.	1		Rather less than before.
	1	From time to time, but not too often.	2		Definitely less and less frequent than before.
	0	Only occasionally.	3		Almost not. Maybe just a little bit.
		I feel cheerful:			**I have a sudden feeling of panic:**
3		I don't feel it at all.		3	Very often indeed.
2		Rarely.		2	Quite often.
1		Sometimes.		1	Not too often.
0		Most part of time.		0	Never happens.

		I can easily sit down and relax:			**I enjoy a good film, book or radio program:**
	0	Certainly can.	0		Often.
	1	Usually I can.	1		Sometimes.
	2	Not always.	2		Quite rare.
	3	I can't do it at all.	3		Very rarely.

Patient signature_____

Rice. 3.3. Hospital Anxiety and Depression Scale.

Each statement corresponds to 4 answer options, reflecting gradations of symptom severity and coded according to the increasing severity of the symptom from 0 (absence) to 3 (maximum severity). Total scores for the two subscales are obtained by summing the numerical values of the responses. When interpreting the results, the total indicator for each subscale is taken into account, and 3 areas of its values are distinguished:

- ✓ 0-7 - normal (absence of significantly expressed symptoms of anxiety and depression);
- ✓ 8-10 - subclinically expressed anxiety and/or depression;
- ✓ 11 and above - clinically significant anxiety and/or depression.

The scale was filled out by patients under standard conditions, after short instructions for filling it out, within a clear time frame.

Description of the Spielberger-Hanin scale

The Spielberger Anxiety Scale (State-Trait Anxiety Inventory - STAI) is an informative way of self-assessing the level of anxiety at a given moment (reactive anxiety as a state) and personal anxiety (as a stable characteristic of a person). Designed by Ch.D. Spielberger and adapted by Yu.L. Khanin [Psychiatry - Goffman A.G. 2010] .

This scale consists of two subscales: judgments from 1 to 20 determine the presence of situational anxiety, judgments from 21 to 40 determine the presence of personal anxiety (Fig. 3) [39, 98] .

When analyzing the results of self-assessment, one must keep in mind that the overall final score for each of the subscales can range from 20 to 80 points. Moreover, the higher the final indicator, the higher the level of anxiety (situational or personal).

When interpreting the indicators, you can use the following indicative estimates of anxiety:

- ✓ up to 40 points – low,
- ✓ 41 - 54 points - moderate;

✓ 55 or more - high.

Spielberger-Hanin Anxiety Scale

Instructions. Read each of the sentences below carefully and cross out the number in the appropriate box on the right depending on how you feel at the moment. Don't overthink the questions because there are no right or wrong answers.

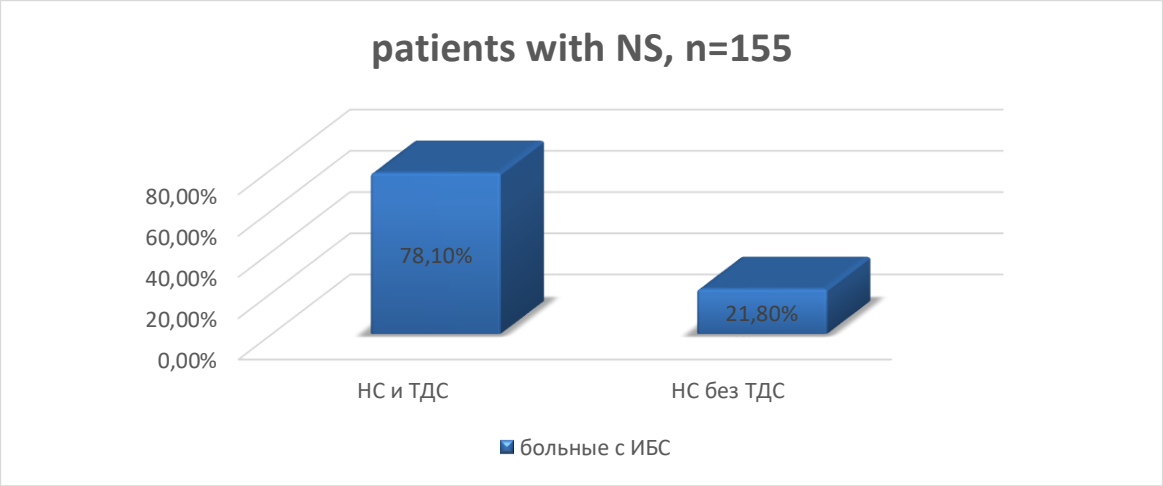
No.	Judgment	Never	Almost Never	Often	Almost always
1	I am calm	1	2	3	4
2	Nothing threatens me	1	2	3	4
3	I'm stressed	1	2	3	4
4	I'm internally constrained	1	2	3	4
5	I feel free	1	2	3	4
6	I'm sad	1	2	3	4
7	I'm worried about possible failures	1	2	3	4
8	I feel peace of mind	1	2	3	4
9	I'm worried	1	2	3	4
10	I feel a sense of inner satisfaction	1	2	3	4
eleven	I'm confident in myself	1	2	3	4
12	I'm nervous	1	2	3	4
13	I can't find a place for myself	1	2	3	4
14	I'm excited	1	2	3	4
15	I don't feel constrained	1	2	3	4
16	I'm happy	1	2	3	4
17	I'm concerned	1	2	3	4
18	I'm too excited and uneasy	1	2	3	4
19	I'm happy	1	2	3	4
20	I'm pleased	1	2	3	4
21	I'm in high spirits	1	2	3	4
22	I get irritable	1	2	3	4
23	I get upset easily	1	2	3	4
24	I wish I could be as lucky as others	1	2	3	4
25	I'm very worried about troubles and can't forget about them for a long time	1	2	3	4
26	I feel a surge of energy and a desire to work	1	2	3	4
27	I'm calm, cool and collected	1	2	3	4
28	I'm worried about possible difficulties	1	2	3	4
29	I worry too much about little things	1	2	3	4
thirty	I'm quite happy	1	2	3	4

31	I take everything to heart	1	2	3	4
32	I lack self confidence	1	2	3	4
33	I feel defenseless	1	2	3	4
34	I try to avoid critical situations and difficulties	1	2	3	4
35	I get blues	1	2	3	4
36	I'm happy	1	2	3	4
37	All sorts of trifles distract and worry me	1	2	3	4
38	There are times when I feel like a failure	1	2	3	4
39	I'm a balanced person	1	2	3	4
40	I feel anxious when I think about my own affairs and worries.	1	2	3	4

FULL NAME.:	Case history no.:
Age:	Survey date:
Address:	Phone number:

Signature_____

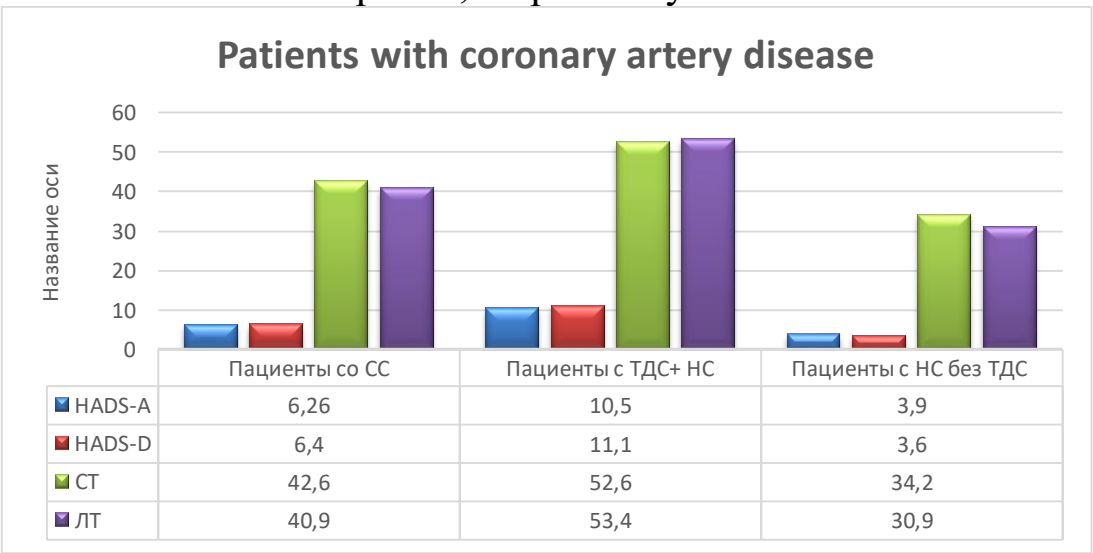
Fig.3.4. Spielberger-Hanin Anxiety Scale



Rice. 3.5. *Distribution of the main group depending on the presence of anxiety-depressive syndrome.*

When testing using the above scales, we determined that 122 patients with NS had anxiety-depressive syndrome.

The study revealed that patients with NS had significantly high scores in all parameters of the above scales (Fig. 3.6.). The hospital scale among patients with stable angina had on average the following values: HADS - D -6.43±0.35 points and HADS - A 6.17 points, while patients with UA were statistically higher and were equal to HADS - D -9 .0±0.5 points and HADS - A 9.5±0.52. But special attention is drawn to the average value of these indicators among patients with NS and ADS, HADS - D -11.1±0.61 points and HADS - A 10.6±0.58 points, respectively.



	Пациенты со СС	Пациенты с ТДС+ НС	Пациенты с НС без ТДС
HADS-A	6,26	10,5	3,9
HADS-D	6,4	11,1	3,6
CT	42,6	52,6	34,2
ЛТ	40,9	53,4	30,9

Fig.3.6. *Indicators of the hospital HADS and Spielberger-Hanin scales among patients with coronary artery disease.*

Note: HADS-D-depression, HADS-A-anxiety, ST-situational anxiety, LT-personal anxiety.

When conducting a survey of patients using the Spielberger-Khanin scale, the picture was identical. Among patients with SS, situational anxiety (ST) was 42.55 ± 2.3 points, trait anxiety (TA) 40.86 ± 2.24 points; among patients with NS, CT 49.1 ± 2.7 points and LT 47.7 ± 2.6 points, and in patients with NS and ADS, respectively, 52.6 ± 2.9 and 53.4 ± 2.93 points.

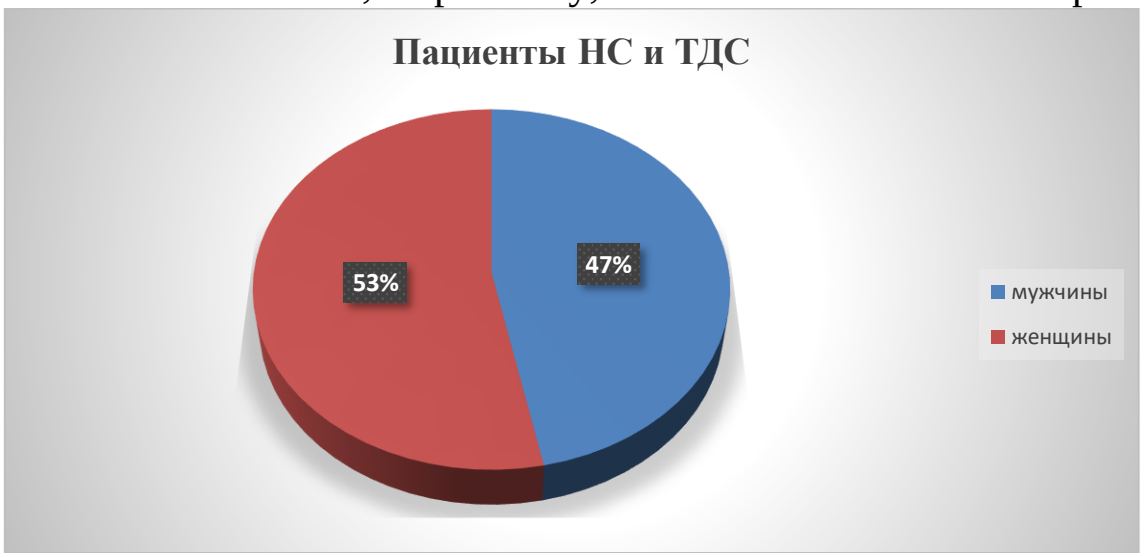


Fig.3.7. *Distribution of patients by gender.*

The study revealed that ADS is more common among females (Fig. 3.7.). Indicators of the severity of anxiety-depressive syndrome in both groups were not statistically different.

Table 3.3.

Indicators of the hospital HADS and Spielberger-Hanin scales among patients with NS and ADS depending on gender.

Indicators	women (n= 65)	men (n= 57)	P-value
HADS-D (score)	11.0±0.6	11.1±0.7	>0.5
HADS-A(score)	10.5±0.4	10.6±0.6	>0.5
ST(point)	53.6±2.8	53±2.4	>0.5
LT(point)	53.5±3.1	52.1±2.9	>0.5

Note: HADS-D-depression, HADS-A-anxiety, ST-situational anxiety, LT-personal anxiety.

For a comparative assessment of the cardiac parameters of patients with NS with and without ADS, ECG and echocardiography parameters were studied.

Table 3.4.

Echocardiography and ECG indicators in patients with NS depending on the presence or absence of ADS.

Index	1st group, NS+ ADS n =122	2nd group, NS n =33	Group 3 SS, n= 47	P-value	
LVEF (%)	49.5±1.9	50.6±1.8	54.4±2.3	>0.5 >0.1 >0.2	P1 P2 P3
CDR (cm)	5.9±0.2	5.6±0.3	5.8±0.2	>0.5 >0.5 >0.5	P1 P2 P3
DAC (cm)	5.3±0.2	5.5±0.2	5.3±0.3	>0.5 >0.5 >0.5	P1 P2 P3
LVL (cm)	1.29± 0.09	1.28± 0.08	1.24± 0.09	>0.5 >0.5 >0.5	P1 P2 P3
IVS (cm)	1.28± 0.08	1.25± 0.09	1.17± 0.08	>0.5 >0.5 >0.5	P1 P2 P3
RV (cm)	2.75± 0.18	2.75± 0.17	2.73± 0.19	>0.5 >0.5 >0.5	P1 P2 P3
LA (cm)	3.49± 0.17	3.64± 0.21	3.43±0.2 0	>0.5 >0.5 >0.5	P1 P2 P3
Aorta (cm)	3.07± 0.13	3.07± 0.15	3.09± 0.12	>0.5 >0.5 >0.5	P1 P2 P3
ST segment depression (%)	70.4±2.9***	34.3±1.6	-	<0.001	P1
T wave inversion (%)	34.3±1.4*	30.1±1.3 #	14.4±0.6 ^^^	<0.001 <0.001 <0.05	P1 P2 P3

*Note. *^#- Significant compared with NS with and without ADS, as well as with stable angina (* - P1 <0.05, ** - P 1 <0.01, *** - P 1 <0.001, ^ - P2 <0.05, ^^ - P 2 <0.01, ^^^ - P 2 <0.001, # P3 <0.05, ## - P <0.01, ### - P <0.001).*

From table 3.4. It can be seen that among patients with NS, LVEF was statistically reduced than patients with SS. In patients with NS and ADS, LVEF was slightly reduced than in patients with NS without ADS. And also cases with ST segment depression are 39% more common in patients with NS and ADS, in contrast to patients without ADS.

The above data indicate that comorbid conditions as psychosomatic disorders lead to destabilization of coronary artery disease, in turn, destabilized variants of coronary artery disease can increase the incidence of fatal cases.

Chapter Conclusion

Thus, using the above data, we can conclude that when testing on the HADS and Spielberger-Hanin scales among patients with NS, 78.1% have the presence of ADS, which can explain the increased incidence of ST segment elevation/depression and inversion wave T. It is also necessary to emphasize that ADS is 6% more common among females, although the average scores on the HADS and Spielberger-Hanin scales in both men and women were not statistically different, which explains the frequent cases of destabilization of IHD among women .

Features of the psycho-emotional status of patients with coronary heart disease

202 patients with coronary artery disease were under observation . Among them were 102 women and 100 men, the average age was 63.75 ± 11.37 years (Fig. 3.8.).

