MINISTRY OF HEALTH OF THE REPUBLIC OF UZBEKISTAN

SAMARKAND STATE MEDICAL UNIVERSITY

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# CLINICAL AND GENETIC FEATURES OF IHD DESTABILIZATION IN WORKING-AGE PATIENTS AND WAYS TO CORRECT THEM

Tashkent 2026

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# CLINICAL AND GENETIC FEATURES OF IHD DESTABILIZATION IN WORKING-AGE PATIENTS AND WAYS TO CORRECT THEM

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*The monograph presents current data on the clinical and molecular genetic aspects of the development of coronary heart disease in men at a working age, taking into account the etiopathogenetic risk factors for the development of the disease, in particular dyslipidemia and imbalance of the cytokine system. This monograph presents modern literary sources of the CIS countries and foreign countries. The studied literature data allowed the authors to consider some molecular genetic predisposition factors for the development of coronary heart disease in men, especially at a young age. The main etiopathogenetic factors are dyslipidemia, cytokine imbalance and its relationship with genetic markers (genotypes of pro-inflammatory and anti-inflammatory cytokines). The molecular genetic profile of unstable angina in young men, as determined by our clinical and laboratory studies, is presented in relation to its underlying etiopathogenetic risk factors.*

# ABBREVIATIONS

GWAS-Genome wide association studies

IL - Interleukin

NO - Nitric oxide

SNP - Single Nucleotide Polymorphism

ASP - Atherosclerotic plaque

AG - Arterial hypertension

BP - Blood pressure

Ao - Aorta

WHO - World Health Organization

NA - New-onset angina

HB - Hypertension

DBP - Diastolic blood pressure

DLP - Dyslipidemia

DNA - Deoxyribonucleic acid

CHD - Coronary artery disease

BMI - Body mass index

LVMI - Left ventricular myocardial mass index

CA - Coronary artery

CAG - Coronary angiography

CoeffA - atherogenic coefficient

CAD - coronary artery disease

CVD - cardiovascular disease

EDV - end-diastolic volume

EDV - end-diastolic dimension

ESD - end-systolic dimension

ESV - end-systolic volume

LV - left ventricle

HDL - high-density lipoprotein

LDL - low-density lipoprotein

VLDL - very low-density lipoprotein

mRNA - matrix ribonucleic acid

IVS - interventricular septum

UCS - unstable angina

LPA - low physical activity

AMI - acute myocardial infarction myocardium

ACS - acute coronary syndrome

ST-segment elevation acute coronary syndrome

ST-segment depression acute coronary syndrome

TC - total cholesterol

PICS - post-infarction cardiosclerosis

PSN - progressive angina

RFLP - long restriction fragment polymorphism

PCR - polymerase chain reaction

SBP - systolic blood pressure

DM - diabetes mellitus

GFR - glomerular filtration rate

TG - triglycerides

LVPT - left ventricular posterior wall thickness

IVST - interventricular septal thickness

LVEF - left ventricular ejection fraction

RF - risk factors

# FOREWORD

Cardiovascular ailments represent a critical challenge for healthcare systems worldwide and within individual nations, consistently ranking as the primary driver of mortality and premature incapacitation. Projections indicate that by 2030, these conditions could claim the lives of roughly 23.6 million individuals. However, the outlook for any given person can vary considerably, influenced by the presence of risk factors and the effectiveness of interventions and preventative strategies. The World Health Organization identifies our nation, alongside others, as a region with a heightened susceptibility to cardiovascular disease. Data from 2020 reveals that a substantial 60% of fatalities in Uzbekistan stemmed from circulatory system disorders, with coronary heart disease accounting for 32.5% of these.

Consequently, there is a growing emphasis on thoroughly investigating the genesis and progression of coronary heart disease, particularly its acute manifestations, considering variations in patient demographics such as sex, age, and other attributes. Historically, unstable angina was an infrequent occurrence among working-age men. Yet, recent trends show a notable rise in its prevalence, posing a considerable economic and social burden due to the early incapacitation and loss of life it causes in this demographic. Over the past few decades, there has been a marked escalation in the prevalence of risk factors that significantly contribute to the development of coronary heart disease. The observed trend of coronary heart disease appearing at younger ages in men is strongly linked to key lifestyle choices, including tobacco use, unhealthy eating habits, lack of physical activity, demanding and hazardous work environments, and stress. These factors, in turn, contribute to the onset of obesity, abnormal blood lipid levels, diabetes, and high blood pressure that begins at an earlier age.

**Evolving Patterns in Coronary Heart Disease Progression**

Contemporary clinical investigations are scrutinizing the trajectory of coronary heart disease (CHD), especially its acute manifestations, across diverse population segments. A striking and troubling trend has emerged among men of working age:

- **Increased Occurrence:** Unstable angina (UA), traditionally less common in younger males, is now frequently identified within this demographic.
- **Economic and Social Ramifications:** The growing prevalence of CHD within the labor force contributes to elevated rates of early incapacitation and untimely mortality, imposing substantial financial strain.
- **Lifestyle and Environmental Contributors:** This "earlier onset" of cardiac illness is predominantly driven by an escalation in contemporary risk factors, encompassing:

- Smoking and suboptimal dietary practices.
- Inactive routines and demanding, high-pressure professional settings.
- Unsafe occupational environments.

These behavioral and environmental elements serve as key accelerators for the premature development of chronic ailments such as excessive weight, abnormal lipid levels, diabetes, and elevated blood pressure, all of which hasten the progression of heart disease in younger cohorts.

Lipid dysregulation plays a central role among these contributors, driving up atherogenic lipoproteins in the blood beyond healthy limits. Studies indicate that for working-age men, a combination of low high-density lipoprotein (HDL) and elevated low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and triglycerides is strongly linked to coronary heart disease (CHD) and may serve as crucial predictors. A family history of heart problems represents a substantial, unchangeable risk factor for early-onset CHD. It appears that individuals with a genetic predisposition to CHD sometimes encounter additional adverse environmental factors that exacerbate their risk. Consequently, for working-age men, early detection and proactive measures, including addressing modifiable elements, could help offset these inherited susceptibilities. Investigating how both adaptable and fixed genetic markers influence the instability and worsening of cardiac issues in younger men could lead to improved CHD prevention strategies for those genetically prone. Such comprehensive efforts could help prevent the disease,

initiate earlier prevention, or at least postpone its appearance, ultimately improving the severity of the condition for working-age men.

Across many sectors, our country's healthcare system is working to sharpen its ability to detect coronary heart disease early and to roll out new prevention and treatment methods. We're aiming to bring our medical system up to international standards, making sure everyone receives comprehensive, regular check-ups to pinpoint those at risk for heart disease. This makes understanding the risk factors that lead to early coronary heart disease in younger men a crucial undertaking right now.