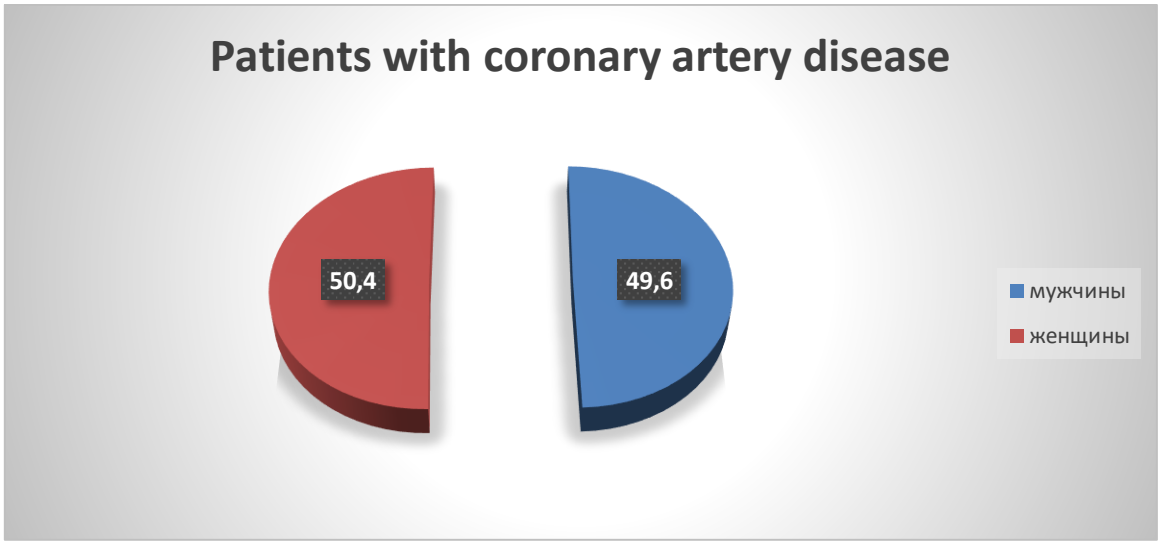


Fig.3.8. *Distribution of patients with coronary artery disease by gender* .

Among these patients, arterial hypertension occurred in 140 patients (69.3%), diabetes - in 44 patients (21.8%), 52 patients (25.7%) had previously suffered a myocardial infarction, arrhythmia was observed in 29 (14.35%)), anemia - 33 (16.3%), previous stroke - 10 (5.0%), COPD - 11 (5.4%), obesity - 97 (48.1%), other diseases 27 (13, 36%) (Fig. 3.9.).

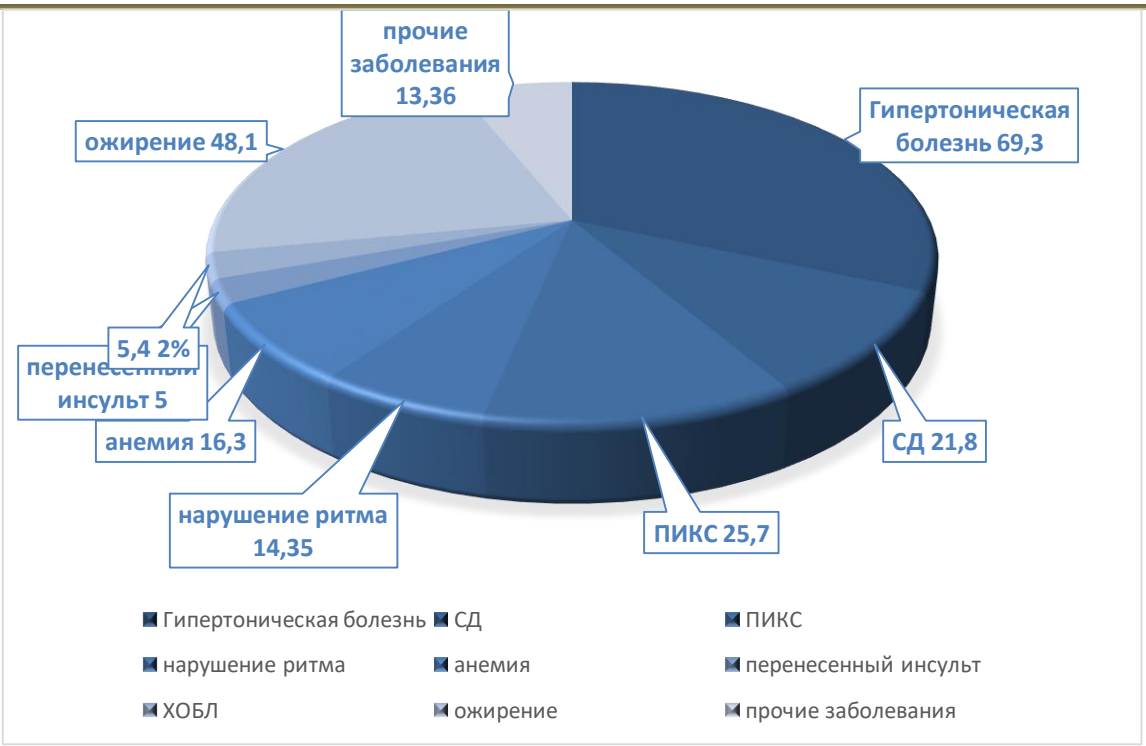


Fig.3.9. *. Distribution of patients depending on the frequency of occurrence of concomitant conditions.*

In our study, in 19 (9.26%) patients, the equivalent of angina pectoris was paroxysmal shortness of breath. 26 (12.68%) patients with NS had an atypical nature of the pain syndrome.

To solve general clinical problems, patients, thanks to two scales (hospital HADS scale and Spielberger- Khanin scale), were conditionally divided into 2 groups: group 1 - patients with comorbidity with anxiety-depressive syndrome (n = 122) and group 2 - patients without anxiety-depressive syndrome (n = 33) .

On table 3.3.1. it can be seen that the indicators of biochemical studies between patients with NS with and without ADS, as well as between a comparable group of patients with SS, are statistically insignificant, but it is necessary to emphasize the fact that among patients with ADS, the level of sUA was higher by 104.5 μmol/l, than in patients without ADS.

After identifying an increased level of UA in the blood of patients with UA with ADS, we decided to study the characteristics of the blood lipid profile in patients with unstable angina, as well as the relationship between the level of UA and ADS.

Table 3.5.

Indicators characterizing biochemical data in patients with NS and SS, M±m

Index	Group 1 (NS), n=155		Patients with SS, n =47	P-value	
	Patients with NS and ADS, n =122	Patients with NS, n =33			
AST, mkat/l	0.64 ±0.04	0.65 ±0.04	0.61 ±0.03	>0.5 >0.5 >0.5	P1 P2 P3
ALT, mkat/l	0.71 ± 0.05	0.72 ± 0.05	0.74 ± 0.06	>0.5 >0.5 >0.5	P1 P2 P3
Bilirubin: - total, µmol/l	18.7 ± 0.8	19.7 ± 0.8^	21.4 ± 1.1	>0.5 <0.05 >0.2	P1 P2 P3
MK, µmol/l	452.7±14.1 ***	348.2±11.9	351.6±12.4 ^^^	<0.001 <0.001 >0.5	P1 P2 P3
Urea	7.4 ± 0.4	6.9 ± 0.4	6.8 ± 0.4	>0.2 >0.1 >0.5	P1 P2 P3
Creatinine, mmol/l	90.9 ± 4.4	81.9 ± 3.1	85.4 ± 3.2	>0.5 >0.2 >0.5	P1 P2 P3
GFR, ml/min	117.18 ±5.9	107.85 ±3.9	99.6 ±7.3	>0.1 >0.2 >0.5	P1 P2 P3
Blood glucose , mmol/l	6.52 ± 0.31	5.85 ± 0.30	5.5 ± 0.28^	>0.1 <0.0 5 >0.5	P1 P2 P3
H b , g/l	88.7 ± 4.8	89.3 ± 4.6	92.8 ± 3.1	>0.5 >0.5 >0.5	P1 P2 P3

Note:^# - differences relative to the data from the compared group are significant (* - P1 with <0.05, ** - P1<0.01, *** - P1<0.001, ^ - P2<0.05, ^ ^ - P2<0.01, ^^^ - P2<0.001, # - P3<0.05, ## - P3<0.01, ### - P3<0.001)*

On the tab. 3.5. it can be seen that the indicators of biochemical studies between patients with NS with and without ADS, as well as between a comparable group of patients with SS, are statistically insignificant, but it is necessary to emphasize the fact that among patients with ADS, the level of sUA was higher by 104.5 μmol/l, than in patients without ADS.

Table 3.6.

Indicators characterizing lipid metabolism and the level of sUA in the blood in patients with ischemic heart disease, M±m

Index	Group 1, NS+ ADS, n =122	Group 2, NS, n =33	3 group SS, n =47	P-value	
THC, mmol/l	6.7±0.3 **	5.6±0.2	6.2±0.3	<0.01	P1
				>0.2	P2
				>0.1	P3
HDL cholesterol, mmol/l	0.85± 0.07	0.95± 0.08	0.93± 0.09	>0.5	P1
				>0.5	P2
				>0.5	P3
LDL cholesterol, mmol/l	4.1±0.2	3.8±0.2	3.9±0.2	>0.2	P1
				>0.5	P2
				>0.5	P3
CA	6.9±0.3 ***	4.9±0.2 #	5.6±0.3 ^^	<0.001	P1
				<0.01	P2
				<0.05	P3
MK μmol/l	452.7±14.1 ***	348.2±11.9	351.6±12.4 ^^^	<0.001	P1
				<0.001	P2
				>0.5	P3

*Note. *^#- Significant compared with NS with and without ADS, as well as with stable angina (* - P1 <0.05, ** - P 1 <0.01, *** - P 1 <0.001, ^ - P2 <0.05, ^^ - P 2 <0.01, ^^^ - P 2 <0.001, # P3 <0.05, ## - P <0.01, ### - P <0.001). P 1, P 2, P 3 – reliability of differences between 1gr and 2gr, 1gr and 3gr and 2gr and 3gr, respectively.*

Analysis of the research results showed that among patients with NS and ADS, the indicators of total cholesterol and LDL cholesterol were statistically significantly higher in comparison with patients with NS and without ADS, as well as patients with SS (Table 3.3.2). The atherogenic coefficient was statistically increased in all groups of patients, while the optimal value is considered when KA is 2-3. But among patients with NS and ADS, KA was significantly higher and was equal to 6.9±0.3 . In addition, the level of uric acid was also statistically different (452.7±14.1 μmol/l in patients with NS and 348.2±11.9 μmol/l in patients with SS) among these groups, which shows the connection between hyperuricemia and dyslipidemia.

Chapter Conclusion

Thus, the obtained analyzes of the lipid profile and the level of sUA among patients with NS with ADS, as well as patients with NS without ADS, showed that in patients with NS with ADS the level of sUA is 104.5 μmol/l higher than among patients without ADS and 101. 1 μmol/l is higher than among patients with SS. In addition, CA among patients with NS with ADS is 2 times higher than the norm. The presence of asymptomatic HU and lipid profile disturbances may be one of the main factors in the occurrence of ADS among patients with coronary artery disease and contribute to an increase in the frequency of attacks of NS.

CHAPTER 4.
Serum pro- and anti-inflammatory cytokines and depression in coronary heart disease

Depression is a risk factor for cardiovascular disease and death in many ways, directly and indirectly. It is independently associated with smoking, diabetes and obesity, which are risk factors for coronary artery disease (CHD). Patients with depression are more likely to fail to comply with treatment recommendations, including diet. However, depression often goes undetected by non-psychiatrist clinicians [165]. ¯ Several large meta-analyses and reviews show that, even after controlling for traditional risk factors for coronary heart disease, depression is independently associated with a 1.5- to 2-fold increase in the risk of coronary heart disease. Ruguli [172] shows an overall relative risk (RR) of CAD of 1.64 (95% confidence interval [CI], 1.29 to 2.08) in patients with depression and 2.69 (95% CI, 1. 63-4.43) in a subgroup of patients with major depressive disorder (MDD).

The INTERHEART trial, which included more than 25,000 patients from 52 countries, examined multiple risk factors for acute myocardial infarction[177]. The researchers found that after controlling for several variables, the psychosocial factor index—a combined measure of depression, general stress, life events, and locus of control—was found to be a stronger risk factor for acute myocardial infarction than hypertension, diabetes, or obesity. Depression for 2 or more weeks was associated with an odds ratio (OR) of 1.55 (95% CI, 1.42–1.69) for acute myocardial infarction.

An analysis of the EPIC-Norfolk prospective study, with a follow-up period of 6 to 10 years, found that participants who had major depression in the year preceding their baseline assessment were 2.7 times more likely to die from coronary heart disease, even after controlling for several other cardiac risk factors and antidepressant use [179]. Depression in patients with pre-existing heart disease is strongly associated with negative outcomes. Overall, depression is associated with a 3- to 4-fold increased risk of recurrent heart attacks and death. It predicts future cardiac mortality and morbidity in patients with coronary artery disease without a recent heart attack, and mortality and morbidity in patients with a recent myocardial

infarction. Depression also predicts morbidity and mortality in patients undergoing coronary artery bypass grafting, as assessed over a follow-up period of 2 to 12 years, as well as mortality and readmission rates in patients with established congestive heart failure. Several biological mechanisms have been proposed to explain the association between depression and CAD. There is considerable physiological overlap between these different mechanisms, and different subtypes or aspects of depression may be associated with different physiological processes. Increased platelet reactivity, which causes increased platelet aggregation and blood clot formation, may play an important role in linking depression and CAD. In response to activation, platelets release serotonin, which acts at 5-HT2 receptors as a weak direct agonist that promotes platelet aggregation, enhances the platelet aggregation response to other agonists, and causes vasoconstriction in arteries[179]. Depression has been associated with increased platelet 5-HT2 receptor binding and, in particular, increased platelet 5-HT2 receptor density, especially in patients who were contemplating or attempting suicide. Musselman and colleagues [153] reported that treatment with paroxetine for 6 weeks reduced platelet activation in 15 patients with depression, and Atar and colleagues [97] reported that escitalopram also had an antiplatelet effect in 20 healthy participants. It remains to be seen whether these effects are clinically significant. An increased inflammatory response has been found in people with depression, including increases in proinflammatory cytokines (eg, interleukin [IL]-1, IL-6, and tumor necrosis factor) as well as acute phase proteins (eg, C-reactive protein). These inflammatory markers have been associated in a number of studies with congestive heart failure, atherosclerosis, myocardial infarction and stroke[97]. Attempts to prove that there is an additive effect of depression on the elevated levels of cytokines commonly found in patients with heart disease have yielded mixed results. Lesprance et al [143] showed a significant association between depression and elevated levels of intracellular adhesion molecule, a soluble marker of endothelial activation, in 1 of 481 patients tested 2 months after acute coronary syndrome. They also found that depressed patients who were not taking statins had significantly higher levels of C-reactive protein than patients who were not depressed. However, there were no differences in IL-6 levels between depressed patients and those who were not depressed. Schins and colleagues [170] found no significant difference between inflammatory markers, including IL -6, C -reactive protein, and tumor necrosis factor-α, in patients with and without depression following

myocardial infarction, even though levels were higher than normal in both cases. groups. Depression is associated with greater activity of the hypothalamic-pituitary-adrenal axis, as evidenced by increased levels of corticotropin release, higher cortisol levels, greater amounts of catecholamines (epinephrine and norepinephrine), and resistance to the dexamethasone suppression test. The results of a study by Otte and colleagues [158] indicate that depression is significantly associated with elevated cortisol levels in patients with CAD. Catecholamines cause vasoconstriction and volume expansion, which may be beneficial in the short-term response to acute threats, but in a chronic condition can ultimately lead to heart failure. Elevated catecholamine levels are associated with mortality from left ventricular dysfunction and heart failure.

Severe depression appears to be accompanied by immune dysregulation [33]. Peripheral cytokines may be influenced by the neuroendocrine system [51], which is regulated by corticosteroids derived from the adrenal cortex. Plasma concentrations of the proinflammatory cytokines IL-1 and IL-6 are increased in patients with depression; in patients taking antidepressants, the decrease in plasma IL-1β levels appears to be related to treatment. The development of depression is also associated with increased concentrations of inflammatory biomarkers in the blood; for example, proinflammatory and antiviral cytokines (IL-2, TNF-α and IFN-α) are associated with influenza-like and depressive symptoms [81].

People with depression have elevated concentrations of several inflammatory biomarkers, including TNF-α, IL-4, and CRP, which may predict cardiac morbidity and mortality [83].

There are associations between inflammatory triggers and the occurrence of coronary heart disease (CHD) [83]. In CAD, lipids accumulate in the intima of the coronary arteries, which is associated with infiltration of mononuclear cells and proliferation of smooth muscles. Traditional risk factors for cardiovascular disease, chronic inflammation and a sedentary lifestyle play an important role in increasing the risk of CAD. Diet can also significantly influence the T cell-mediated immune response, although it does not appear to have any effect on B cell function or the production of proinflammatory mediators. Cytokines play an important role in the activation of adhesion molecules and the expression of chemokines involved in the attraction of leukocytes [83].

Some researchers have suggested that TNF-α, IL-2 and IL-10 may be potential markers in predicting cardiovascular events. C-reactive protein

(CRP) and IL-6 have also been identified as independent risk factors for future myocardial infarction [199].

Method for determining the concentration of cytokines in blood serum

The levels of pro- and anti-inflammatory cytokines TNF -α, IL-1β, IL-4 and IL-10 were examined in all patients with unstable angina . The level of cytokines TNF -α, IL-1β, IL-4 and IL-10 in blood serum was determined by enzyme-linked immunosorbent assay (ELISA).

(using the example of IL -1 β).

Human interleukin-1 was determined in the test samples (blood serum) using enzyme-linked immunosorbent assay.

The operating principle of the "ELISA-1 IL " kit is based on the "sandwich" version of the enzyme-linked immunosorbent assay. To implement this option, two monoclonal antibodies with different epitope specificities for IL -1 were used. One of them is immobilized on the solid phase (inner surface of the wells), the second is conjugated with peroxidase. At the first stage of the analysis , IL -1 contained in calibration and test samples binds to antibodies immobilized on the inner surface of the wells. At the second stage of the analysis, immobilized IL -1 interacts with the conjugate of the second antibodies - peroxidase. The amount of bound conjugate is directly proportional to the amount of IL -1 in the test sample.

During incubation with the substrate mixture, the solution in the wells becomes colored. The degree of coloring is directly proportional to the amount of bound labeled antibodies. After measuring the optical density of the solution in the wells, the concentration of IL -1 in the samples being determined is calculated based on the calibration curve .

The operating principle of the test system for determining cytokines is based on the sandwich method of enzyme-linked immunosorbent assay using horseradish peroxidase as an indicator enzyme. After completing the main stages of work, a solution of the substrate-chromogenic mixture is prepared 10-15 minutes before the end of incubation.

Then the wells of the plate are washed three times by adding 300 µl of washing solution to each of them and 3-5 times with distilled water, followed by removing it by shaking the plate over the sink. Add 200 µl of a substrate-chromogenic mixture solution to all wells. Incubate for 20 minutes at room temperature in the dark.

Stop the reaction by adding 50 µl of 1 N sulfuric acid solution. Accounting for results determining the activity of bound peroxidase is

carried out using an automatic microplate photometer at a wavelength of 492 nm, setting zero absorbance for wells with a standard without a detectable cytokine in solution.

Quantitative assessment of the results is carried out by constructing a calibration curve or using the commercial computer program " Microplatemanager ", reflecting the dependence of optical density on concentration for the standard antigen and allowing comparison of the studied samples with it. The sensitivity of the method is 5-30 pg/ml.

Analysis of some cytokines depending on the psychoemotional status in patients with NS

As is known, one of the objectives of this study is to study the serum levels of TNF -α, IL -1 β , IL-4 and IL-10 cytokines in patients with NS with ADS (group 1) and NS without ADS (group 2) , as well as analysis of relationships with the level of sUA in the blood.

The results of determining the pro-inflammatory cytokines TNF -α, IL -1 β pg/ml in patients with NS with and without ADS indicate a statistically significant increase compared to the group with SS (Table 4.1.). In the group with unstable angina, the level of TNF -α and IL -1 β was significantly higher than in the group with stable angina (P<0.05).

Table 4.1.

Levels of TNF-α, IL-1β, IL-4 and IL-10 cytokines in patients with coronary artery disease with and without ADS (stable and unstable angina)

Index	SS (n=47)	Group 1 (n=122)	Group 2 (n=33)	P-value	
TNF -α pg/ml	66.3±2.2	72.2±2.3	66.2±2.1	>0.1	P1
				>0.5	P2
				<0.05	P3
IL -1 β pg/ml	90.9±2.8	99.6±3.6	88.5±3.7	<0.05	P1
				>0.5	P2
				<0.05	P3
IL-4 pg/ml	22.4±0.9	20.3±0.7	23.0 ± 0.9	>0.1	P1
				>0.5	P2
				<0.02	P3
IL-10 pg/ml	13±0.5	12.2±0.5	14.2±0.6	>0.2	P1
				>0.1	P2
				<0.01	P3
MK µmol/l	351.6±11.3	452.7±18	348.2±10.7	<0.001	P1
				>0.5	P2
				<0.001	P3

P 1, P 2, P 3 – significance of differences between CC and 1gr, CC and 2gr, 1gr and 2gr, respectively.

The levels of anti-inflammatory cytokines such as IL-4 and IL-10 were statistically different (P1 <0.01) between patients with NS with ADS and patients with NS without ADS and were as follows: patients with NS and ADS –20.3 pg/ml and 12, 2 pg/ml; NS without ADS - 23.0 pg/ml and 14.2 pg/ml, respectively; with SS IL-4 and IL-10 - 22.4 pg/ml and 13.0 pg/ml, respectively .

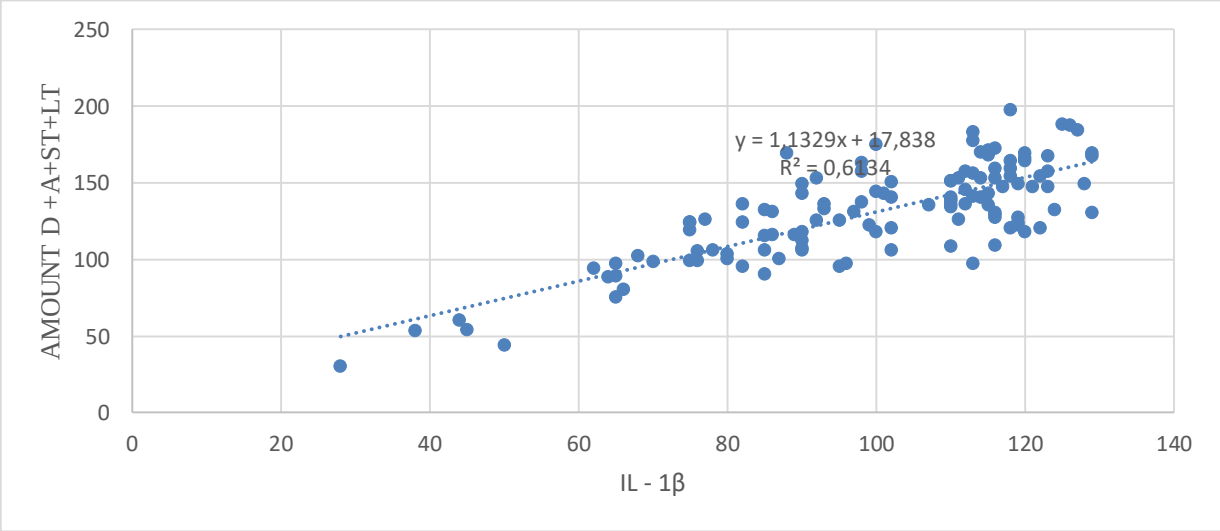


Figure 4.1. *Assessment of the correlation between the sum of ADS indicators and IL - 1 β in patients with NS (P-value<0.05).*

Note : D - depression, A - anxiety, ST-situational anxiety, LT -personal anxiety

When studying the correlation between pro-inflammatory interleukin IL -1β and ADS indicators (Fig. 4.1.), it turned out that there is an average correlation between them ($R^2 = 0.6134$) .

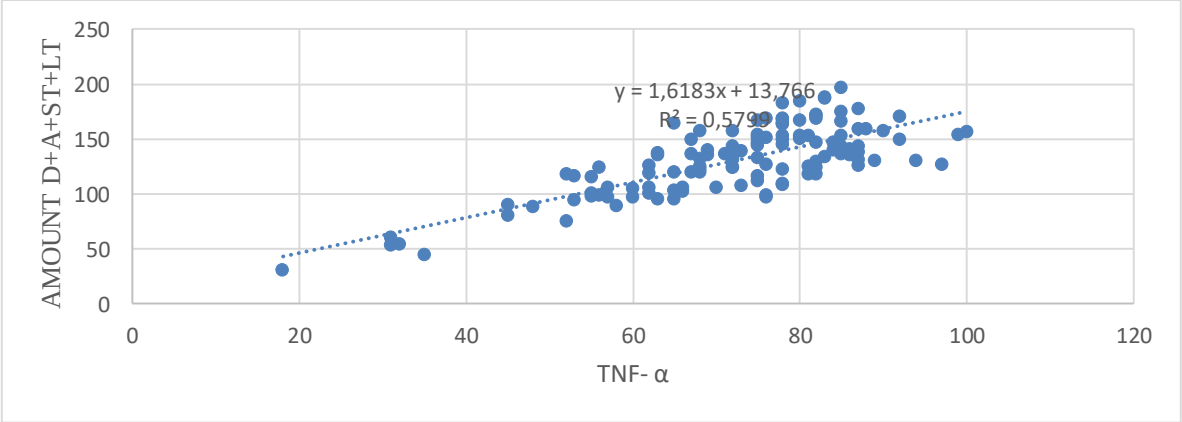
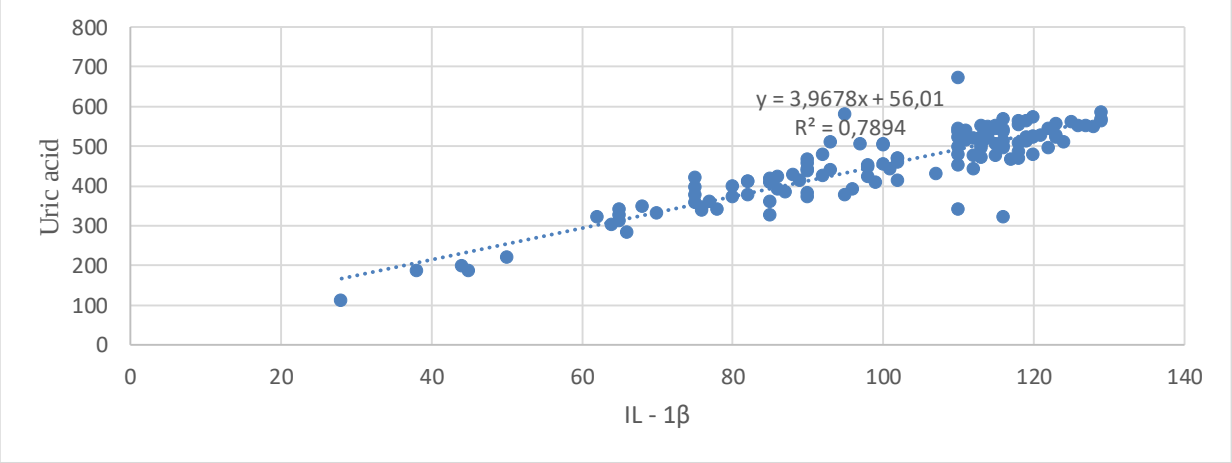


Figure 4.2. *Assessment of the correlation between the sum of ADS and TNF -α indicators in patients with NS (P-value<0.05).*

Note: D - depression, A - anxiety, ST-situational anxiety, LT-personal anxiety .

When studying the relationship between the sum of ADS indicators and TNF -α, an average strength of correlation was also revealed (R^2 = 0.5799).

Taking into account the identified peculiarity in the level of UA and its frequency of occurrence among patients with NS, we analyzed the relationship between the cytokine balance and the psychosomatic state depending on the content of UA in the blood.



***Drawing. 4.3** . Assessment of the correlation between the average value of UA in the blood and IL -1 β in patients with NS (P-value<0.05).*

As can be seen from Figure 4.3. and 4.4. the correlation between MK and pro-inflammatory IL -1 β , TNF -α cytokines is strong (R^2 = 0.7894, R^2 = 0.7662, respectively).

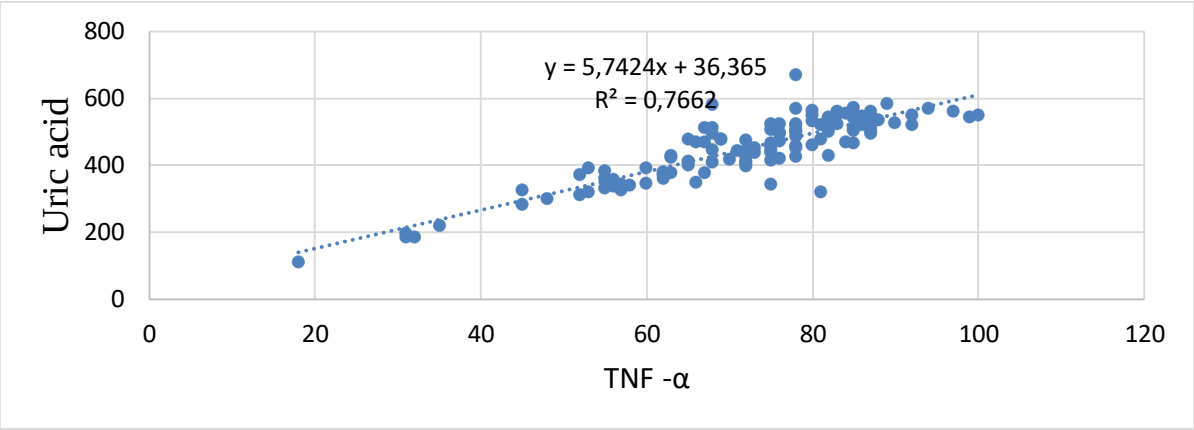


***Figure 4.4** . Assessment of the correlation between the average value of sUA in the blood and TNF -α in patients with NS (P-value<0.001).*

On table 4. 4 . One can see statistically significant differences in the level of TNF -α (P <0.05) among patients with NS with ADS and SS, which

confirms the worsening of the inflammatory process among this category of patients.

Among patients with NS with ADS and with increased levels of sUA, one can also see increased levels of pro-inflammatory cytokines, as well as statistically significant indicators of the level of sUA, in contrast to patients with NS without ADS and SS (P <0.001).

Table 4.2.

Indicators of interleukins TNF-α, IL-1β, IL-4 and IL-10 in patients with coronary artery disease (stable and unstable angina) depending on the level of sUA among patients with NS with ADS

Indicators	NS + ADS (n=122)		SS (n=47)	P-value	
	Patients with elevated levels (≥360 µmol/l) of sUA, n =78	Patients with normal level (≤360 µmol/l) sUA, n =44			
TNF -α pg/ml	103.3±4.6	93.1±3	90.9±3.7	>0.1 <0.05 >0.5	P1 P2 P3
IL -1 β pg/ml	74.3±3.4	68.5±2.5	66.3±2.8	>0.2 >0.1 >0.5	P1 P2 P3
IL-4 pg/ml	19.8±0.9	21.2±0.9	22.3±0.9	>0.2 >0.1 >0.5	P1 P2 P3
IL-10 pg/ml	11.7±0.4	13.0±0.6	13.4±0.6	>0.1 <0.02 >0.5	P1 P2 P3
MK µmol/l	538.2±23.4	301.2±11.4	351.6±15.6	<0.001 <0.001 <0.01	P1 P2 P3

Table 4.3.

Indicators of interleukins TNF-α, IL-1β, IL-4 and IL-10 in patients with coronary artery disease (stable and unstable angina) depending on the level of sUA among patients with NS with and without ADS

Indicators	NS without	NS + ADS	SS (n=47)	P-value	
	Patients with elevated levels (≥360 µmol/l) of sUA, n =10	Patients with elevated levels (≥360 µmol/l) of sUA, n =78			
TNF -α pg/ml	98.4±3.6	103.3±4.1	90.9±3.0	>0.5 >0.1 <0.02	P1 P2 P3
IL -1 β pg/ml	73.8±2.9	74.3±2.8	66.3±2.1 ^	>0.5 <0.05 <0.02	P1 P2 P3
IL-4 pg/ml	23.7±1.0 ***	19.8±0.7 #	22.3±0.9	<0.001 >0.2 <0.05	P1 P2 P3
IL-10 pg/ml	14.6±0.5 ***	11.7±0.5 #	13.4±0.6	<0.001 >0.1 <0.05	P1 P2 P3
MK µmol/l	424.4±15.5 ***	538.2±23.4 ###	351.6±13.5 ^^^	<0.001 <0.001 <0.001	P1 P2 P3

Note: # - differences relative to the data from the compared group are significant (- P1<0.05, ** - P1<0.01, *** - P1<0.001, ^ - P2<0.05, ^^ - P2< 0.01, ^^^ - P2<0.001, # - P3<0.05, ## - P3<0.01, ### - P3<0.001)*

Thus, among patients with stable and unstable angina associated with BGU, the levels of pro-inflammatory cytokines TNF -α, IL -1β were statistically significant (P<0.001). Difference between indicators TNF -α among patients with NS+ADS and SS was 12.4 ±1.1 pg/ml (P <0.02), between the indicators IL -1 β 8.0 ±0.7 pg/ml (P <0.02). And also the levels of anti-inflammatory cytokines IL -4 and IL -10 were slightly reduced among patients with NS with ADS, which indicates an imbalance in the cytokine balance, in particular among this category of patients (IL-4-19.8±0.7 pg/ml and IL-10 - 11.7±0.5 pg/ml). But the indicators of anti-inflammatory cytokines IL-4 and IL-10 among patients with NS without ADS did not differ significantly from the indicators of the group of patients with stable angina pectoris and the statistical significance was equal to P <0.2, P <0.1, respectively .

Table 4.4.