# CHAPTER 1

## Literature review

**The prevalence and characteristics of coronary heart disease (CHD) among the working-age population are significant epidemiological concerns.**

This condition presents a substantial challenge for healthcare systems worldwide and within individual countries [79, 100, 153]. Data from the WHO highlights the devastating impact, with 16.7 million annual deaths attributed to cardiovascular diseases (CVD), 7.4 million of which are directly due to CHD [216]. Europe alone sees 4.3 million CVD-related deaths, with over 2 million occurring within the European Union, representing a substantial 48% and 42% of all mortalities, respectively [193]. Uzbekistan, over the past two decades, has witnessed an escalating burden of CHD, reflected in increased incidence and mortality rates that align with global trends [120]. The State Statistics Committee of the Republic of Uzbekistan reported a 13.5% surge in overall mortality in 2020 compared to 2019, totaling 175,600 deaths, with CHD accounting for a significant 60% [5]. Looking ahead, forecasts suggest an 18% increase in CHD prevalence by 2030 relative to 2013, and a projected global mortality of approximately 23.6 million people by 2030 [6]. Furthermore, direct medical costs are expected to nearly double by 2030 compared to 2010 [133]. Crucially, an individual's outlook can be positively or negatively altered based on the presence of risk factors and the effectiveness of implemented treatment and prevention measures [136, 152].

The World Health Organization draws attention to a disquieting paradox: despite notable achievements in therapeutic approaches, health promotion strategies, sophisticated diagnostic instrumentation, and substantial financial outlays aimed at the prevention of coronary heart disease (CHD) in both high-income and low-income countries, this pathology continues to be the predominant cause of mortality, contributing to one-third of all deaths. Furthermore, a global trend, including in

Uzbekistan, indicates that CHD is affecting younger individuals, drawing in broader population segments. This rise in younger CHD patients, particularly those with specific forms of the disease, presents a significant societal and economic challenge. It leads to premature loss of productivity and early deaths among a demographic that represents the core workforce and intellectual capital of a society. In Europe, CHD accounted for 14% of all deaths among individuals under 45 in 2016, a figure mirrored closely in the Russian Federation at 13.6%. In Uzbekistan, mortality from CHD among the working-age population has recently surged by two to three times, often attributed to "young heart attacks." While mortality rates in the working population are notably higher for men, this gender disparity diminishes in older age groups, where deaths occur with similar frequency for both sexes.

Certain authors characterize NVI as an intermediate phase in ischemic heart disease, oscillating between its chronic and acute forms. It signifies a period of heightened vulnerability in coronary artery disease, preceding the onset of cardiovascular events. Although NVI represents a severe manifestation of ischemic heart disease, it is considered amenable to reversal, particularly in the working-age population, with the provision of comprehensive and timely medical support.

"Younger individuals presenting with ischemic heart disease commonly exhibit stable angina, non-obstructive coronary artery disease (NVI), acute coronary syndrome (ACS), myocardial infarction (AMI), and sudden cardiac arrest. Coronary heart disease (CHD) is a pervasive condition, impacting individuals as young as their thirties, with a prevalence of one in ten in their forties, and one in four among those over fifty. For younger populations (under 45), CHD is estimated to affect 3% to 10%. Within this younger cohort, stable angina accounts for 0.4% to 1.6% of cases, while acute myocardial infarction (AMI) is observed in over half, with a striking 92-95% male predominance.

Despite progress in diagnostic tools and preventative measures, working-age individuals experiencing acute myocardial infarction (AMI) continue to confront concerningly elevated mortality rates, both prior to hospitalization (ranging from 36% to 50%) and during their inpatient care (15-16%). A substantial portion of these

in-hospital deaths, approximately 40.4%, occur within the initial 24 hours of treatment. Furthermore, half of all AMI-related fatalities happen within the first 1.5 to 2 hours of symptom onset, with many patients succumbing before emergency medical services can arrive [170]. Compounding this issue, only 60% of younger individuals experiencing angina are adequately informed about their condition and adhere to medication regimens. The remaining 40% of cases go undiagnosed, leading to a lack of necessary diagnostic and therapeutic interventions [127]. These collective observations underscore the critical necessity for a standardized strategy encompassing early detection, treatment, and prevention of coronary heart disease in working-age men.

## Modern views on the etiological causes of coronary heart disease in people of working age

Medical experts acknowledge coronary heart disease as a disorder with diverse underlying causes. Its hallmark is a mismatch, either acute or sustained, between the oxygen the heart muscle needs and what the coronary arteries can supply. For younger individuals, disruptions to coronary blood flow can be triggered by conditions like atherothrombosis, arterial spasms, or direct blockages. Furthermore, factors unrelated to coronary artery atherosclerosis can also lead to these circulatory impairments, such as pronounced arterial winding, compromised endothelial function, insufficient local nitric oxide generation, or an atypical predisposition to experiencing cardiac pain [54, 107, 128]. The pathogenetic mechanisms of CHD frequently involve a combination of factors, where atherosclerotic CA stenosis coexists with reversible fluctuations in coronary blood flow influenced by vascular tone (e.g., spasm or ED). Data from coronary angiography (CAG) indicates that approximately 80% of acute myocardial infarction (AMI) incidents in working-age individuals are attributable to coronary atherosclerosis, while approximately 20% occur in vessels exhibiting no or only minor alterations [41].

A primary and frequently encountered origin of coronary heart disease (CHD) involves the constrictive effects of atherosclerotic plaque within the coronary

arteries, resulting in a luminal reduction ranging from 50% to 70%. This arterial narrowing can remain asymptomatic for extended periods before manifesting as either sudden or persistent coronary events. The genesis of these atherosclerotic alterations in the coronary arteries is rooted in dysfunctions across biochemical, immunological, and molecular genetic pathways. Various elements, including endothelial dysfunction (ED), localized spasms of the coronary arteries, compromised microcirculation, inflammation of the vascular wall, and other contributing factors, actively promote the progression of CHD [10]. The gravity of coronary heart disease is assessed by the extent and magnitude of coronary artery constriction, the position and spread of the atherosclerotic plaque (ASP), the quantity of affected coronary vessels, and the condition of auxiliary blood supply. Atherosclerotic changes preferentially target specific vessels, predominantly impacting large and medium-sized muscular and musculofibrous arteries. Nevertheless, even within the arterial network, this pathological process exhibits predilection for certain "hotspots" [74], frequently emerging in regions of the coronary artery subjected to the most significant hemodynamic stress from blood flow—specifically, at the junctures of major collateral branches, where numerous curves and bifurcations are present [192].

Based on coronary angiography findings reported by R.V. Zeynalov et al. (2016), single-vessel atherosclerotic involvement of the coronaries is more prevalent among individuals of working age. The anterior descending artery is implicated in 56-80% of such cases, the right coronary artery in 15.6-39%, and the circumflex artery in 14-26% [41, 202]. Conversely, pathologies affecting the left main coronary artery, widespread multivessel disease, and coronary calcification are considerably less common in working-age populations compared to older demographics [157].

Research highlights distinct characteristics of coronary artery disease (CAD) in individuals of working age compared to older demographics. In younger patients, the most prevalent finding is single-vessel atherosclerotic lesions, with a typical distribution across the coronary arteries:

- **Anterior Descending Artery:** Affected in 56%–80% of cases.

- **Right Coronary Artery:** Involved in 15.6%–39% of cases.
- **Circumflex Artery:** Seen in 14%–26% of cases.

Notably, working-age individuals exhibit a significantly lower incidence of multivessel disease, left main coronary artery involvement, or extensive coronary calcification when contrasted with their elderly counterparts.

The Enigma of "Unobstructed" Coronary Arteries

A considerable diagnostic hurdle in younger patients arises when CAD symptoms manifest despite seemingly normal or "clean" coronary arteries on angiography. This phenomenon is frequently attributed to either vasospasm or endothelial dysfunction (ED).

Key clinical observations reveal:

- **Prevalence:** Nearly two-thirds of working-age CAD patients demonstrate coronary artery dysfunction even in the absence of visible blockages.
- **Elevated Risk:** Patients experiencing coronary dysfunction face a 1.5-fold increased rate of cardiovascular complications (CVCs). This risk further escalates to 1.8 times higher for those with even mild atherosclerosis.
- **Mortality Impact:** Mortality rates are 1.3 to 1.5 times greater in these groups compared to individuals without dysfunction.
- **Compounded Prognosis:** While vasospastic angina alone carries an annual mortality rate of 0.5%, the outlook significantly deteriorates when coronary atherosclerosis and spasms coexist.

For clinicians, the paramount challenge remains the accurate diagnosis and effective management of patients presenting with clear ischemic symptoms but minimal structural damage on standard imaging. These "subtly altered" arteries necessitate a more refined therapeutic strategy, prioritizing vascular function over mere physical obstructions.

Would you prefer to delve into the specific diagnostic methodologies employed to identify endothelial dysfunction, or perhaps explore the treatment protocols for vasospastic angina in the subsequent section?

In younger CAD patients, coronary artery blood flow can be compromised not only by atherothrombosis, spasm, and arterial obstruction but also by other non-atherogenic factors [79]. These non-atherogenic causes of coronary heart disease in young individuals may include (Table 1.1):

**These non-atherogenic causes of coronary heart disease in young individuals may include**

| № | Cardiac causes | Extracardiac causes |
|---|---|---|
| 1 | Left ventricular myocardial hypertrophy of various origins | Anaemia and arterial hypotension, which contribute to a reduction in oxygen delivery to myocardial tissue |
| 2 | Embolism caused by particles of vegetation that have broken off from heart valves affected by infective endocarditis. | Hyperthermia of various origins, increased blood pressure and heart rate, which contribute to an increase in myocardial oxygen demand. |
| 3 | Embolism caused by particles of a mural thrombus developing on the surface of an artificial valve. | Involvement of the immune system in antiphospholipid syndrome, which develops in systemic connective tissue diseases, including systemic lupus erythematosus. |
| 4 | Various types of cardiomyopathy. | Various mechanical injuries and electrical injuries. |
| 5 | Congenital and acquired heart defects of valvular origin. | Development of CA thrombosis in coagulopathies and nephrotic syndrome. |
| 6 | Various congenital malformations of the CA. | Blood system disorders. |
| 7 | Development of coronary artery disease in systemic vasculitis (Takayasu's disease). | Coronary spasm due to cocaine, ethanol, and amphetamine intoxication. |
| 8 | Various myocardial ‘bridges’ and others | Development of DIC syndrome with CA thrombosis. |
| 9 | Primary tumours of the heart or sprouting and metastasis of extracardiac tumours. | Iatrogenesis (catheterisation of the CA during CAG, traumatic damage to the CA during aortic valve replacement). |
| 10 | Dissection of the ascending aorta with subsequent formation of a haematoma near the mouth of the CA. | |

In conclusion, while the etiologies and clinical manifestations of coronary heart disease (CHD) in younger adults exhibit considerable heterogeneity, the disease's

progression is characterized by significant individual variability. A deeper insight into the factors influencing Coronary Heart Disease within this population, gained by examining distinct clinical, hemodynamic, and etiopathogenetic indicators, along with the description of atherosclerotic lesions, is essential. This comprehensive insight will furnish the requisite data for the development of individualized therapeutic interventions and the implementation of more efficacious strategies for the prevention of severe complications.

## Modern Views on the Pathogenesis of Coronary Heart Disease in Working-Age Individuals

Coronary artery disease is understood as a condition with multiple contributing factors, where the underlying mechanism involves the buildup of plaque within the heart's arteries. This arterial narrowing, known as coronary atherosclerosis, can go unnoticed for extended periods. Eventually, it may manifest as chest pain (angina), or more critically, as a sudden heart attack (myocardial infarction) or even unexpected death from cardiac arrest. Atherosclerosis itself is a long-term ailment marked by alterations in the inner lining of the coronary arteries. These changes include the deposition of fats, sugars, and blood elements, along with the growth of fibrous tissue that forms plaques, and calcification, affecting the artery walls. The consequence of these developments is the creation of atherosclerotic plaques that constrict the coronary arteries, hindering their normal function and consequently reducing the delivery of oxygen and vital nutrients to the heart muscle. This deficiency triggers oxygen deprivation (hypoxia), damage to heart cells, and scarring of the heart tissue (cardiosclerosis), ultimately leading to problems with the heart's function and the body's overall circulation. A sudden blockage of blood flow, caused by a clot in a coronary artery or prolonged, severe constriction, results in the death of heart muscle tissue (ischemic necrosis or infarction), localized to the area supplied by the affected artery. If this lack of blood flow persists for over 40 minutes, the damage to the heart muscle becomes permanent.

Atherosclerosis arises from a multifaceted interplay involving the coronary artery lining, blood components, dissolved biochemicals, and localized disruptions in blood flow within these arteries. In a healthy state, the coronary vessel walls possess minute, impermeable gaps that prevent lipoproteins from entering. However, when subjected to harmful agents like endothelin, serotonin, catecholamines, elevated cholesterol, and angiotensin II, these gaps between the endothelial cells widen, allowing LDL particles to infiltrate the inner arterial layer.

The fundamental process of atherosclerosis is initiated by the generation of singlet oxygen, which leads to the oxidation of LDL cholesterol. These oxidized LDL particles then move into the arterial sub-lining, where they exert a damaging influence on the vascular endothelium. This damage sets off a chain reaction: chemotactic signals attract monocytes, smooth muscle cells, and macrophages. As macrophages engulf the oxidized LDL, they transform into foam cells.