Indicators of interleukins TNF-α, IL-1β, IL-4 and IL-10 in patients with coronary artery disease (stable and unstable angina) depending on the level of sUA among patients with UA without ADS and without it

Indicators	NS without ADS (n=33)		SS (n=47)	P-value	
	Patients with normal level (≤360 µmol/l) sUA, n =10	Patients with elevated levels (≥360 µmol/l) of sUA, n =23			
TNF -α pg/ml	84.2±3.5 **	98.4±3.4	90.9±3.1	<0.01 >0.2	P1 P2
IL -1 β pg/ml	62.9±2.2 ***	73.8±2.7 #	66.3±2.8	<0.001 >0.5 <0.05	P1 P2 P3
IL-4 pg/ml	22.7±0.8	23.7±1.1	22.3±0.8	>0.5 >0.5 >0.2	P1 P2 P3
IL-10 pg/ml	13.9±0.6	14.6±0.6	13.4±0.5	>0.5 >0.5 >0.1	P1 P2 P3
MK, µmol/l	315.0±12.3	424.4±16.3	351.6±14.9	<0.001 <0.05 <0.001	P1 P2 P3

When studying the indicators of pro- and anti-inflammatory cytokines in patients with NS without ADS, depending on the level of UA, we identified statistically significant indicators between the indicators of pro-inflammatory cytokines TNF -α and IL -1 β (P <0.01 and P <0.001, respectively) among patients with elevated levels of uric acid in contrast to patients with SS.

Then, in each group, patients, depending on the level of LDL cholesterol, were divided into 2 more subgroups: 1st subgroup with low (less than 4.0 mmol/l), 2nd subgroup with high (more than 4.0 mmol/l) levels LDL cholesterol (Table 4.1.5).

When studying the levels of cytokines depending on the level of LDL cholesterol, it turned out that patients with unstable angina and ADS who had high LDL levels (above 4.0 mmol/l) had statistically significant indicators, i.e. TNF -α - 72.6±3.1 pg/ml and IL -1 β - 100.4±4.2 pg/ml, in contrast to patients with stable angina, which shows the connection between cytokine imbalance not only with increased levels of sUA, but also with lipid metabolism disorders in these patients.

Table 4.5.

Indicators of interleukins TNF-α, IL-1β, IL-4 and IL-10 in patients with coronary artery disease (stable and unstable angina) depending on the level of LDL cholesterol in the blood

Indicators	NS + ADS (n=122)		SS(n=47)	P-value	
	Patients with elevated LDL cholesterol levels (≥ 4.0 mmol/l) (n =92)	Patients with normal LDL cholesterol levels (≤ 4.0 mmol/l) (n = 30)			
TNF -α pg/ml	72.6±3.1	71.4±2.2	66.3±2.5	>0.5 >0.1 >0.1	P1 P2 P3
IL -1 β pg/ml	100.4±4.2	97±3	90.9±3.7	>0.5 >0.1 >0.2	P1 P2 P3
IL-4 pg/ml	19.9±0.8	21.4±0.8	22.3±0.9 ^	>0.2 <0.05 >0.5	P1 P2 P3
IL-10 pg/ml	11.9±0.6	13.2±0.6	13.04±0.5	>0.1 >0.2 >0.5	P1 P2 P3
LDL mmol/l	4.64±0.2 ***	2.36±0.2 ###	3.9±0.2 ^^	<0.001 <0.01 <0.001	P1 P2 P3

Table 4.6.

Indicators of interleukins TNF-α, IL-1β, IL-4 and IL-10 in patients with coronary artery disease with and without ADS (stable and unstable angina) depending on the level of LDL cholesterol in the blood

Indicators	NS + ADS	NS without ADS	SS (n=47)	P-value	
	Patients with elevated LDL levels (≥ 4.0 mmol/l) (n = 92)	Patients with elevated LDL levels (≥ 4.0 mmol/l) (n = 22)			
TNF -α pg/ml	72.6±2.3	65.4±2.1	66.3±2.2 ^	<0.02 <0.05 >0.5	P1 P2 P3
IL -1 β pg/ml	100.4±4.3 *	88.6±3.8	90.9±3.3	<0.05 >0.1 >0.5	P1 P2 P3
IL-4 pg/ml	19.9±0.8	22.5±0.8	22.3±0.9 ^	<0.02 <0.05 >0.5	P1 P2 P3
IL-10 pg/ml	11.9±0.5 **	14.0±0.5	13.0±0.4	<0.01 >0.1 >0.1	P1 P2 P3
LDL mmol/l	4.64±0.2	4.5±0.2 #	3.9±0.2 ^^	>0.5 <0.01 <0.05	P1 P2 P3

Between patients with NS with ADS, in contrast to patients without ADS, there was an increase in the level of IL -1 β pg/ml by 11.8 pg/ml (P <0.05) , as well as a decrease in IL-10 by 2.1 pg/ml (P <0.01).

As a result, a slight increase in the concentration of TNF -α and IL -1β (72.6 ± 2.3 and 100.4 ± 4.3, respectively) in the blood serum was detected in groups with LDL cholesterol levels greater than 4.0 mmol/l . But among patients with NS with high levels of LDL cholesterol, the levels of these pro-inflammatory cytokines were statistically higher than among patients with CV with elevated levels of LDL cholesterol (IL -4-19.9±0.8 pg/ml and IL -10 - 11, 9±0.5 pg/ml).

Table 4.7.

Indicators of interleukins TNF-α, IL-1β, IL-4 and IL-10 in patients with coronary artery disease without ADS (stable and unstable angina) depending on the level of LDL cholesterol in the blood

Indicators	NS without ADS (n=33)		SS (n=47)	P-value	
	Patients with elevated LDL levels (≥ 4.0 mmol/l) (n = 22)	Patients with normal LDL levels (≤ 4.0 mmol/l) (n = 11)			
TNF -α, pg/ml	65.4±2.9	67.8±2.2	66.3±2.6	>0.5 >0.5	P1 P2
IL -1 β pg/ml	88.6±3.1	88.4±2.8	90.9±4	>0.5 >0.5 >0.5	P1 P2 P3
IL-4 pg/ml	22.5±1	23.4±0.9	22.3±0.7	>0.5 >0.5 >0.5	P1 P2 P3
IL-10 pg/ml	14.0±0.5	14.4±0.5 #	13.0±0.5	>0.5 >0.2 <0.05	P1 P2 P3
LDL mmol/l	4.5±0.2 ***	2.2±0.1 ###	3.9±0.2 ^	<0.001 <0.05 <0.001	P1 P2 P3

When studying the indicators of the above-studied cytokines in patients with NS without ADS, depending on the level of LDL, unreliable statistical data were revealed (P<0.5), which once again shows the connection between the progression of NS in patients with ADS.

Chapter Conclusion

Thus, the results of the study showed that in patients with NS with ADS, there is an average correlation between the pro-inflammatory cytokines TNF -α and interleukin IL -1β with ADS indicators (R^2 =0.5799, R^2 =0.6134) . The correlation between UA and pro-inflammatory IL -1 β , TNF -α cytokines turned out to be strong (R^2 =0.7894, R^2 =0.7662, respectively), which shows a direct connection between cytokine imbalance and an increase in the level of UA in the blood. In addition, among patients with NS with ADS, the level of LDL cholesterol is 2.28 mmol/l higher than in patients with NS without ADS and 0.74 mmol/l higher than in patients with SS. When studying the levels of cytokines depending on the level of LDL cholesterol, it turned out that patients with NS with ADS who had high levels of LDL cholesterol (above 4.0 mmol/l) had statistically significant indicators, i.e. TNF -α was higher by 7.11 pg/ml and IL -1 β by 11.8 pg/ml in contrast to NS patients without ADS. A comparative analysis of the

tension in the functioning of these systems during the atherosclerotic process revealed the presence of a close relationship between individual parameters of immune inflammation, UA metabolism and the presence of a psycho-emotional factor.

CHAPTER 5.
Features of polymorphism of some cytokine genes in patients with unstable angina depending on the psycho-emotional status and BGU among the Uzbek population, similarities and differences from foreign studies

Demonstration of a common genetic substrate for depression and immune activation is of significant scientific and clinical interest and may reveal mechanisms by which the innate immune system and depression are intertwined. Indeed, twin studies have shown a heritable link between depression and inflammation [193]. In this review, we will look at inflammatory genes that determine the pattern of depression, and, in particular, polymorphisms that enhance or attenuate this process. Research has begun to reveal the plastic nature of inflammatory genes, particularly the impact of adverse childhood events on the immune system and later susceptibility to depression. More recently, genome-wide association studies (GWAS) have been used to identify candidate genes for depression. GWAS have achieved impressive results in other pathologies such as diabetes and rheumatoid arthritis, but have so far had limited success in treating depression. Finally, gene expression studies and transcriptomics have begun to complement and supplant GWAS in genome-wide studies. Gene expression studies have begun to track inflammation-related gene networks implicated in the pathogenesis of depression, and improved technologies such as RNA-seq have allowed broader and more sensitive studies than previous gold standard gene expression microarrays [175]. A new picture is emerging of the networks and pathways linking behavior and the immune system. In this review, we focus on the relationship between genetic polymorphisms in immune genes and depression risk, severity, and response to antidepressant treatment, including major depressive disorder (MDD), recurrent depression, dysthymia, childhood-onset major depression, and geriatric depression. In addition, we included studies examining the prevalence of depression in subjects with medical conditions such as heart disease, cancer, and those receiving cytokine therapy such as interferon-alpha (IFN- α).

In this study, we included pharmacogenetic studies to better understand the mechanisms involved in the relationship between immune system activation and depression in relation to antidepressant response, as well as candidate gene expression studies and transcriptomics.

The interleukin-1-beta (*IL-1β*) gene is highly polymorphic, with the -511 C/T variation (rs16944) being a particular target of study. The first study of the -511T polymorphism was carried out by Yu *et al* (2003), who found that a subgroup of patients with major depressive disorder homozygous for the “low-yielding” 511C allele had more severe depressive symptoms and a less favorable response to fluoxetine treatment compared with 511T carriers. Then Tadic *et al* (2008) demonstrated that the C/C genotype showed a slower and less pronounced response to paroxetine than patients with the C/T or T/T genotype. There was no association between the 511T gene variant and response to treatment with mirtazapine (Tadic *et al.* , 2008). In the Chinese population (Hwang *et al* , 2009) depressed patients carrying the C/C genotype showed a significantly earlier age of onset of depression compared to depressed patients who were C/T heterozygous or homozygous for the T allele. Similar results were also found in patients with dysthymia who had a higher prevalence of the 511C allele compared to controls (Fertuzinhos *et al* , 2004). In contrast, an association was found between the "high output" T variant and depressive symptoms in subjects with Alzheimer's disease (McCulley *et al* , 2004) and schizophrenia (Rosa *et al* , 2004). Kim *and etc.* (2013) found that the T/T form of IL-1β-511 was associated with depression at baseline and 1-year follow-up in breast cancer patients. However, in the Taiwanese sample it was not associated with MDD (Chi *et al* , 2011). The variance of these polymorphic effects across 511 SNPs may be influenced by early life stress exposure. A study of 1053 Caucasian Hungarian volunteers (Kovács *et al* , 2016) found that the presence of the A allele of rs16944 (equivalent to T 511) in combination with childhood abuse led to increased depressive and anxiety symptoms in adulthood. However, the same SNP had a weak protective effect against depressive symptoms (but not anxiety) when the individual was exposed to life stressors as an adult (and not maltreated as a child). Tartter *and etc.* (2015) examined 511 variants in a study of 444 Australian young people. The C allele was associated with greater depressive symptoms following interpersonal stress. The same result was not found after exposure to other stressors, such as negative health and work outcomes, and depressive symptoms did not appear until the age of 20,

leading the authors to suggest that the genetic effects of exposure to adverse childhood events only emerge later in life. adolescence.

Recently, in addition to 511 (C/T), a polymorphism in the promoter region of the *IL-1β gene* at position 31 with major recurrent depression was examined in patients. Concordance analysis showed that the combination of the T/T genotype for polymorphic locus 31 and the C/C genotype at position 511 was associated with depression, whereas controls presented a heterozygous combination at both polymorphic loci (Borkowska *et al* , 2011). Instead, no clear evidence was found for childhood depression (Misener *et al* , 2009 ; 2008) or geriatric depression (Luciano *et al* , 2010). In a study of 599 Caucasian lung cancer patients, Reyes-Gibbey *and etc*. (2013a) found an association between *IL-1β* T-31C and a cluster of symptoms of pain , depressed mood, and fatigue.

In a sample of 256 patients with MDD, three SNPs located in the regulatory regions of the *IL-1β gene were studied* : 3953 C/T (rs1143634) in position 5, rs1143643 (A/G) in intron 6, and the aforementioned rs16944 (A/G) in promoter region. In addition, this study also assessed whether any of these SNPs were associated with response to antidepressant treatment and neural substrates of emotion processing. They found a significant association between the G/G genotype of rs16944 (same as CC 511) and the G/G genotype of rs114643 with a lack of remission after 6 weeks of antidepressant treatment. Interestingly, functional magnetic resonance imaging showed that in a subgroup of patients, the same genetic variants were associated with reduced cortical sensitivity to emotional stimulation (Baune *et al* , 2010). The 3953 C/T polymorphism (rs1143634) has also been studied in subjects with post-stroke depression, but with negative results (Kim *et al* , 2011). In an article focusing on 773 elderly Koreans (Kang *et al* , 2014), a significant association was also found between *IL-1β* 3953 C/T and depression, but this association was lost after applying Bonferroni correction. In another study, *IL-1β SNP rs1143643* did not increase depressive symptoms when combined with childhood trauma. However, the minor A allele did provide protection against depression due to trauma in adulthood (Kovács *et al* , 2016a). This same allele has previously been associated with better response to antidepressant therapy (Baune *et al* , 2010). Finally, Ridout *et al* (2014) studied 198 American children aged 3–5 years from different ethnic groups who had been maltreated in the previous 6 months. They found an association between the rs1143633 AA genotype and more severe MDD symptoms when exposed to contextual stressors such as loss, instability, or poverty. However, the study was limited by the small

number of children homozygous for AA. A haplotype (A1) consisting of three SNPs (rs4141134, rs11674595, and rs7570441) of the IL-1 receptor type 2 (*IL-1R2*) was found to be associated with subsyndromal depression in a study of 167 cancer patients and caregivers in the United States (Dunn *et al.* , 2013). IL-1R2 is a decoy cytokine receptor that binds IL-1B. The study suggested that decreased IL-1R2 expression leads to excess IL-1B, which is responsible for depressive symptoms.

Kim *et al* (2011) investigated anti-inflammatory ***IL-4*** . They found a significant association between major depression after stroke and the "low-yielding" genotype C/C polymorphism + 33T/C *IL-4* (Kim *et al* , 2011), but no association between breast cancer patients and depression (Kim *et al* , 2013a). Moreover, they found that subjects with the +33C allele showed an association between an increased number of physical disorders and depression later in life (Kim *et al* , 2013b).

Illy *et al* (2012) found evidence for the involvement of the rs2443248 (T/G) SNP among a group of cancer patients, with the minor G allele being associated with more severe depression, fatigue, sleep and pain. **I L -6** has been one of the most studied interleukins, due to its high association with depression (Liu *et al* , 2012 ; Valkanova *et al* , 2013), although this connection is not certain (Chocano-Bedoya *et al* , 2014). IL-6 is secreted mainly by monocytes and macrophages peripherally and by astrocytes and microglia in the CNS. Several different studies have found no significant associations between MDD, childhood depression or post-stroke depression, and polymorphisms at position 634 or position 174 of the *IL-6 gene* (Clerici *et al* , 2009 ; Hong *et al.* , 2005 ; Misener *et al* , 2008 2009). However, in a prospective study of patients treated with pegylated IFN- α and ribavirin for hepatitis C virus (HCV) infection, Bull *et al* (2009) found that the functional polymorphism G-174C (rs1800795) in the promoter region *of IL-* Gene *6* predicted depressive symptoms but not fatigue. Having two copies of the "high IL-6" G allele polymorphism was associated with a marked increase in depressive symptoms compared with the "low IL-6" C allele (Bull *et al* , 2009). This discovery was later reproduced by Udina *et al.* (2013) , who again found that the presence of the CC genotype rs1800795 was associated with less severe IFN- α- *induced depression* . On the contrary, Kovacs *and etc.* (2016b) found that in the presence of stressful life events, the risk of depression was higher in those homozygous for the low-producing C allele (rs1800795). However, they caution that this effect may be part of a broader haplotype, exerting its influence on gene expression in an independent manner. Tartter *and etc.* (2015) also found that CC carriers

for IL-6 174 were more likely to experience depressive symptomatology following chronic interpersonal stress, but not other stressors. They also noted that 174G provided protection against inflammation in adolescence but increased the risk of inflammation in adulthood, possibly indicating an age-related function. Roetker *et al.* (2012) found that women homozygous for rs1800795 (CC/GG) had an increased risk of depression, but only in the presence of other risk genes. In a study of 398 women with breast cancer, Doong *et al* (2014) also reported an association between patients homozygous for the high-producing G allele of *IL-6* (rs2069845) and a cluster of symptoms of pain, fatigue, sleep disturbance and depression, potentially arising as an interaction between SNPs for *IL-13* and tumor necrosis factor-alpha (*TNF-α*). In another study of breast cancer patients (Saad *et al* , 2014) homozygosity for the G allele of rs2069840 was associated with subsyndromal depression. **IL-8** is involved in neutrophil recruitment. *The IL-8* gene polymorphism at position 251 (T/A) has been examined in subjects with post-stroke depression with negative results (Kim *et al* , 2011). Kim *and etc.* (2013a) also examined *IL-8* -251T/A in breast cancer patients and again found no association between these alleles and depression. Later, the same research group found an association between an increase in physical disorders and depression later in life in people with the *IL-8* 251A variant in the aforementioned study (Kim *et al* , 2013b). However, Kang *et al.* (2014) found no association between *IL-8* −251T/A and depression in a study of 732 elderly Koreans.