**The Development of Atherosclerotic Lesions**

The buildup of these foam cells results in the formation of fatty deposits and streaks, a phase termed lipoidosis. Intriguingly, these early fatty streaks can manifest even within the first year of life, with coronary lipoidosis frequently commencing in childhood (between 10 and 15 years of age).

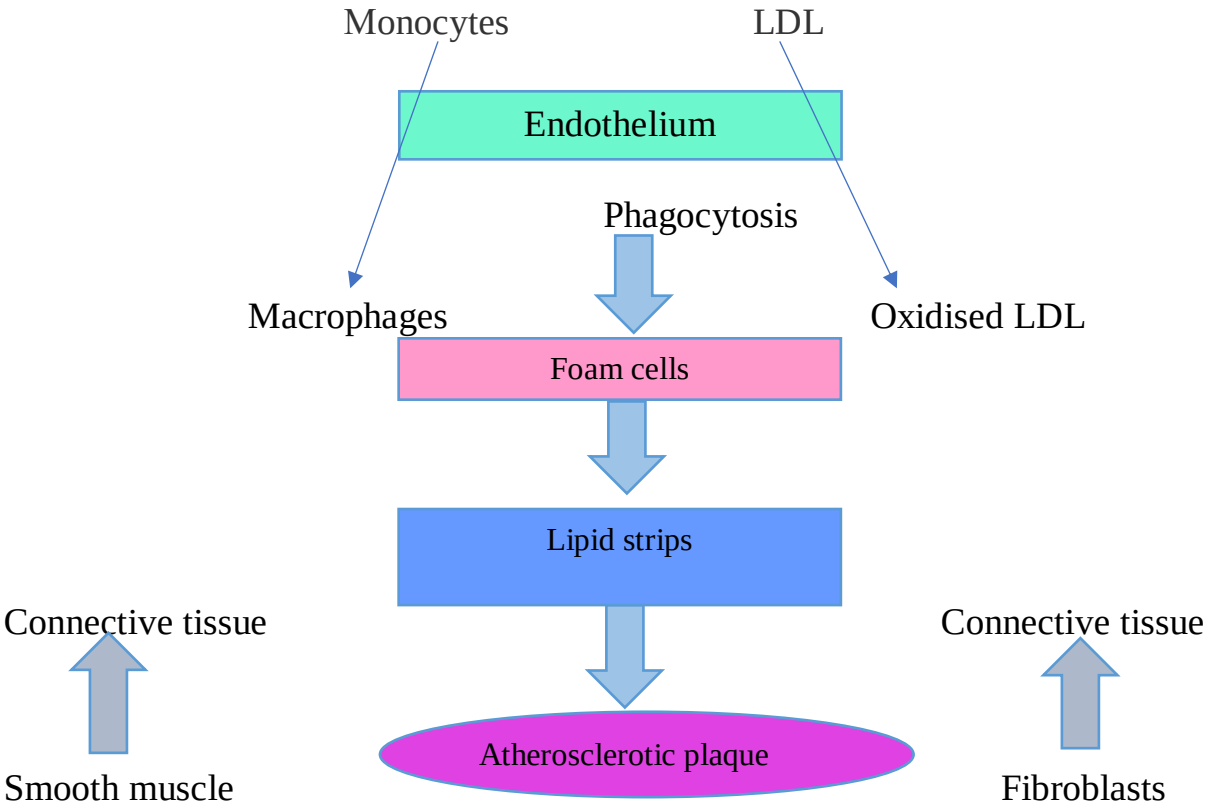
The progression unfolds through several distinct stages:

- **Endothelial Response:** Oxidative stress triggers endothelial cells to generate molecules that promote the adhesion and movement of white blood cells and monocytes into the arterial wall.
- **Plaque Formation:** Gradually, fibrous tissue develops around the lipid accumulations. As foam cells die, they release more lipids, expanding the central core. Collagen fibers then thicken, creating a protective fibrous covering over the lipid core, shielding it from the bloodstream.
- **Vascularization and Inflammatory Activity:** The plaque's interior may develop new, delicate blood vessels. Their propensity to leak can lead to internal bleeding and localized inflammation, further compromising the stability of the affected area.

• **Terminal Stages.** In the concluding phase, termed atherocalcinosis, the accumulation of calcium salts and robust fibrous tissue leads to a substantial stiffening of the plaque. This fully developed fibrous plaque ultimately projects into the vessel's interior, constricting the passage and severely impeding blood circulation. (Figure 1.1) [61].

**Figure 1.1**

**Figure 1.1. Mechanism of atherosclerosis development**




Atherosclerotic plaques (ASPs) within coronary arteries are categorized as either stable or unstable, a distinction primarily determined by the integrity and thickness of their fibrous cap. Stable ASPs are distinguished by a robust, thick fibrous cap, abundant in collagen. In contrast, unstable plaques exhibit a delicate fibrous capsule, typically less than 65 μm thick, and display evidence of ongoing inflammation, with the cap infiltrated by active immune cells such as macrophages, mast cells, and activated T cells. Furthermore, unstable plaques possess a substantial lipid core, exceeding 40% of the plaque's total volume, and often show signs of

hemorrhage and microcalcification within this core. The expansion of the lipid core contributes to an overall increase in plaque size. This growth, coupled with the action of specific enzymes like collagenases, elastases, and metalloproteinases, renders the plaque's fibrous cap vulnerable and prone to rupture under certain conditions.

The likelihood of an atherosclerotic plaque breaking open is influenced by where it's situated, the makeup and dimensions of its fatty center, and the forces exerted by blood flow. Several elements can trigger this rupture. These include spasms in the coronary arteries, elevated levels of LDL and triglycerides, a reduction in smooth muscle cells and collagen production, heightened macrophage activity and cell death within the plaque, strenuous physical exertion, smoking, emotional distress, overconsumption of food, dyslipidemia, exposure to cold, intake of alcohol or energy drinks, rapid heart rate, abrupt fluctuations in blood pressure, overstimulation of the sympathoadrenal system, and pressure differences across narrowed arterial segments. These pressure gradients, combined with the mechanical stresses of "stretching-compression" at arterial bifurcations and bends, ultimately compromise the structural integrity of the plaque. Once a plaque ruptures, the blood's clotting system is activated, platelets aggregate, and a clot forms, obstructing the vessel's passage. This blockage then leads to a lack of oxygen in the heart muscle supplied by the compromised coronary artery.
Coronary artery atherosclerotic plaques (ASPs) are classified as either stable or unstable, primarily determined by the strength and thickness of their fibrous caps.