IL-10 is an anti-inflammatory cytokine. A study examining a polymorphism at position 819 in *IL-10* found no evidence of an association with MDD (Jun *et al* , 2002). Similarly, no associations were found in another study of childhood depression and polymorphisms 819 (C/T), 1082 (G/A), or 592 (C/A) (Misener *et al* , 2008); and no associations were found in patients with one depressive episode, with or without stressful life events before their onset (Haastrup *et al* , 2012). On the other hand, in a study of patients suffering from bipolar disorder (type I or II) or MDD, an association was found between a polymorphism at position 1082 (G/A) and MDD (Clerici *et al* , 2009). In particular, the A/A genotype with “low IL-10 production” was significantly more common in patients with MDD than in controls. Similar results were obtained by Kim *et al* (2011), who found a significant association between post-stroke depression and the A-allele-A/A genotype of the same polymorphism (Kim *et al* , 2011). A further study conducted in patients with end-stage renal disease also confirmed these results (Holtzman *et al* , 2012). A study of 732 elderly Koreans found no

association between *IL-10* 1082 G/A (rs1800896) alleles and depression (Kang *et al* , 2014). Similarly, 1082 G/A was not correlated with depression in breast cancer patients (Kim *et al* , 2013) and did not influence the association between physical health and incident depression in late life (Kim *et al* , 2013). Continuing the negative findings, 1082 G/A was not associated with late- onset depression in a study of older Brazilians (Torres *et al* , 2013). However, in a study of >900 older Americans (Rana *et al* , 2014), rs1800896 was found to be associated with optimism when present at a multigene locus with MAO-a and fibrinogen gamma chain SNPs. Conflicting evidence for a genetic association between depression and IL-10 has been found by SNP analysis of the genomic region of the *IL-10 gene cluster* . *IL-10* rs1518111 was investigated in a study of 167 cancer patients and caregivers (Dunn *et al* , 2013), and the rare A/A configuration was found to be associated with subsyndromal depression. This non-coding SNP has unknown function but has previously been associated with Behçet's disease.

In our study, we studied the IL-1 β gene polymorphism—replacement of cytosine (C) with thymine (T) at position –511. DNA was isolated from peripheral blood lymphocytes using perchlorate extraction with ethanol precipitation. Gene variants carrying point nucleotide substitutions - IL-1 β (–511) in the C/T promoter region. The features of the distribution of frequencies of alleles and genotypes of the polymorphic variant of the IL - 10 C / T 819 gene (rs1800871) were studied. in patients with coronary artery disease and healthy individuals of Uzbek nationality . In 97 patients with unstable angina of Uzbek nationality, genotyping of the polymorphic C/T locus of the IL -10 C / T 819 (rs1800871) gene was performed . The results of which are presented in detail below [175] .

Method of conducting molecular genetic research

DNA extraction

The material for DNA extraction was venous blood from the cubital vein with a volume of 3-5 ml (Beckton - Dickinson vacutainers were used for blood collection) with an anticoagulant/preservative 15% tripotassium EDTA (Ethylendianin - tetraaceticacid). Blood for further processing could be stored for up to 24 hours at a temperature not exceeding +4°C.

To obtain genomic DNA, a two-step method of blood cell lysis was used. By double centrifuging the entire volume of whole blood in RCLB buffer (Redcells lysis buffer) at a speed of 1500 rpm for 15-20 minutes,

erythrocyte lysis was carried out. The use of RCLB causes osmotic shock to red blood cells, leading to their swelling and further destruction.

The supernatant containing destroyed erythrocytes was carefully drained from the tube, and the remainder of the supernatant was aspirated. The clot of leukocyte mixture remaining at the bottom was lysed in leukocyte lysis buffer WCLB (White cellslysis buffer , lysing buffer of white blood cells) in an amount depending on the volume of the leukocyte mixture. WCLB is also a preservative for storing buffy cell lysates even at room temperature. In this state, the lysates could be stored indefinitely.

Instructions for lysis buffers:

RCLB WCLB

1 mM NH_4HCO_3 100mM Tris-Cl (pH 7.6)

115 mMNH_4Cl 40 mMEDTA (pH 8.0)

Autoclave 50 mM$NaCl$

0.05% Sodiuma with ide

After autoclaving

0.2% SDS

Further purification of buffy cell lysates is based on the method of alcohol-salt treatment according to S. Miller et al. (1988) as modified by a laboratory at Stanford University.

NaCl to 400 µl of leukocyte lysate , mix on a shaker and place in ice for 10-20 minutes, then centrifuge at 1200 rpm for 15 minutes. The supernatant is taken into another Eppendorf tube and 100% ice-cold ethanol is added. When gently shaken, a quaternary strand of the DNA molecule appears in the mixture; the mixture is centrifuged at 1200 rpm for 15 minutes; the supernatant is removed, and the whitish stain remaining at the bottom of the tube is washed again in 80% ethanol at 1200 rpm for 10 minutes. The supernatant is drained, the remaining alcohol is carefully removed, the test tube is left open until the alcohol has completely evaporated (for 12 hours at room temperature or in a thermostat at 40-45°C for 2 hours).

Tris - EDTA) solution diluted with distilled water in a ratio of 1:3 (TE: water) pH 8.0 is added to the test tube with dried DNA .

DNA was stored at $-20\ ^0$ C.

Methods for identifying allelic variations of polymorphic loci of cytokine genes

Polymerase chain reaction (PCR) was performed on thermal cycler Rotor - Gene -2000 from CorbettResearch using appropriate

primers and 10 µl of PCR mixture (manufactured by NPO Litech) containing 2 mM $MgCl_2$, *Taq* DNA polymerase and Cresol Red dye. Visualization The results were carried out by electrophoresis in a 2% agarose gel with ethidium bromide at 150 V and 290 mA.

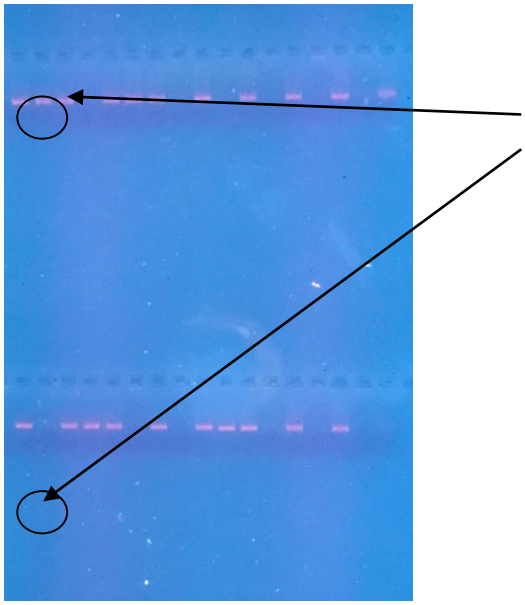
To detect the studied polymorphisms, amplification of certain sections of the corresponding genes was carried out.

Gene	Polymorphic locus	Cytogenetic localization	Rs	Localization	Primer structure
IL -1β	T-511C	2q13-2q14	rs16944	Intron	5′-TGG CAT TGA TCT GGT TCA TC-3′ and 5′-GTT TAG GAA TCT TCC CAC TT-3′
IL -10	C-819T	1q31-1q32	rs1800871	Intron	5'AACTTCTTCC ACCCCATCTTT-3' and 5'-ATCCTCAAAGT TCCCAAGCAG-3

Determination of polymorphism -511 C / T of the IL -1β gene and IL -10 -819 C / T was carried out by PCR, using diagnostic kits for identifying polymorphisms in the human genome by PCR “SNP-express” produced by SPF “Litech”. To study polymorphisms of pro-inflammatory cytokine genes, the Interleukin 1β Mutation kits (IL 1β gene, polymorphism -511 C / T) were used . To detect polymorphism of anti-inflammatory cytokine genes, the “Interleukin 10 Mutation-3” kits (gene –IL-10, polymorphism –C-819T) were used.

All kits are designed for 120 determinations, including controls. Two amplification reactions were carried out in parallel with the isolated DNA sample - with two pairs of allele-specific primers. The results of the analysis allow us to give three types of conclusions: normal homozygote; heterozygote; mutant homozygote. Composition of the “SNP-express” reagent kit: 1. “Norm” reaction mixture – 300 µl. 2. Reaction mixture “mutation” – 300 µl. 3. Diluent – 4 ml. 4.Taq polymerase – 50 µl. 5. Mineral oil – 4 ml. Detection was carried out using 50 x TAE buffer, ethidium bromide and agarose produced by SPF "Litekh". The study of gene polymorphism was carried out in 3 stages: 1. Isolation of DNA from whole blood leukocytes. 2. Carrying out PCR (amplification). 3. Detection of amplification products by horizontal electrophoresis.

At the final stage, the amplification products were separated by horizontal electrophoresis according to the following scheme: 1. TAE buffer prepared in distilled water with a 50-fold dilution of 50 x TAE (pH = 8.3) was poured into the electrophoresis apparatus. 2. 3% agarose was prepared for 1 gel: to 1.5 g of agarose add 1 ml of 50x TAE buffer and 55 ml of distilled water (evaporation reserve included). The prepared mixture was melted in a microwave oven at low power. To 50 ml of molten agarose, 5 µl of a 1% ethidium bromide solution was added. 4. The molten agarose was immediately poured into the gel loading plate. To obtain pockets in the agarose gel for applying samples, a comb was installed on the plate using a bulldog clamp; after the gel solidified, the clamp was removed. 5. 10 µl of the amplifier was applied into the gel pockets in the sequence corresponding to the sample numbering. 6. The electrophoretic chamber was connected to the power source and the voltage was set corresponding to the electric field strength of 10-15 V/cm of the gel. Electrophoretic separation of amplification products was carried out in the direction from the cathode (-) to the anode (+) for 15 minutes. Electrophoretic separation was monitored visually by the movement of the dye strip. 7. The gel from the mold was transferred to the glass of a UV transilluminator and the results were analyzed visually with a protective screen and using a program. Fragments of the analyzed DNA appeared as luminous orange-red bands under UV radiation with a wavelength of 310 nm. The results were interpreted in the following ways: normal homozygote, heterozygote, mutant homozygote.



Heterozygote

normal homozygote

mutant homozygote

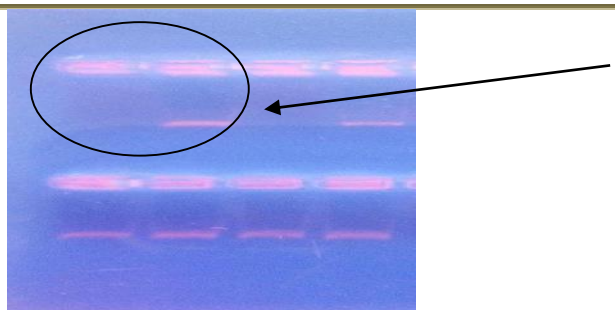


Fig. 5.1 *Electropherogram -511 C / T of the IL -1β gene in ultraviolet light (310 nm) after electrophoresis*

Statistical data processing

Statistical processing of the results was carried out using statistical software packages Arlequin 2006 (version 3.5.2.2.), Excel 20 17 , *SISA* and a number of formulas given below.

Polymorphism of locus -511C>T (rs 16944) IL -1β gene in patients with unstable angina, depending on the psychoemotional status and BGU

One of the objectives of the study was to assess the genetic polymorphism of the IL -1 β gene at position -511 T/C (rs16944) and IL -10 at position -819 S/T (rs1800871) in patients with coronary artery disease with ADS and BGU to determine predictors of prognosis for the development of unstable variants of angina pectoris . In this regard, the frequency of occurrence of the C/T alleles in locus 511 of the IL -1 β gene was studied in 97 patients with NS and 40 healthy donors of Uzbek ethnicity, with no clinical manifestations of the disease .

In Table 5.1, you can see that among patients with coronary artery disease, the T allele is 36.7% more common than among healthy individuals. The C allele, in contrast to the T allele, is more common in the control group and also accounts for 36.7%.

Among patients with NS, compared to the control group, the homozygous variant C/C at position -511 T/C of the IL -1β gene polymorphism was 47.4% less common, the homozygous variant T/T by 35.36%, and the heterozygous variant C/T at 11.9% more (Table 5.1).

Table 5.1.

Allele frequency distribution 511 S/T (rs16944) of the IL -1β gene in patients with NS and healthy individuals

Allele	Frequency (%)		χ2	P-value	OR	Lower gr. 95% CI	Upper gr. 95% CI
	Basics gr. (n=97)	Control (n=40)					
C	43.3	80.0	15.36	0.000	0.19	0.08	0.46
T	56.7	20.0	15.36	0.000	5.24	2.19	12.54

Table 5.2.

Frequency distribution of the polymorphic locus -511C>T (rs16944) of the IL-1β gene in patients IHD and healthy individuals

Genotype	Frequency (%)		χ2	R	OR	Lower gr. 95% CI	Upper gr. 95% CI
	NS (n =97)	Control (n =40)					
S/S	22.6	70	27.36	0.000	0.13	0.06	0.29
S/T	31.9	20	1.99	0.158	1.88	0.78	4.55
T/T	45.36	10	15.56	0.000	7.47	2.47	22.62

An analysis of the polymorphism of the studied IL -1β T / C 511 (rs16944) gene was carried out in healthy donors and in patients with NS, depending on the presence or absence of ADS. A study of the frequency distribution of the C and T alleles of the IL-1β gene (T511C) in the group of patients with coronary artery disease in comorbidity with and without ADS, and in the group of practically healthy individuals revealed that the C and T alleles of the IL-1β gene (T511C) occurred with different frequencies (Table 5.2).

The carriage of SNP IL-1β (T511C) in patients with NS with ADS and healthy individuals turned out to be different. Among patients, the minor allele T prevailed with a frequency of 81.3, and the major allele C prevailed with a frequency of 18.7, which is 4 times less common than in the control group ($\chi2$= 37.74 ; p <0.001) (Table 4.2.3).

Table 5.3.

Distribution of frequencies of alleles 511 C/T (rs16944) of the IL-1β gene in patients with NS and healthy individuals depending on ADS

Allele	Frequency (%)		χ2	P- value	OR	Lower gr. 95% CI	Upper gr. 95% CI
	NS+ADS (n= 67)	Control (n=40)					
C	18.7	80	37.74	0.000	0.06	0.02	0.16
T	81.3	20	37.74	0.000	16.62	6.22	44.42

It was found that in groups of patients with NS and ADS, carriers of homozygous and heterozygous alleles, the values of the interleukin-1 gene

were significantly higher than those of the control group. Thus, in patients with NS with ADS and carriers of the homozytic variant of the T/T allele, the highest rates of psychoemotional disorders were determined, which on average amounted to 13.28 ± 0.7 on the HADS - D scale points; HADS - A 13.31± 0.7 points. When questioning patients with the homozygous T /T variant of the IL-1β SNP gene allele (T511C) on the Spielberger-Khanin scale, the average score was ST- 54.7± 3.0 , LT-53.4± 2.6 .

To study the relationship between alleles 511 T/C (rs16944) of the IL -1β gene with sUA levels, patients were divided into 2 groups: group 1 (n =50) patients with elevated levels (≥360.0 μmol/l) of sUA ; Group 2 (n =47) patients with normal levels (≤360.0 μmol/l) of sUA.

According to Table 5.4 , it can be seen that among patients with elevated levels of sUA, the T allele of the IL -1β gene (T511C) rs16944 *was found* statistically more often than among patients with normal levels of sUA. Among patients with NS with BGU, the minor allele T prevailed with a frequency of 73.4, and the major allele C prevailed with a frequency of 26.6, which is 2.5 times less common than among patients without BGU.

Table 5.4.

Distribution of frequencies of alleles 511 C/T (rs16944) of the IL-1β gene in patients with NS and healthy individuals depending on the level of sUA in the blood

Allele	Frequency (%)		χ2	P- value	OR	Lower gr. 95% CI	Upper gr. 95% CI
	MK above 360 μmol/l (n =47)	Control (n=40)					
C	26.6	80	23.71	0.000	0.10	0.04	0.26
T	73.4	20	23.71	0.000	10.46	3.83	28.56
Allele	Frequency (%)		χ2	P- value	OR	Lower gr. 95% CI	Upper gr. 95% CI
	MK below 360 μmol/l (n =50)	Control (n=40)					
C	6 0	80	4.15	0.042	0.38	0.14	0.98
T	40	20	4.15	0.042	2.67	1.02	6.96

Next, the average values of LDL cholesterol were studied depending on different allele variants of the IL -1β (T511C) rs16944 gene among patients with unstable angina.

Table 5.5.