**Plaque Stability:**

- **Stable Plaques:** These possess a robust, collagen-rich fibrous cap, offering structural resilience and resistance to tearing.
- **Unstable (Vulnerable) Plaques:** These are high-risk formations characterized by:
  - A very slender fibrous cap (less than 65 micrometers).
  - Significant inflammatory activity (marked by the presence of macrophages, mast cells, and T cells).
  - A substantial lipid core, constituting over 40% of the plaque's overall volume.

- Presence of internal microcalcifications or bleeding.

As the lipid core grows, the plaque releases enzymes like collagenase, elastase, and metalloproteinases. These enzymes weaken the cap, rendering it progressively more delicate and susceptible to rupture.

**Factors Contributing to Plaque Rupture:**

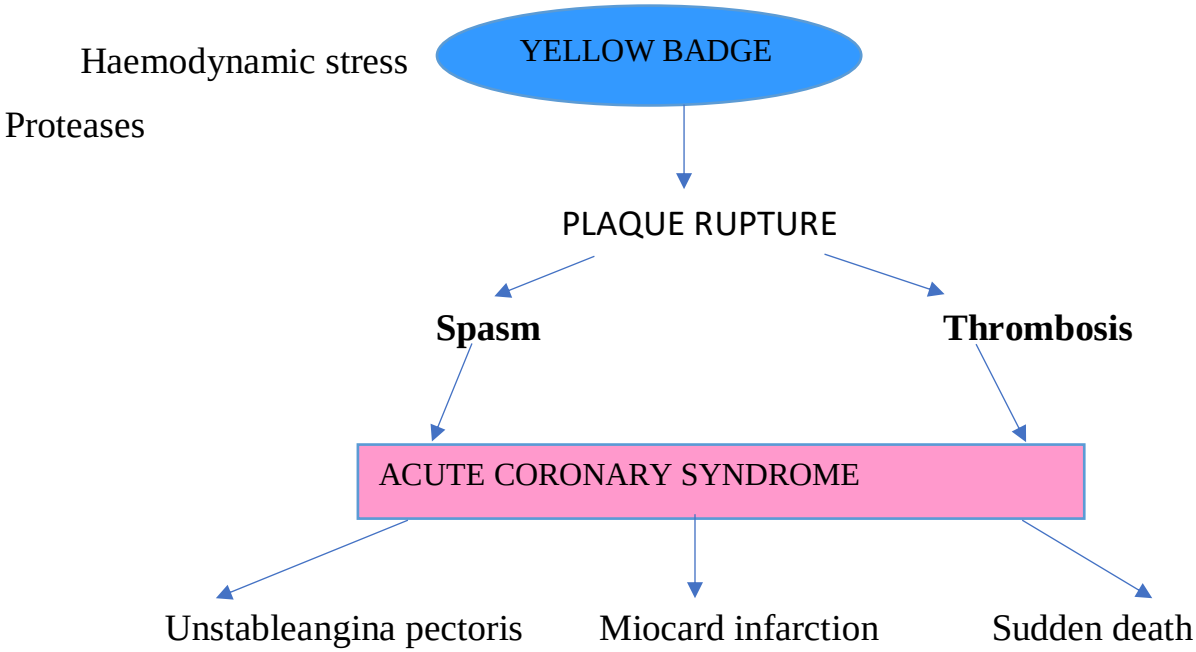
The probability of a plaque rupturing is influenced by its anatomical position, the size of its lipid core, and its interaction with blood flow dynamics. Rupture frequently results from a combination of intrinsic biological and extrinsic factors:

- **Biological/Internal Factors:**
  - Coronary artery spasms and localized pressure differences around the narrowed area.
  - Metabolic imbalances: Elevated LDL and triglycerides, or dyslipidemia.
  - Cellular alterations: Reduced collagen production and programmed cell death (apoptosis) of smooth muscle cells and macrophages.
  - Physiological stressors: Rapid heart rate (tachycardia), abrupt changes in blood pressure, and heightened activity of the sympathoadrenal system.
- **External/Lifestyle Factors:**
  - Intense physical exertion or severe emotional distress.
  - Smoking and consumption of alcohol or energy beverages.
  - Dietary influences, such as overeating.
  - Environmental elements, including sudden body cooling.

Mechanical stress, specifically "compression" at points where coronary arteries branch and bend, compromises the integrity of atherosclerotic plaques [39, 40]. Should such a plaque rupture, it triggers a cascade of events: the blood coagulation system is activated, platelets aggregate, and a thrombus forms, obstructing the vessel lumen. This blockage then manifests as myocardial ischemia in the region supplied by the compromised coronary artery [4, 107]. Consequently, the primary pathway for coronary artery damage involves plaque inflammation and subsequent rupture, culminating in platelet aggregation and thrombus formation. This chain of events is

a direct precursor to acute coronary complications like stroke, myocardial infarction, and sudden cardiac death (Scheme 1.2) [40].

**Scheme 1.2. Complications of coronary atherosclerosis**




The field of medical genomics, a relatively new discipline, has emerged thanks to significant advancements in modern molecular genetics, such as the complete sequencing of the human genome. This specialized area of study investigates how genetic variations impact the susceptibility to and progression of various diseases. Within this framework, understanding the contribution of genetic polymorphisms to ischemic heart disease (IHD) in working-age individuals is crucial, particularly when considering the interplay with their immune status, as illuminated by contemporary immunological insights. Genetic information is divided into three categories: family history, phenotype, and genotype. These are considered important for identifying patients at high risk for developing IHD and for whom appropriate medical interventions may be indicated. The study of Ischemic Heart Disease (IHD) relies heavily on genetic factors, notably because the disease is known for its severe progression, high mortality rates, and propensity to cause early disability among younger populations around the world. Molecular genetic techniques that analyze potential genes can be used to identify c oronary heart disease (CHD) before clinical symptoms manifest. These genes

contain polymorphic alleles that may be present at birth or acquired throughout life and, when exposed to particular negative environmental factors, can make people more susceptible to illnesses and pathological conditions. Patients with genetic risk factors for CHD are especially susceptible to lifestyle risk factors like smoking, unhealthy lifestyle choices, physical inactivity, being overweight or obese, unhealthy diets, stress, and harmful environmental conditions. The additive nature of the combined effects of various genetic and environmental risk factors has been well-documented. For individuals of working age who possess a genetic predisposition, actively addressing modifiable risk factors can serve as a preventative measure against the development of unfavorable genetic predispositions that could later lead to disease.

The concept of genetic polymorphism underpins genetic predisposition. Unlike genetic mutations, polymorphisms exhibit less pronounced phenotypic manifestations, meaning certain polymorphisms can either facilitate or impede disease progression under specific adverse circumstances. Single nucleotide polymorphisms (SNPs) are frequently responsible for genetic predisposition. When SNPs occur in non-coding regions of the human genome, they represent allelic variants. A SNP is characterized by a single nucleotide difference in homologous chromosomal regions compared to the standard deoxyribonucleic acid (DNA) sequence, arising from point mutations. The modulation of gene expression by polymorphic variants is a contributing factor to the pathogenesis of a spectrum of diseases. This observation accentuates the significance of characterizing individual genetic profiles to facilitate the formulation of bespoke, anticipatory, and prognostic lifestyle regimens.

The progress in molecular genetics, including the mapping of the human genome, has led to the development of medical genomics. This discipline investigates how genetic variations influence disease onset and an individual's vulnerability to health issues. Genetic information is generally classified into three categories: family medical history, observable traits (phenotype), and an individual's genetic composition (genotype). Identifying individuals at elevated risk for ischemic

heart disease (IHD) is vital for implementing timely medical interventions. Ischemic heart disease (IHD) holds a prominent position in genetic risk factor investigations. This is attributed to its global prevalence, rapid advancement, and the potential for severe outcomes, such as elevated mortality rates and premature disability, particularly impacting younger demographics worldwide.

The concept of genetic polymorphism underpins the understanding of an individual's inherent susceptibility to certain diseases. Unlike outright mutations, genetic polymorphisms often have subtler phenotypic effects, meaning they can either facilitate or impede disease development under specific adverse circumstances. Single nucleotide polymorphisms (SNPs) are frequently implicated in genetic predispositions. When SNPs occur in non-coding DNA regions, they represent distinct allelic variations. A SNP is characterized by a single nucleotide difference within homologous chromosomal regions compared to the standard DNA sequence, stemming from point mutations. The influence of these polymorphic variants on gene expression plays a role in the pathogenesis of various diseases, highlighting the significance of analyzing individual genetic profiles to tailor preventive and predictive lifestyle interventions.

The inherent likelihood of developing a particular disease is understood through the lens of genetic polymorphism. In contrast to genetic mutations, polymorphisms exhibit a less obvious influence on a person's observable characteristics. Consequently, under specific unfavorable environmental pressures, these polymorphisms can either foster or inhibit the progression of a disease. Single nucleotide polymorphisms (SNPs) are frequently implicated in genetic predisposition. When SNPs occur within non-coding segments of the human genome, they are identified as allelic variants 115, 139, and 140. A SNP is characterized by a single nucleotide variation in the deoxyribonucleic acid (DNA) sequence within homologous chromosomal regions, originating from point mutations. Polymorphic variants, through their influence on gene expression, play a role in theictogenesis of various diseases. This highlights the critical need to analyze

an individual's unique genetic makeup to craft tailored, effective lifestyle interventions for both prevention and prediction.

The pathogenesis of atherosclerosis is significantly influenced by immune-mediated inflammation, with pro- and anti-inflammatory cytokines serving as key markers of this inflammatory state (98, 117, 155). Numerous genetic investigations have elucidated new mechanisms responsible for the formation of polymorphic structures within cytokine genes (25, 98, 115, 173, 169). Recent data have accumulated regarding genetic polymorphisms in cytokine genes and their corresponding receptors. These polymorphisms are linked to allelic variants of cytokine genes, which arise from single nucleotide polymorphism (SNP) mutations located in the non-coding regions of the genes [30, 47, 67]. In the majority of instances, SNP substitutions occur within the 5'- or 3'-terminal regulatory regions of genes, such as the promoter or intron regions. These substitutions consequently affect the rates of gene transcription and translation, as well as the stability of messenger ribonucleic acid (mRNA). The ultimate effect is an alteration in the production and functional activity of the synthesized protein, leading to either an increase or decrease in the quantity and biological activity of the synthesized peptide. Only a small fraction, 5%, of point SNP mutations are found within the exons of a given gene [67, 117, 140, 169].

Polymorphic genetic loci in cytokine genes serve as crucial indicators for predicting an individual's predisposition or resistance to various diseases. The intrinsic variability within cytokine genes and their receptor counterparts directly influences cytokine expression, thereby modulating the complex biological pathways regulated by these signaling molecules. Studies consistently highlight that the functional characteristics of cytokines are intrinsically linked to the regulatory mechanisms governing their gene expression. Gene expression, a foundational biological process, involves the decoding of genetic information from DNA into mRNA and subsequently into proteins, commencing with the transcription of their nucleotide sequences (67, 117).

Within a healthy human organism, a substantial proportion of genes remain unexpressed, and the quantitative degree of expression exhibits pronounced inter-individual variability (67, 117, 140). Conversely, during pathological states, there is either an activation of specific genes of interest or, conversely, a repression of previously active genes. Gene expression proceeds in a sequential manner: the activation of one gene often precipitates the expression of another or multiple genes, with the magnitude of this expression being contingent upon gene polymorphism (74, 169). A critical task in molecular genetics involves studying the distinct patterns of cytokine gene expression. Genetic misregulation of cytokines contributes to the development of chronic inflammatory conditions and also systemic illnesses affecting the entire body.

## Molecular Genetic Diagnostics

Contemporary clinical practice permits the identification of Ischemic Heart Disease (IHD) preceding the emergence of somatic symptoms. This is accomplished through the analysis of candidate genes — specific polymorphic alleles present congenitally. While these alleles do not confer an absolute guarantee of disease, they can instigate pathological conditions upon an individual's exposure to unfavorable environmental stressors. The relationship between an individual's genetic endowment and IHD is frequently characterized as additive. This signifies that a genetic predisposition becomes substantially more hazardous when conjoined with exogenous "maladaptive habits" or environmental determinants, such as:

- Nicotine and substance dependence.
- Sedentary lifestyles and obesity.
- Chronic psychological stress and compromised environmental quality (e.g., atmospheric pollution).
- Nutritional imbalances.

For the economically active segment of the population, the early ascertainment of these genetic risks is critically important. Through aggressive intervention

targeting modifiable risk factors, individuals can effectively attenuate or mitigate the negative influence of their genetic predisposition.

## The Role of Genetic Polymorphism

The concept of genetic predisposition is rooted in polymorphism, a phenomenon distinct from conventional genetic mutations. Whereas mutations typically manifest with a direct and observable impact on an individual's traits (phenotype), polymorphisms operate with greater subtlety. Their influence can be context-dependent, with a specific polymorphism potentially conferring either protection against or susceptibility to a disease, depending on environmental interactions.

Single Nucleotide Polymorphisms (SNPs) are the most significant contributors to genetic predisposition.

- **The Process:** A SNP occurs when a single nucleotide within the DNA sequence is altered at a particular site on a chromosome.
- **The Outcome:** Even when these alterations occur in regions of the genome that do not code for proteins, they generate allelic variations that modulate gene expression.