Distribution of frequencies of IL-1β (T511C) rs16944 alleles in patients with NS and healthy individuals depending on the level of LDL cholesterol in the blood

Allele	**Frequency (%)**		**χ2**	**P-value**	**OR**	**Lower gr. 95% CI**	**Top. gr. 95% CI**
	Patients with elevated LDL levels (≥ 4.0 mmol/l) (n = 74)	Control (n=40)					
C	41.9	80	15.25	0.000	0.18	0.07	0.44
T	58.1	20	15.25	0.000	5.55	2.25	13.67
Allele	Frequency (%)		χ2	P-value	OR	Lower gr. 95% CI	Upper gr. 95% CI
	Patients with normal LDL levels (≥ 4.0 mmol/l) (n = 23)	Control (n=40)					
C	47.8	80	6.98	0.008	0.23	0.07	0.71
T	5 2 , 2	20	6.98	0.008	4.36	1.41	13.46

When distributing the C and T alleles in patients with elevated and normal LDL cholesterol levels , it turned out that 58.1% of patients with high LDL cholesterol levels had T alleles, while in patients with normal LDL cholesterol levels this figure was 52.2% (Table 5.5.).

In addition to all the listed diagnostic methods, connections of some cytokines with the polymorphic locus -511C>T (rs16944) were identified IL -1 β gene .

Patients who had heterozygous C/T and homozygous T/T genotypes of the IL -1β (T511C) rs16944 gene had 14.6 and 11.6 pg/ml higher concentrations of the TNF -α cytokine, as well as 20.1 and 21.7 pg/ml higher levels of interleukin IL-1β, respectively. In contrast to pro-inflammatory ones, the levels of anti-inflammatory cytokines IL -4 and IL -10 in patients with genotypes C/T and T/T of the IL -1β gene (T511C) rs16944 were reduced, which indicates a significant cytokine imbalance in sick carriers of the T allele of the IL gene -1β .

Table 5.6.

The level of concentration of some cytokines depending on the polymorphism of the locus-511C>T (rs16944) of the IL-1β gene in patients with NS

Indicators cytokine concentrations	Genotype IL -1 T / C 511			P- value	
	S/S	S/ T	T/T		
	1	2	3		
TNF -α pg/ml	62.9± 3.2**	77.5 ± 4.7 ^	74.5± 4.2	<0.001	P1

				<0.001 >0.2	P2 P3
IL-1β pg/ml	78.8 ± 4.1**	98.9 ± 6.8^^	100.5± 7.1	<0.001 <0.001 >0.2	P1 P2 P3
IL -4 pg/ml	19.74±0.9	18.2±0.7	18.1±0.8	>0.5 <0.001 <0.001	P1 P2 P3
IL -10 pg/ml	13.61±0.6	12.7±0.9^^	12.04±0.5	>0.5 <0.001 <0.001	P1 P2 P3

*Note: *^#- Significant compared to genotypes C/C, C/T, T/T (* -P1<0.05, ** - P1<0.01, *** - P1<0.001, ^ -P2 <0.05, ^^ - P2<0.01, ^^^ - P2<0.001, # P3<0.05, ## - P<0.01, ### - P<0.001).P1, P2 , P3 – reliability of differences between S/S and S/T, S/S and T/T, S/T and T/T, respectively.*

Chapter Conclusion

Thus, in the course of our study, it was revealed that among patients with NS the T allele of the IL -1β gene is 36.7% more common than among individuals in the control group. It was revealed that in patients with NS with ADS, increased levels of sUA and LDL cholesterol, the T allele of the IL -1β gene (T511C) rs16944 was 33.4% and 5.9% more common than among the control group. When studying the levels of pro-inflammatory cytokines TNF -α and IL-1β among patients with genotypes C/C, C/T and T/T, it was revealed that patients with the T/T genotype had statistically higher rates than patients with the homozygous variant of the C/ genotype From the IL -1β gene (T511C) rs16944 .

Patients with C/T and T/T alleles of the IL -1β (T511C) rs16944 gene are more predisposed to the development of ADS, cytokine imbalance and atherosclerotic changes, which in turn worsens the clinical course of the underlying disease and therefore requires more careful monitoring and treatment of patients to improve the prognosis of coronary artery disease.

Polymorphism of locus -819 C/T (rs1800871) IL -10 gene in patients with unstable angina depending on the psychoemotional status and BGU

In this study, the distribution of frequencies of alleles and genotypes of the -819 C/T occus (rs1800871) was carried out. IL -10 gene in patients with coronary artery disease with comorbid conditions to establish an “unfavorable” combination leading to a high probability of developing the

disease in the Uzbek population. The features of the distribution of frequencies of alleles and genotypes of the polymorphic variant 819 were studied C / T (rs1800871) of the IL -10 gene in patients with coronary artery disease and healthy individuals of Uzbek nationality . In 97 patients with unstable angina of Uzbek nationality, genotyping of the polymorphic locus of the IL -10 gene (C819T) rs1800871 was carried out .

The study of genotype polymorphism (Table 5.3.1) revealed that in the group of patients with NS the frequency of the homozygous T/T variant of the IL -10 gene (C819T) rs1800871 significantly exceeds the indicators of the control group of individuals (31.0% versus 17.5%, respectively, $\chi^2 = 2.59$; P = 0.108; OR = 2.11).

Table 5 .7.

Distribution of allele frequencies of the IL-10 gene (C819T) rs1800871 in patients with NS and healthy individuals

Allele	Frequency (%)		χ2	P-value	OR	Lower gr. 95% CI	Upper gr. 95% CI
	Basics gr. (n=97)	Control (n=40)					
C	69	82.5	2.59	0.108	0.47	0.19	1.19
T	31	17.5	2.59	0.108	2.11	0.84	5.31

The frequency of the heterozygous variant of the IL -10 gene (C819T) rs1800871 in this group of patients was almost no different from the control group. The analysis of the distribution of frequencies of alleles and genotypes of the IL -10 (C819T) rs1800871 gene polymorphism showed the presence of statistically significant differences in the T and C alleles of the T/ T and C/C genotypes in the group of patients with coronary artery disease in comparison with the control group of healthy individuals (Table 5.8 .).

Table 5 .8.

Distribution of the polymorphic locus -819 C/T (rs1800871) of the IL-10 gene in patients IHD and healthy individuals

Genotype	Frequency (%)		χ2	R	OR	Lower gr. 95% CI	Upper gr. 95% CI
	NS (n= 97)	Control (n=40)					
S/S	54.6	72.5	3.76	0.052	0.46	0.21	1.02
S/T	28.8	20	1.15	0.284	1.62	0.67	3.95
T/T	16, 6	7.5	1.92	0.166	2.44	0.67	8.88

To identify possible relationships, a search was carried out for the association of NS variants associated with ADS and the level of UA in the blood of the C/T polymorphism of the IL -10 gene in the study population.

When comparing alleles of the IL -10 (C819T) rs1800871 gene between groups of patients with unstable forms of coronary artery disease with asymptomatic hyperuricemia and healthy individuals, it was noted that the T allele in the group of patients with HC with asymptomatic hyperuricemia occurs significantly more often than in the group of practically healthy individuals (61.7 % compared to 17.5%, respectively, χ^2 =17.41; p=0.000) (Table 5.9.).

Thus, the specificity of the IL -10 (C819T) rs1800871 gene polymorphism is shown , manifested by the association of the T/T genotype combination with an unstable form of the disease in the Uzbek population.

The results of a molecular genetic study showed the importance of the polymorphic locus -819 C/T (rs1800871) IL -10 gene in the formation of a genetic predisposition to coronary artery disease associated with asymptomatic hyperuricemia in the Zbek population.

Table 5.9.

Distribution of allele frequencies of the IL-10 gene (C819T) rs1800871 in patients with *NS and healthy individuals depending on the level of sUA in the blood*

Allele	Frequency (%)		χ2	R	OR	Lower gr. 95% CI	Upper gr. 95% CI
	Patients with elevated sUA levels (≥ 360 µmol/l (n =47)	Control (n=40)					
WITH	38.3	82.5	17.41	0.000	0.13	0.05	0.36
T	61.7	17.5	17.41	0.000	7.60	2.78	20.76

The data obtained indicate that the markers of increased risk of destabilization of coronary artery disease with asymptomatic hyperuricemia in people of Uzbek ethnicity are the IL -10 (T819 T) genotype and the -819 T allele, and the markers of reduced risk are the IL -10 (C819C) genotype and the -819C allele .

Studying the degree of relationship between the IL -10 gene polymorphism and the concentration of LDL cholesterol, serum uric acid and the presence of psycho-emotional disorders in patients with coronary artery disease is of particular interest in the processes of progression of coronary artery disease and the atherosclerotic process .

When forming groups of patients with NS into groups depending on the concentration of sUA in the blood, we registered an association of its level with the polymorphism of the IL -10 gene (C819T) rs1800871 .

Table 5.10.

Average UA level depending on the polymorphic locus -819 C/T (rs1800871) of the IL-10 gene

Indicators	S/S (n=53)	S/T (n=28)	T/T (n=16)	P-value	
MK, µmol/l	316.2±11.2 *	452.3±20.3 #	596.0±20.3 ^^^	<0.05 <0.001 <0.05	P1 P2 P3

*Note: *^#- Significant compared to genotypes C/C, C/T, T/T (* -P1<0.05, ** - P1<0.01, *** - P1<0.001, ^ -P2 <0.05, ^^ - P2<0.01, ^^^ - P2<0.001, # P3<0.05, ## - P<0.01, ### - P<0.001).P1, P2 , P3 – reliability of differences between S/S and S/T, S/S and T/T, S/T and T/T, respectively.*

The data shown in table 5.10. indicate that the presence of the T allele in the genotype leads to disruption of purine metabolism. Patients with the homozygous T/T genotype were more susceptible to the presence of asymptomatic hyperuricemia and the average value of sUA in the blood was 596.0 µmol/l, while patients with the C/C genotype had 316.6 µmol/l. The UA values in the group with the T/T genotype were statistically significantly higher than in patients with the C/C and C/T genotypes (P<0.0 1 , p<0.0 1 , respectively).

To determine the connection between 819 (rs1800871) C/T polymorphism of the IL -10 gene with ADS, the frequency distributions of the C and T gene alleles were studied in the group of patients with NS with and without ADS, and in the group of practically healthy individuals, it was revealed that the C and T alleles of the IL -10 (C819T) rs1800871 gene occurred with different frequencies (Table 5.11.). For a more detailed study of the frequency of occurrence of the IL -10 (C819T) rs1800871 gene polymorphism, patients with coronary artery disease were studied separately depending on ADS.

It was found that in groups of patients with NS with ADS carriers of homozygous and heterozygous alleles - the IL -10 gene (C819T) rs1800871 was significantly higher than the control group. When distributing average values on anxiety scales, the data is in Table 5.3.5. It can be seen that patients with the homozygous T/T variant of the IL -10 gene (C819T) rs1800871 had high rates of anxiety and depression, which shows the relationship of ADS with this genotype.

Table 5.11.

Distribution of allele frequencies of the IL-10 gene (C819T) rs1800871 in patients with NS and healthy individuals depending on ADS

Allele	Frequency (%)		χ2	R	OR	Lower gr. 95% CI	Upper gr. 95% CI
	NS + ADS (n= 67)	Control (n=40)					
WITH	58.9	82.5	6.71	0.010	0.30	0.11	0.76
T	41, 1	17.5	6.71	0.010	3.38	1.31	8.74

Table 5.11.

The average value of indicators of anxiety-depressive syndrome according to the HADS and Spielberger-Hanin scores, depending on the polymorphic locus -819 C/T (rs1800871) of the IL-10 gene

	Alleles	HADS-A	HADS-D	ST	LT
IL -1 T / C 819	C/C	8.5±0.3***	8.4±0.4***	43.9±1.4***	42.0±1.5***
	C/T	11±0.4 ###	11.1±0.4 ###	50.7±2.3 ###	48.9±2.1 ##
	T/T	13.7±0.6 ^^^	13.5±0.7 ^^^	55.1±1.9 ^^^	51.25±2.3 ^^^

*Note: *^#- Significant compared to genotypes C/C, C/T, T/T (* - P1 <0.05, ** - P 1<0.01, *** - P 1<0.001, ^ -P2 <0.05, ^^ - P 2<0.01, ^^^ - P 2<0.001, # P3 <0.05, ## - P <0.01, ### - P <0.001). P 1, P 2, P 3 – reliability of differences between S/S and S/T, S/S and T/T, S/T and T/T, respectively.*

Gene polymorphism relationship analysis IL -10 (C819T) rs1800871 with ADS indicators in IHD indicates significant relationships with the genotype of the patients studied (Table 5.11.).

Depending on the level of LDL cholesterol in the blood, patients were divided into 2 groups: 1st patients with high levels (≥4.0 mmol/l) of LDL cholesterol and 2nd patients with normal levels (≤4.0 mmol/l) LDL cholesterol. It turned out that patients with elevated LDL cholesterol levels had 18.1% more T alleles than the control group (χ2 = 3.93; P = 0.048; OR = 2.55).

Table 5.12.

Distribution of allele frequencies of the IL-10 gene (C819T) rs1800871 in patients with NS and healthy individuals depending on the level of LDL cholesterol in the blood

Allele	Frequency (%)	χ2	R	OR		

	Patients with elevated LDL levels (≥ 4.0 mmol/l) (n = 74)	Control (n=40)				Lower gr. 95% CI	Upper gr. 95% CI
WITH	64.8	82.5	3.93	0.048	0.39	0.15	1.01
T	35, 2	17.5	3.93	0.048	2.55	0.99	6.57
Allele	Frequency (%)		χ2	R	OR	Lower gr. 95% CI	Upper gr. 95% CI
	Patients with normal LDL levels (≥ 4.0 mmol/l) (n = 23)	Control (n=40)					
WITH	82.6	82.5	0.00	0.991	1.01	0.26	3.89
T	17.4	17.5	0.00	0.991	0.99	0.26	3.84

Further, the indicators of some pro- and anti-inflammatory cytokines were studied depending on the polymorphism of the -819 C/T locus (rs1800871) IL -10 gene in patients with coronary artery disease.

Table 5.13.

The level of cytokine concentration depending on the polymorphism of the locus -819 C/T (rs1800871) of the IL-10 gene in patients with NS

Indicators cytokine concentrations	**IL -10 C /T 819**			**Level of significance (P) between groups 1, 2, 3**
	S/S	S/ T	T/T	
	1	2	3	
TNF -α pg/ml	65.0± 3.1*	77.7 ± 4.3	83.2± 5.1^^	<0.05 <0.01 >0.5
IL-1 pg/ml	81.7 ± 5.9*	103.9 ± 8.4	112.4± 9.1^^	<0.05 <0.01 >0.5
IL -4 pg/ml	19.7± 0.8	19.18±0.8 ###	14.1± 0.6^^^	>0.5 <0.01 <0.01
IL -10 pg/ml	13.3± 0.7	12.7± 0.6##	10.6± 0.5^^^	>0.5 <0.01 <0.01

*Note: *^#- Significant compared with genotypes C/C, C/T, T/T, as well as with stable angina (* - P1<0.05, ** - P1<0.01, *** - P1<0.001, ^ -P2<0.05, ^^ - P2<0.01, ^^^ - P2<0.001, # P3<0.05, ## - P<0.01, ### - P <0.001).P1, P2, P3 – significance of differences between S/S and S/T, S/S and T/T, S/T and T/T, respectively.*

As you can see, in table 5.13. the levels of pro-inflammatory cytokines TNF -α and IL-1β were statistically higher in patients with the homozygous T/T genotype than in patients with homozygous C/C and heterozygous genotype of the polymorphic locus -819 C/T (rs1800871) IL -10 gene . In addition, the levels of anti-inflammatory cytokines such as IL-4 and IL-10

in the same patients with the T/T genotype were statistically lower than in patients with the C/C and C/T genotypes of the -819 C/T polymorphic locus (rs1800871) IL -10 gene .

Chapter Conclusion

It was found that among patients with NS, the T allele of the IL -10 gene (C819T) rs1800871 was 13.5% more common than in the control group. When studying alleles of the IL -10 gene depending on the level of sUA in the blood, it was revealed that the T allele was 44.2% more common than in the control group, as well as the average level of sUA in the blood in patients with the homozygous T/T genotype of the study gene was 143.7 μmol/l higher than the heterozygous genotype C/T and 279.8 μmol/l higher than the homozygous genotype C/C of the IL -10 (C819T) rs180087 gene . Among patients with NS and ADS, the T allele was also found 23.6% more often than in the control group, and when comparing average scores on the HADS and Spielberger-Hanin scales, patients with the homozygous variant were statistically significantly higher than those with genotype C/C and C/T, which shows the connection of this allele with the occurrence of ADS. It was found that the T allele of the IL -10 gene was more common among patients with NS with high levels of LDL cholesterol by 17.7% in contrast to the control group and by 17.8% in comparison with patients with normal levels of LDL cholesterol. A high level of LDL cholesterol was associated with the T/T variant of the corresponding gene in the group of patients with NS . The values of LDL cholesterol in this group were statistically significantly higher than in patients with the C/C and C/T genotype of the IL -10 gene ($P< 0.0 1$, $p<0.0 1$ respectively).

CHAPTER 6.
Determination of the effectiveness of pharmacotherapy with febuxostat and divase in patients with coronary artery disease associated with psychoemotional disorder and asymptomatic hyperuricemia depending on the 511 T/C (rs16944) polymorphism of the IL-1β gene and 819 C/T (rs1800871) of the IL-10 gene

Over the past decade, the number of clinical pharmacogenetic tests has grown steadily as understanding of the role of genes in drug response has increased. However, adoption of these tests has been slow, largely due to the lack of robust evidence demonstrating clinical utility.

It has been estimated that more than 770,000 people are injured or die each year in hospitals from drug side effects, costing millions of dollars in healthcare costs each year (Classen *et al.* 1997 ; Lazarou *et al.* 1998). The field of genomic medicine represents one possible solution to reduce healthcare costs associated with side effects and poor response to pharmacotherapy. Specifically, the field of pharmacogenetics involves the use of a patient's genetic makeup in combination with other clinical information to create a personalized drug regimen with greater effectiveness and safety for the individual patient. Many currently prescribed medications have pharmacogenetic data to guide the correct dosage or selection. In addition, pharmacogenetic analyzes are routinely performed during drug development (Liou *et al.* 2012).

Although it has long been understood that genes play a role in drug response (Scott, 2011), an explosion of new discoveries from genome-wide association studies (GWAS) and large population-based cohort studies has brought pharmacogenetic testing to the forefront of the personalized medicine movement. Advances in genomic technologies, allowing more accurate, faster and cheaper tools for data generation and clinical trials, largely explain the rapid pace of discovery and development. In fact, the significant reduction in the cost of these new technologies has created something of a dilemma in that it may be cheaper to perform a whole-

genome analysis instead of a single-gene test, generating much more information than is necessary [175].

Despite the rapid pace of discovery and test development, routine use of pharmacogenetic tests is hampered by a lack of data demonstrating clinical utility or evidence that use of the test will improve health outcomes for a given patient [143]. Although randomized controlled trials (RCTs) remain the gold standard for clinical evidence, very few have been performed in pharmacogenetics.

Beginning in 2003, the US Food and Drug Administration (FDA) approved changes to package inserts for some drugs to include pharmacogenetics information [73]. In 2003, it is estimated that about 1.5% of the top 200 drugs contained pharmacogenomics information in the package insert (Zineh *et al*. 2006). Repeating their analysis with the most recent list of the top 200 drugs sold in the US (Bartholow, 2011), 11% of drugs now contain pharmacogenetic information. This 10-fold increase reflects the rapid accumulation of evidence on the role of genetic polymorphisms in drug safety and response.

Current evidence supports the need for concerted educational efforts among diverse groups to translate new findings from pharmacogenomic research into meaningful changes in clinical practice. Although clinical education skills exist in the fields of pharmacogenomics and genomic medicine, they overwhelmingly emphasize awareness and knowledge of pharmacogenomic information rather than how to apply these data in clinical practice. Accordingly, although clinicians agree that genetic variation can influence drug response, most of us do not feel knowledgeable or informed enough to make drug treatment choices based on these data [15]. Traditional didactic lecture formats have shown limited benefit in improving practitioner understanding and retention of clinical pharmacogenomic information [16].

Future approaches to training health care professionals in pharmacogenomics and genomic medicine must address these needs. Educational strategies that address practical needs, such as the clinical value of pharmacogenomic testing, integration of test results into EHRs, and reimbursement for testing, will be essential to translating pharmacogenomic science into practice [17] . Innovative educational approaches, such as applying personal genotype data to clinical case scenarios and using flipped classrooms and team-based learning models to support practitioner learning, have been explored and should be expanded [36]. Additionally, electronic

or other tools are needed for clinicians to support on-site training and clinical use of pharmacogenomic and genomic data [5].

Currently, pharmacogenetic testing is the most promising for clinical practice and one of the applied tools for personalized medicine. Pharmacogenetic testing allows us to determine the effectiveness and safety of therapy, select the most effective drug as a first-priority therapeutic agent, which allows us to reduce the number and dose of drugs required for adequate treatment. Pharmacogenetic testing identifies changes in pharmacological response associated with the genetic characteristics of patients [5]. Genetic features arise due to nucleotide substitutions in the DNA molecule, which are differently involved in the pharmacodynamics or pharmacokinetics of drugs [36]. Identification of such substitutions makes it possible to predict the pharmacological response and, therefore, to personalize the choice of drug and its dose. The use of pharmacogenetic testing is considered appropriate when the frequency of occurrence of polymorphisms of the gene under study is more than 20% of cases [73].

It is now becoming clear that the pharmacological response in patients with the same disease will not be the same, but will depend on the genotype of each individual, and the concept of personalizing those drugs that were previously considered universal is gaining increasing momentum [75]. Taking into account the comprehensive approach to the treatment of patients with coronary artery disease and the ongoing individualization of therapy, the study of pharmacogenetic aspects is necessary to increase the effectiveness of treatment and improve its safety [73].

From the data presented above, it can be noted that the frequency of occurrence of significant C/T alleles in heterozygous form is 22.68% for the IL -1β gene (T 511 C) rs16944 ; and for the polymorphic variant C/T of the gene for the anti-inflammatory cytokine IL -10 (C819T) rs1800871, the frequency of occurrence of heterozygotes is 28.8%.

The effectiveness of therapy for coronary artery disease with anxiety-depressive syndrome, taking into account the level of sUA in the blood, depending on the variant 511 T / C (rs16944) IL -1β gene

This chapter examined the effectiveness of therapy with febuxotate at a dose of 0.02-0.04 g/day and AMSB S -100 at a fixed dose of NS associated with ADS and BGU in patients with various allelic variants of the IL -1β and IL -10 genes .

the HADS and Spielberger-Hanin scales before taking febuxotate and Divaza in the hospital and before discharge from the hospital was assessed . Patients receiving febuxostat and AMSB S -100 were divided into 3 subgroups depending on the genotypes of the polymorphic allelic variant of the IL -1β and IL -10 genes .

Anxiety indicators after 3 months of therapy in patients with genotype C/T and T/T gene a IL -1β decreased by 4.6±0.2 and 5.62±0.3 points a, respectively, but did not reach the target values, unlike the genotype C/C gene a IL -1β . Indicators of depression in these same patients decreased by 3.97±0.2 and 5±0.3 points a (Table 6.1.).

Table 6.1.

The difference in scores on the HADS scale before the administration of AMSBS-100 and after its administration, depending on the 511 T/C (rs16944) polymorphism of the IL-1β gene

Gene	Genotype	HADS-A		P-value
IL -1 T / C 511		Before treatment	After treatment	
	C/C, n=31	4.4±0.2 ***	4.2±0.2	<0.001
	C/T, n=22	11.5±0.5 ##	6.9±0.4	<0.001
	T/T, n=44	13.3±0.6 ^^^	7.68±0.3	<0.01
Gene	Genotype	HADS-D		P-value
IL -1 T / C 511		Before treatment	After treatment	
	C/C, n=31	4.2±0.2 ***	4.1±0.2	<0.001
	C/T, n=22	11.6±0.5 ##	7.63±0.4	<0.001
	T/T, n=44	13.3±0.5 ^^^	8.3±0.4	<0.01

Note: HADS-A- anxiety, HADS-D-depression.^#- Significant comparison of NS with ADS between gene polymorphism variants C/C, C/T, T/T IL-1 T/C 511(* -P1 <0.05, ** - P1<0.01, *** - P1<0.001, ^ -P2<0.05, ^^ - P2<0.01, ^^^ - P2<0.001, # P3< 0.05, ## - P<0.01, ### - P<0.001).P1, P2, P3 – significance of differences between genotypes C/C and C/T, C/C and T/T, C/ T and T/T respectively.*

Table 6.2.

The difference in scores on the Spielberger-Khanin scale before the administration of AMSBS-100 and after its administration, depending on the 511 T/C (rs16944) polymorphism of the IL-1β gene

Gene	Genotype	ST		P-value
IL -1 T / C 511		Before	After	
	C/C, n=31	32.8±1.4 ***	32.5±1.4	<0.001
	C/T, n=22	54.6±2.5	39.5±1.5	<0.001

	T/T, n=44	54.8±2.3 ^^^	40.4±1.7	>0.5
Gene	Genotype	LT		P-value
IL -1 T / C 511		Before	After	
	C/C, n=31	29.6±0.9***	29.5±0.9	<0.001
	C/T, n=22	51.7±2.2	40.3±1.3	<0.001
	T/T, n=44	53.4±2.1 ^^^	41.3±1.6	>0.2

*Note: ST-personal anxiety, LT-personal anxiety. *^#- Significant comparison of NS with ADS between gene polymorphism variants C/C, C/T, T/T IL-1 T/C 511(* - P1<0.05, ** - P1<0.01, *** - P1<0.001, ^-P2<0.05, ^^- P2<0.01, ^^^- P2<0.001, # P3<0.05, ## - P<0.01, # ## - P<0.001).P1, P2, P3 – significance of differences between genotypes C/C and C/T, C/C and T/T, C/T and T/T, respectively.*

When studying the Spielberger-Khanin scale indicators after therapy, patients with the C/T genotype, unlike patients with the T/T genotype, achieved target values. This once again confirms the severe course of anxiety-depressive syndrome among patients with the homozygous T/T variant of the IL -1 gene T / C 511 (rs16944) (Table 6.2).

Persons with a heterozygous C/T variant before taking febuxostat had an average sUA value of 437.0±15.4; after 3 months of therapy it decreased to 315.0±11.8 (P <0.001). In patients with the homozygous T/T variant, the level of significance was (P ≥0.2) and decreased to 305.0 ± 11.9 μmol/l, while patients with the homozygous genotype C/C 511 T / C (rs16944) polymorphism of the IL -1β gene had 301.0±10.1 μmol/l (Table 6.3).

Table 6.3.

The difference in sUA levels before and after febuxostat administration depending on the 511 T/C (rs16944) polymorphism of the IL-1β gene

Gene	Genotype	MK level before treatment	MK level after treatment	Difference level MK	P-value
IL -1 T/C 511	C/C, n=31	330.5±10.7 ***	301.0 ± 10.1	29.5±0.9	<0.001
	C/T, n=22	437.0 ± 15.4	315.0 ± 11.8	122±3.8	<0.001
	T/T, n=44	434.1±18.5 ^^^	305.0 ± 11.9	129.1±5.4	>0.2

*Note: *^#- Significant compared to NS with increased levels of sUA (* -P1<0.05, ** - P1<0.01, *** - P1<0.001, ^-P2<0.05, ^^- P2<0.01, ^^^- P2<0.001, # P3<0.05, ## - P<0.01, ### - P<0.001).P1, P2, P3 – significance of differences between genotypes C/C and C/T, C/C and T/T, C/T and T/T respectively.*

Thus, the results obtained indicate the advisability of prescribing febuxostat in treatment regimens for patients with coronary artery disease associated asymptomatic hepatitis, who have the S/T heterozygous variant 511 T / C (rs16944) IL -1β gene polymorphism .

The study examined the dynamics of changes in LDL cholesterol levels before and after treatment with febuxostat as part of basic therapy.

Patients with homozygous T/T genotypes of the IL -1β gene before treatment had statistically higher LDL cholesterol levels than the homozygous C/C variant and the heterozygous C/T genotype. After 3 months of treatment, patients with the C/C, C/T and T/T genotypes did not reach the target level, but in patients with the heterozygous C/T genotype, the LDL cholesterol level decreased by 1.14±0.1 mmol/l in contrast to patients with homozygous variant T/T and C/C of the IL -1β gene (Table 6.4).

Table 6.4.

The difference in LDL cholesterol levels before and after febuxostat administration depending on the 511 T/C (rs16944) polymorphism of the IL-1β gene

Gene	Genotype	LDL cholesterol level before treatment (mmol/l)	LDL cholesterol level after treatment (mmol/l)	Difference level LDL cholesterol (mmol/l)	P-value	
IL -1 T/C 511	C/C, n=31	3.82±0.2 ***	3.17±0.2	0.65±0.1	<0.001	P1
	C/T, n=22	4.33±0.2 #	3.19±0.2	1.14±0.1	>0.2	P2
	T/T, n=44	4.03±0.2	3.2±0.2	0.83±0.1	<0.05	P3

P 1, P 2, P 3 – significance of differences between the difference in LDL cholesterol S/S and S/T, S/S and T/T, S/T and T/T, respectively

Table 6.5.

Achieving target levels of LDL cholesterol and sUA depending on the 511 T/C (rs16944) polymorphism of the IL-1β gene

Genotype	Reached target LDL cholesterol (≤1.8 mmol/l), n =48	Did not reach target LDL cholesterol (≥1.8 mmol/l), n =49	Reached target sUA (≤360 μmol/l), n =64	Did not reach target sUA (≥360 kmol/l), n =33
S/S	19 (19.6%)	17 (17.5%)	25 (25.8%)	6 (6.1%)

S/T	15 (15.4%)	11 (11.3%)	17 (17.5%)	8 (8.2%)
T/T	14 (14.4%)	21 (21.6%)	22 (22.68%)	19 (19.6%)

During 3 months of treatment, 19 (19.6%) patients with the C/C genotype, 15 (15.4%) patients with the C/T genotype and 14 (14.4%) patients with the T/T genotype of the IL gene - 1 T/S 511 reached the target value (≤1.8 mmol/l), 49 patients (S/S -17.5%; S/T- 11.3%; T/T-21.6%) despite patients undergoing therapy had elevated LDL cholesterol levels (≥1.8 mmol/l). In particular, there were more of them among patients with the T/T genotype. When studying the level of UA, one can also see that patients with the C/C genotype were more quickly amenable to correction than patients with the C/T genotype and T/T of the IL -1β gene (Table 6.5).

Table 6.6.

The level of cytokine status indicators before and after the administration of febuxostat and AMSBS-100 depending on the 511 T/C (rs16944) polymorphism of the IL-1β gene

Indicators of cytokine status	**Genotype IL -1 T/C 511**						**P-value**
	C/C, n=31		C/T , n=22		T/T , n=44		
	Before	After	Before	After	Before	After	
TNF -α pg/ml	65.0±2.3	38.8±1.5	77.7±2.7	44.5±1.7	83.2±3.1	47.1±1.6	1-2 <0.001 1-3 <0.001 2-3 >0.2
IL-1 β pg/ml	81.7±3.4	32.4±1.2	103.9±4.5	32.7±1.2	112.4±4.7	35.9±1.4	1-2 <0.001 1-3 <0.001 2-3 >0.2
IL -4 pg/ml	19.7±0.7	22.8±0.9	19.2 ± 0.9	22.5±0.8	14.1±0.6	22.7±0.8	1-2 >0.5 1-3 <0.001 2-3 <0.001
IL -10 pg/ml	13.3±0.5	16.1±0.7	12.7±0.6	15.5±0.7	10.6±0.4	16.4±0.5	1-2 >0.5 1-3 <0.001 2-3 <0.001

P 1, P 2, P 3 – significance of differences between the difference in cytokines (TNF -α, IL-1β, IL-4, IL-10) S/S and S/T, S/S and T/T and S/T and T/T respectively.

Patients with a heterozygous C/T genotype and a homozygous T/T genotype before treatment, in contrast to patients who had a homozygous C/C variant of the IL -1β gene (T 511 C) rs16944 had statistically high levels of pro-inflammatory cytokines TNF -α and IL-1β ; after complex therapy with the inclusion of a uricosuric drug and AMSB S -100 , these indicators

decreased, but did not reach the target values (Table 4.9-4.10.). Thus, the results of the study showed the presence of a pleiotropic hypolipidemic effect of febuxostat in the complex of basic therapy for patients with coronary artery disease with ADS and BGU.

Chapter Conclusion

When re-testing on the HADS - A scale It was found that anxiety scores after therapy in patients with the C/T and T/T genotypes decreased by 4.6±0.2 and 5.62±0.3 points, respectively. HADS Depression Scores - D in the same patients they decreased by 3.97±0.2 and 5.0±0.3 points . When testing on the Spielberger-Khanin scale, a decrease in CT by 5.62±0.3 points and LT by 5.0±0.3 points was found in patients with the T/T genotype of the IL -1β gene (T 511 C) rs16944 . In addition, in individuals with a heterozygous S/T variant, before taking febuxostat, the average sUA value was 437.0 ± 15.4; after 3 months of therapy it decreased to 315.0 ± 11.8 ($P < 0.001$). In patients with the homozygous T/T variant, the significance level was $P \geq 0.2$. LDL cholesterol levels before treatment were high in all three genotypes of IL -1β gene carriers (T 511 C) rs16944 , after correction with basic therapy and febuxostat, carriers of genotypes C/C, C/T and T/T of the IL -1β gene (T 511 C) rs16944 did not reach the target level, but in patients with the heterozygous C/T genotype, the level of LDL cholesterol decreased by 1.14±0.1 mmol/l , in contrast to patients with the homozygous variant T/T and C/C of the IL -1β gene (T 511 C) rs16944 . And also when studying cytokine indicators, it was found that patients with the homozygous T/T genotype had significantly greater positive dynamics. Thus, the levels of pro-inflammatory cytokines TNF -α and IL-1β decreased by 36.1±1.6 pg/ml and 76.5±2.6 pg/ml, respectively. The levels of anti-inflammatory cytokines IL-4 and IL-10 increased by 8.6±0.4 pg/ml and 5.8±0.3 pg/ml, respectively.