By scrutinizing these individual genetic profiles, healthcare professionals can transition towards a paradigm of predictive and personalized medicine, enabling the design of specific lifestyle interventions and preventive measures precisely aligned with an individual's unique genetic blueprint. The immune system's inflammatory response is fundamental to the progression of atherosclerosis, and the balance of cytokines that promote or suppress inflammation serves as a vital marker of this activity. Atherosclerosis's development is significantly driven by inflammation orchestrated by the immune system, with cytokines that either fuel or dampen this inflammation being central to its assessment. Extensive genetic investigations have illuminated novel pathways involved in the formation of polymorphic variations within cytokine genes. Cytokines are indispensable signaling molecules that orchestrate inflammatory and immune responses. Emerging data indicates that

single nucleotide polymorphisms (SNPs) within these genes and their corresponding receptors are the primary determinants of functional variability in these proteins.

## How SNPs Influence Gene Expression

While point mutations within the protein-producing exons of a gene are uncommon (occurring only about 5% of the time), most single nucleotide polymorphisms (SNPs) are located in the non-coding regions. These non-coding areas, specifically the regulatory sequences at the 5' and 3' ends of genes, such as promoters and introns, are where these variations are predominantly found.

These genetic substitutions have a multifaceted impact on a cytokine's "journey" from gene to functional molecule:

- **Rate of Protein Production:** They dictate the speed at which the gene's instructions are read and translated into a protein.
- **Messenger RNA Lifespan:** They influence how long the mRNA molecule remains available for protein synthesis before being broken down.
- **Cytokine Levels and Activity:** Consequently, these alterations can modify the quantity and biological potency of the synthesized cytokine peptide, thereby increasing or decreasing its presence and effect within the body.

## Clinical Significance of Cytokine Polymorphism

The presence of different forms (polymorphisms) in cytokine genes serves as a crucial diagnostic tool for assessing an individual's predisposition or resistance to diverse diseases. Given that cytokines are the immune system's messengers, the specific genetic variants an individual carry will control the production of these mediators. The process of gene expression functions as a regulatory mechanism: genetic information is first encoded in DNA, then transcribed into mRNA, and finally translated into active proteins. Regarding coronary heart disease, the equilibrium of these synthesized proteins dictates whether the body's inflammatory response is effectively managed or contributes to the instability of arterial plaques. In a typical human, gene expression is not uniform; many genes remain inactive, and

the degree of activity varies greatly among individuals. During disease, genes of interest may become activated, or previously active genes may be suppressed. Gene expression unfolds in a step-by-step manner, where the activation of one gene can lead to the expression of others, with the level of expression being influenced by genetic variations. Investigating the expression patterns of individual cytokine genes is instrumental in tackling a major challenge in molecular genetics. Inherited disruptions in cytokine regulation can foster the development of chronic inflammatory conditions and widespread health problems.

Disruptions in the homeostatic balance of IL-1β protein production dramatically modify the inflammatory profile within atherosclerotic plaques, representing a crucial trigger for their genesis and destabilization [140]. The subsequent expression of cytokine genes, which exert both local and systemic effects, drives a significant expansion of inflammatory processes and tissue injury, concurrently elevating gene expression levels manifold [139]. A salient feature of cytokine gene expression is its inherent tissue specificity, which is governed by the activation of cellular signaling pathways. This specificity is attributable to the unique repertoire of transcription factors present in different cell populations [98]. When particular ligands bind to their corresponding lymphocyte receptors, a series of intracellular signaling events unfold. These events ultimately lead to the formation of complexes at the regulatory regions of cytokine genes, involving both always-present and/or activatable transcription factors. This binding then either triggers or suppresses gene expression [140]. The level of receptor expression itself is shaped by genetic differences at variable locations and varies in frequency across different illnesses [117]. For this study, two genes strongly implicated in coronary heart disease (CHD) were chosen from global repositories: the pro-inflammatory IL-1β C/T 3953 (rs1143634) and the anti-inflammatory IL-10 A/G 1082 (rs1800896). The IL-1β gene, found on chromosome 2q13-21, is a complex structure with 22 exons and nine introns. A key genetic variant, C(+3953)T, occurs in the fifth exon, involving a cytosine (C) to thymine (T) change. Other point mutations, including T-35C and G-511A, are present in the promoter region.

## The IL-1β Gene (rs1143634)

Located on chromosome **2q13-21**, the IL-1β gene is a complex structure consisting of 22 exons and nine introns. A critical genetic marker, known as **C(+3953)T**, occurs in the fifth exon of this gene. This transition mutation involves the replacement of cytosine (C) with thymine (T). Additionally, other point substitutions, such as T-35C and G-511A, are found within the promoter region.

### Biological Function and Impact

The IL-1β gene is responsible for encoding the **pro-inflammatory cytokine IL-1β**, an inducible protein that is essential for triggering the inflammatory response following tissue damage.

- **Production Sources:** This cytokine is primarily synthesized by activated macrophages, monocytes, stimulated B lymphocytes, and fibroblasts.
- **Regulatory Role:** It governs immune responses throughout every phase of the inflammatory process.
- **Polymorphic Effects:** Genetic variations within the promoter and intron regions can lead to either an increase or decrease in the production of endogenous IL-1β. High levels of this cytokine are particularly linked to the inflammatory cycles that drive atherosclerosis.

The IL-1β 3953 C/T gene exhibits three distinct genotypes, each dictating a specific level of IL-1β production: C/C is linked to normal production, C/T to elevated production, and T/T to significantly heightened production (36, 63, 146). This polymorphism profoundly impacts inflammatory responses. Individuals with the wild-type C allele maintain normal IL-1β cytokine levels and regulated inflammation. Conversely, the presence of the T allele is associated with more vigorous and acute inflammation, often leading to severe complications and potentially chronic inflammatory states. The T allele is known to drive increased expression of the IL-1β 3953 C/T gene. The high-producing IL-1β C(+3953)T variant, when present in individuals carrying the T allele (either as a single copy or two copies), results in a 2- to 4-fold greater synthesis of IL-1β cytokine compared to

those with the homozygous C variant (36, 117, 137). The C (+3953) allele is the most common, but its full functional implications are still under investigation.

The IL1B gene is responsible for producing IL-1-beta, a cytokine belonging to the interleukin 1 (IL-1) family. This protein plays a role in modulating both immune responses and inflammatory pathways. A specific genetic marker, denoted C (+3953) T, identifies a point in the IL1B gene's DNA sequence where a cytosine (C) base is replaced by a thymine (T) base at position 3953. This substitution defines the marker.

C/C

S/T

T/T

Marker association with diseases. The marker is associated with a change in immunity and reaction to the inflammatory process, which is accompanied by vulnerability to various infectious, autoimmune, and oncological diseases.

Immunity is a complex of the body's reactions aimed at protecting itself from infections and substances that differ in biological properties (from antigens). Innate protective factors are protein-cytokines produced by blood and tissue cells (monocytes, macrophages, granulocytes, lymphocytes).