Thus, the effectiveness of pharmacotherapy with fixed dosages of febuxostat and AMSB S -100 is generally higher in patients with NS associated with ADS and BGU who are carriers of the heterozygous allelic variant C/T and the homozygous variant T/T of the IL -1β gene (T 511 C) rs16944 than in carriers of normal homozygote C/C, which indicates a rational correction of endothelial dysfunction associated with asymptomatic hyperuricemia and ADS , which is one of the early signs of severe forms of vascular pathology . The treatment technology used has made it possible to significantly improve the effectiveness of the use of pharmacological agents in the treatment of coronary artery disease with ADS and BGU.

The effectiveness of therapy for coronary artery disease with anxiety-depressive syndrome, taking into account the level of sUA in the blood, depending on the variant 819 S/T (rs1800871) IL -10 gene

To study the role of 819 C/T (rs1800871) IL -10 gene polymorphism on the outcome of treatment with febuxostat and AMSB S -100 , psycho-emotional indicators were studied before and after treatment in patients with coronary artery disease associated with ADS and BGU. The study revealed that patients who had the heterozygous C/T variant of the IL -10 gene polymorphism (C 819T) rs1800871, as well as the homozygous T/T variant, had clinically significant anxiety/depression, in contrast to patients with the C/C genotype, who had subclinically expressed anxiety/depression, after 3 months of therapy with febuxostat and AMSB S -100, these indicators on the HADS -A scale decreased by 3.6±0.2 and 5.4±0.2 points (P <0.001), respectively and HADS - D by 4.6±0.2 and 6.0±0.3 points (P <0.001), which shows the rational selection of these drugs (Tables 6.7-6.8.).

Table 6.7.

Values of HADS scale indicators depending on 819 C/T (rs1800871) polymorphism of the IL-10 gene before and after administration of AMSBS-100 in patients with coronary artery disease

Gene	Genotype	HADS-A		P-value
IL -1 T / C 819		before	after	
	C/C, n=53n=53	8.5±0.3***	6.0±0.2	<0.001
	C/T, n=28	11±0.4 ###	7.4±0.3	<0.001
	T/T, n=16	13.7±0.6 ^^^	8.3±0.3	<0.001
Gene	Genotype	HADS-D		P-value
IL -1 T / C 819		Before treatment	After treatment	
	C/C, n=53	8.4±0.4 ***	6.2±0.3	<0.001
	C/T, n=28	11.1±0.7 ###	6.5±0.3	<0.001
	T/T, n=16	13.5±0.74 ^^^	7.5±0.3	<0.001

Note: HADS-A-anxiety, HADS-D-depression.^#- Significant comparison of NS with ADS between gene polymorphism variants C/C, C/T, T/T IL-10 C/T 819(* -P1 <0.05, ** - P1<0.01, *** - P1<0.001, ^ -P2<0.05, ^^ - P2<0.01, ^^^ - P2<0.001, # P3< 0.05, ## - P<0.01, ### - P<0.001).P1, P2, P3 – significance of differences between genotypes C/C and C/T, C/C and T/T, C/ T and T/T respectively.*

Table 6.8.

Values of the Spielberger-Khanin HADS scale depending on the 819 C/T (rs1800871) polymorphism of the IL-10 gene before and after the administration of AMSBS-100 in patients with coronary artery disease

Gene	Genotype	ST		P-value
IL -1 T / C 819		before	after	
	C/C, n=53	43.9±1.4 ***	35.9±1.3	<0.001
	C/T, n=28	50.7±2.3 ###	39.3±1.3	<0.001
	T/T, n=16	55.1±1.9 ^^^	40.1±1.7	<0.001
Gene	Genotype	LT		P-value
IL -1 T / C 819		before	after	
	C/C, n=53	42.0±1.5 ***	35.4±1.3	<0.001
	C/T, n=28	48.9±2.1 #	38.5±1.5	<0.001
	T/T, n=16	51.25±2.34 ^^^	42.2±1.8	<0.05

*Note: ST - personal anxiety, LT - personal anxiety. *^#- Significant comparison of NS with ADS between gene polymorphism variants C/C, C/T, T/T IL-10 C/T 819(* - P1<0.05, ** - P1<0.01, *** - P1<0.001, ^ -P2<0.05, ^^ - P2<0.01, ^^^ - P2<0.001, # P3<0.05, ## - P<0.01, # ## - P<0.001).P1, P2, P3 – significance of differences between genotypes C/C and C/T, C/C and T/T, C/T and T/T, respectively.*

Table 6.9.

The difference in sUA levels before and after febuxostat administration depending on the 819 C/T (rs1800871) polymorphism of the IL-10 gene

Gene	Genotype	MK level before treatment	MK level after treatment	P-value
IL -10 S/T 819	C/C, n=53	316.2±11.2***	294.6±9.2	<0.001
	C/T, n=28	452.3±20.3 ^^^	294.5±10.2	<0.001
	T/T, n=16	596.0 ± 20.3 ###	365.5±12.9	<0.001

*Note: *^#- Significant compared to NS with increased levels of sUA (* - P1 <0.05, ** - P 1 <0.01, *** - P 1 <0.001, ^ - P2 <0.05, ^^ - P 2<0.01, ^^^ - P 2<0.001, # P3 <0.05, ## - P <0.01, ### - P <0.001). P 1, P 2, P 3 – significance of differences between genotypes C / C and C / T , C / C and T / T , C / T and T / T , respectively .*

During treatment with febuxostat in individuals with the homozygous genotype T\T 819 C/T (rs1800871) polymorphism of the IL -10 gene, before taking febuxostat the average sUA value was 596.0 μmol/l, and after its administration it decreased to 365.6±12.9 μmol/l (P <0.001). Therefore, the

appointment of febuxostat in the treatment regimen of patients with NS associated asymptomatic HU is advisable in carriers of T/T and C/T homo- and heterozygous 819 C/T (rs1800871) IL -10 gene polymorphism (Table 6.9.).

It should be noted that when taking febuxostat, patients who had the homozygous variant of the T/T genotype often complained of sleep disturbances, insomnia and frequent dizziness. Such adverse events were observed in 3 patients.

When studying the average value of LDL cholesterol, we did not identify statistically significant indicators (P >0.5) (Table 6.2.4). But patients with the T/T genotype were more difficult to treat and only 15 patients achieved the target level, while patients with the C/C genotype 23 patients and with the C/T genotype of the IL -10 gene 18 patients achieved the target levels (Table 6.11.).

Table 6.10.

The difference in LDL cholesterol levels before and after febuxostat administration depending on the 819 C/T (rs1800871) polymorphism of the IL-10 gene

Gene	Genotype	LDL cholesterol level before treatment	LDL cholesterol level after treatment	P-value
IL -10 (S819T)	C/C, n=53	3.9±0.2	3±0.2	>0.5
	C/T, n=28	3.9±0.2	3.1±0.1	>0.5
	T/T, n=16	4.6±0.2	3.7±0.2	>0.5

P 1, P 2, P 3 – significance of differences between the difference in LDL S/S and S/T, S/S and T/T and S/T and T/T, respectively

When studying sUA parameters before and after prescribing febuxostat in Table 6.2.5, it can be noted that patients with a heterozygous C/T variant of the IL -10 gene (C819T) are much more amenable to correction of sUA levels in the blood, which will reduce the risk of developing cardiovascular accidents caused by hyperuricemia, because hyperuricemia can stimulate vascular smooth muscle cell proliferation, angiotensin II production, and oxidative stress, which increases endothelial dysfunction.

Table 6 .11.

Achieving target levels of LDL cholesterol and sUA depending on 819 C/T (rs1800871) polymorphism of the IL-10 gene

Genotype	Achieved target LDL cholesterol (≤1.8 mmol/l), n = 56	Did not reach target LDL cholesterol (≥1.8 mmol/l), n =41	Reached target sUA (≤360 µmol/l), n =58	Did not reach target sUA (≥360 µmol/l), n =39
S/S	23(23.7%)	11 (11.3%)	16 (16.5%)	14 (14.4%)
S/T	18 (18.6%)	12 (12.3%)	24 (24.7%)	13 (13.4%)
T/T	15 (15.5%)	18(18.5%)	18 (18.5%)	12 (12.4%)

Table 6.12.

The level of cytokine status indicators before and after the administration of febuxostat and AMSBS-100 depending on the 819 C/T (rs1800871) polymorphism of the IL-10 gene

Indicators of cytokine status	IL -10 S/T 819 Genotype						P-value
	C/C , n=53		C/T , n=28		T/T , n=16		
	Before	After	Before	After	Before	After	
TNF -α pg/ml	65.0±2.2	32.5±1.3	77.7±2.7	35.4±1.5	83.2±2.8	37.1±1.4	1-2 <0.001 1-3 <0.001 2-3 >0.1
IL-1β pg/ml	81.7±2.7	39.7±1.6	103.9±4.5	49.2±1.7	112.4±4.5	47.9±2	1-2 <0.001 1-3 <0.001 2-3 <0.001
IL -4 pg/ml	19.7±0.7	22.8±0.9	19.2±0.7	22.1±0.8	14.1±0.5	23.2±1	1-2 >0.5 1-3 <0.001 2-3 <0.001
IL -10 pg/ml	13.3±0.5	16.3±0.7	12.7±0.4	15.8±0.6	10.6±0.4	16.1±0.7	1-2 >0.5 1-3 <0.001

							2-3 <0.001

P 1, P 2, P 3 – significance of differences between the difference in cytokines (TNF -α, IL-1β, IL-4, IL-10) S/S and S/T, S/S and T/T, S/T and T/T respectively.

When studying the indicators of pro-inflammatory cytokines TNF -α and IL-1β, it can also be noted that patients with the homozygous T/T genotype of the IL -10 gene had a significant difference in indicators after 3 months of therapy, the difference was 46.1±1.7 and 64.5±2.3, respectively, which also indicates rational pharmacotherapy for this group of patients (Table 6.12).

Chapter Conclusion

Thus, it was established that when testing again on the HADS - A scale, anxiety scores after therapy in patients with the C/T and T/T genotypes of the IL-10 gene decreased by 3.6 ± 0.2 and 5.4 ± 0 ,2 points respectively. HADS Depression Scores - D in the same patients they decreased by 4.6±0.2 and 6±0.3 points . When testing on the Spielberger-Khanin scale, a decrease in CT by 15.0±0.5 points and LT by 9.05±0.4 points was found in patients with the T/T genotype of the IL-10 gene . During treatment with febuxostat, individuals with a homozygous T/T variant of the IL -10 gene (C819T) before taking febuxostat had an average sUA value of 596.0 ± 20.3 μmol/l after 3 months of therapy decreased to 365.6 ± 12, 9 μmol/L ($P < 0.001$).

After correction with basic therapy and febuxostat, carriers of the C/T and T/T genotypes of the IL -10 gene did not reach the target level. However, patients with the T/T genotype were more difficult to treat and only 15 patients achieved the target level, while patients with the C/C genotype 23 patients and with the C/T genotype 18 patients achieved the target levels. When studying cytokine parameters, it was found that patients with the homozygous T/T genotype had more positive dynamics. Thus, the levels of pro-inflammatory cytokines TNF -α and IL-1β decreased by 46.1±1.7 pg/ml and 64.5±2.3 pg/ml, respectively. The levels of anti-inflammatory cytokines IL-4 and IL-10 increased by 9.1±0.4 pg/ml and 5.5±0.3 pg/ml, respectively.

Thus, the effectiveness of pharmacotherapy with fixed dosages of febuxostat and AMSB S -100 in general did not differ in patients with NS associated BGU - carriers of the heterozygous allelic variant C/T and homozygous variant T/T of the IL -10 gene (C819T) rs1800871 than in carriers of normal homozygotes nal allelic variant C/C. This indicates a

rational correction of endothelial dysfunction associated with asymptomatic hyperuricemia , which is one of the early signs of severe forms of vascular pathology; the direct effect of febuxostat on the vascular endothelium in combination with an antioxidant, antihypoxic , neuroprotective drug - AMSB S -100 significantly improves organ perfusion and reduces the risk of developing cardiovascular accidents.

CONCLUSION

Currently, cardiovascular diseases play a decisive role in the evolution of overall mortality throughout the world. Coronary heart disease in the structure of cardiovascular diseases is 26.6%. Among the various forms of coronary disease, the leading place is occupied by angina pectoris [44]. The National Heart Foundation of Australia Expert Working Group conducted an extensive study of systematic reviews of evidence on major psycho-emotional risk factors to assess whether there are independent associations between psychosomatic risk factors and the progression of coronary heart disease or the occurrence of acute cardiac events.

Our study examined the relationship of several psychosomatic risk factors to the progression of unstable angina, in particular the level of sUA in the blood, cytokine imbalance, anxiety-depressive syndrome, polymorphism of pro-inflammatory genes, as well as basic indicators of the lipid spectrum. An analysis of the correlation between the studied urinary function parameters, anxiety parameters and the production of immunoregulatory cytokines was carried out.

Studies have shown that in patients with unstable angina and ADS, cases with elevated sUA levels are often observed. Also during the study, frequent cases with high levels of TC and LDL were noted. At the same time, BGU and impaired cholesterol metabolism in patients with NS are interrelated. In addition, an increase in the correlation between the levels of UA in the blood and the anxiety-depressive syndrome in patients with NS was found during the attack, indicating the pathogenetic importance of GU in the mechanisms of the formation of the anxiety-depressive syndrome. A high level of UA and clinically pronounced anxiety, especially during an attack of NA, indicate a single mechanism of their participation in cardiovascular disorders and the formation of coronary artery disease.

This study examined the features of the distribution of frequencies of alleles and genotypes of polymorphic variants of pro-inflammatory and anti-inflammatory genes of such cytokines as I L -1β (T511C) rs16944 and IL -10 (C 819T) rs1800871 , which possibly contribute to the hereditary susceptibility to CHD associated with ADS and BGU.

As a result of our own clinical and laboratory research, the following distribution of frequencies of alleles and genotypes of the T / C polymorphism of the IL -1 β gene in patients with NS with BGU and ADS was revealed : markers of an increased risk of developing NS with BGU and ADS are the genotype of the T / T polymorphic locus -511C>T (rs16944)

IL -1 β gene , markers of reduced risk - genotype S /S polymorphic locus -511C>T (rs16944) IL -1 β gene . Important results were also obtained when studying the relationship of the IL -1 β gene with the level of sUA, anxiety levels, LDL cholesterol, pro-inflammatory and anti-inflammatory cytokines, the association of which is significant in the progression of cardiovascular diseases. Namely, patients with the homozygous T/T variant were more susceptible to the occurrence of ADS and BGU, in addition, the levels of LDL cholesterol and pro-inflammatory cytokines were slightly higher than in patients with the C/C genotype of the IL -1 β gene .

It is important to emphasize that in our region, for the first time, the influence of allelic variants of the I L -1β (T511C) rs16944 and IL -10 (C 819T) rs1800871 genes on the course of NS with and without a combination of comorbid conditions was studied.

The results of our own pharmacogenetic studies indicate that the effectiveness of pharmacotherapy with fixed dosages of the uricosuric drug febuxostat is generally higher in patients with NS associated with BGU and carriers of the heterozygous C/T variant and the homozygous T/T variant of the -511C/T polymorphic locus (rs16944) IL -1 β gene , as well as heterozygous variant C/T and homozygous variant T/T of the polymorphic locus -819 C/T (rs1800871) gene IL -10 than in carriers of normal homozygotes C/C is more favorable, which indicates a rational correction of endothelial dysfunction.

The results obtained from studying the effectiveness of the antioxidant Divaza (antibody to the brain-specific protein S -100) depending on the polymorphism of the genes I L -1β (T511C) rs16944 and IL -10 (C 819T) rs1800871 showed that the presence of alleles C/T and T/T in the genotype of patients, NS in combination with and without comorbid pathologies is accompanied by a pronounced pharmacodynamic effect on the synthesis of proinflammatory cytokines, which, in turn, determine the development of endothelial dysfunction and LV myocardial remodeling.

Thus, modern laboratory diagnostic methods presented in this work have made it possible to confirm the importance of the participation of psychosomatic tests, biochemical, immunological and genetic mechanisms in the pathogenesis of the development of destabilization of coronary artery disease, which in turn will contribute to an improved and personalized approach to the treatment and prevention of this pathological condition, as well as improving prognosis and reducing cardiovascular complications and mortality. Thus, the results obtained from studying the polymorphism of the I L -1β (T511C) rs16944 and IL -10 (C 819T) rs1800871 genes in NS with

BGU and ADS, as well as without them, apparently can allow us to talk about these genes no longer as candidates, but as genes that contribute to the formation of a hereditary predisposition to the development and destabilization of IHD.

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FOR NOTES