Cytokines transmit signals between cells, ensuring the development of an immune response. Cytokines are active in very small concentrations. Their formation and secretion are short-term in response to the presence of an antigen in the body.

Interleukin-1 (IL-1) stands as one of the initial cytokines discovered, acting as a key controller of inflammation and immunity. Its synthesis occurs in many bodily cells, with activated macrophages, keratinocytes, stimulated B-lymphocytes, and fibroblasts being primary sources. IL-1's functions in the immune system are diverse, encompassing the initiation and regulation of immune processes, involvement in the development of both acute and chronic inflammation, and participation in bone tissue breakdown. The IL-1 family is comprised of three structurally similar proteins: interleukin-1-alpha and -1 beta (IL-1A and IL-1B), which are pro-

inflammatory, and IL-1RN (IL-1 receptor antagonist), which exerts anti-inflammatory effects.

These proteins are encoded by the IL1A, IL1B, and IL1RN genes, respectively. The balance between the expression and inhibition of IL-1 synthesis determines the development, regulation, and outcome of the inflammatory process. The biological effects of IL-1B are realized after binding to a specific membrane receptor IL-1RI.

Research has demonstrated that alterations within the IL1A and IL1B genes can influence how these genes are expressed. Specific genetic markers associated with a more active form of the IL1B gene have been pinpointed. Individuals possessing one or two copies of the T allele (meaning they are either heterozygous or homozygous for the high-expression IL1B variant, known as C (+3953) T) produce substantially more of this cytokine – four times more for homozygous carriers and two times more for heterozygous carriers – compared to those with two copies of the common C allele.

The influence of these gene variations on inflammatory responses can be characterized as follows: individuals with the standard gene versions exhibit balanced protein production and controlled inflammation. Conversely, those carrying the T allele experience more vigorous inflammatory reactions.

Regarding periodontitis, individuals with variations in the IL1B C (+3953) T gene may experience more severe inflammation, potentially leading to advanced periodontitis and a chronic condition. Consequently, carriers of this genetic variation face an elevated risk of developing severe forms of periodontitis compared to individuals with the unaltered genotype.

In the context of osteomyelitis, the presence of the T allele is more prevalent among affected patients and shows a significant deviation from its frequency in the general population.

Concerning body composition, individuals carrying the T allele (in either TT or CT genotypes) tend to have lower body weight when contrasted with those who are homozygous for the CC genotype.

**Body Fat and Genetic Linkage**

Individuals possessing at least one T allele (genotypes TT and CT) exhibit a reduced body weight when contrasted with those carrying the CC genotype.

**Implications of Findings:**

- **C/C:** Associated with typical interleukin production levels.
- **C/T:** Linked to elevated interleukin production.
- **T/T:** Correlated with significantly high interleukin production.

A healthcare professional is responsible for interpreting these research outcomes and determining appropriate treatment strategies. This decision-making process integrates these genetic insights with other relevant genetic markers, patient history, clinical observations, and laboratory test results.

**Clinical Relevance:**

This investigation is advised to be performed concurrently with the IL1A C (-889) T marker analysis, given its substantial impact on inflammatory processes.

**Interleukin 1A (IL1A):** This analysis focuses on identifying the C (-889) T mutation within the gene's regulatory region.

## The IL-10 1082 A/G gene (rs1800896)

**The IL-10 1082 A/G gene (rs1800896)** is responsible for regulating the production of the anti-inflammatory cytokine IL-10, a key player in immune responses during inflammatory conditions. It resides on human chromosome 1, in the 1q1-32 region, and comprises four exons. Sequencing revealed polymorphic areas within the IL-10 gene's promoter, such as IL-10.G and IL-10.R in the 5'-flanking region, which differ in their CA repeat counts. Molecular genetic studies have identified six polymorphic variants at positions -41, -127, -592, 652, -819, and -1082 relative to the transcription start site. The A 1082G polymorphism specifically refers to an adenine (A) to guanine (G) nucleotide substitution in the gene's regulatory domain.

This gene exhibits autosomal dominant inheritance, with equal prevalence in both sexes. The presence of one mutated gene copy from a parent is sufficient for disease manifestation, carrying a 50% risk for offspring. The IL-10 gene orchestrates

the production of the anti-inflammatory cytokine IL-10, a key regulator in immune responses. This cytokine acts to dampen inflammation by inhibiting the generation of T-helper cells and gamma-interferon, and by diminishing the activity of macrophages. Furthermore, it curtails the release of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, while simultaneously fostering the viability and expansion of B cells. The IL-10 1082 A/G (rs1800896) gene, which governs the synthesis of the anti-inflammatory cytokine IL-10, is a pivotal determinant in the regulation of inflammatory processes. This gene, situated on chromosome 1q1-32, is structured with four exons and features multiple variable areas within its promoter region, such as "CA" repeat variations. Among the six identified polymorphic sites, the A-1082G variation, characterized by a substitution of adenine (A) with guanine (G), holds particular importance for modulating immune system activity.

The IL-10A/G1082 gene exhibits distinct genotypes, each influencing IL-10 production levels. The A/A genotype is linked to typical IL-10 synthesis, whereas the A/G genotype is associated with increased production, and the G/G genotype with significantly elevated levels [7, 32, 50]. Research indicates a direct relationship between these allelic variants of the IL-10 A/G 1082 gene and the quantity of IL-10 protein produced. Specifically, the A/A genotype results in reduced IL-10 synthesis, while the G/G and G/A genotypes are correlated with high and moderate production, respectively [13, 23, 50].

The impact of IL-10 gene polymorphisms has been extensively investigated across various inflammatory conditions, including atherosclerosis. Efforts have been made to pinpoint specific risk genotypes of this gene in complex cases of acute myocardial infarction (AMI). Genetic research indicates a predisposition to coronary atherosclerosis, acute coronary syndrome (ACS), and AMI linked to specific variant alleles of IL-10 gene polymorphisms at the 1082 G/A locus. While the evidence base is not extensive, several studies have supported the correlation between IL-10 gene polymorphisms at position 1082 G/A and negative cardiovascular events. Early detection of these particular polymorphic variants at the 1082 G/A position of the IL-10 gene in working-age men with coronary heart disease (CHD) could greatly

enhance risk stratification for adverse cardiovascular outcomes [23]. The G-1082A polymorphism within the IL-10 gene is fundamental to cardiovascular well-being. This genetic variation influences the levels of anti-inflammatory interleukin-10, a key regulator of inflammatory processes implicated in conditions such as atherosclerosis, hypertension, and myocardial hypertrophy. Its presence is associated with an elevated susceptibility to atherosclerosis and other cardiac issues, as it dictates the intensity of the anti-inflammatory response, which is vital for managing the chronic inflammation characteristic of cardiovascular diseases.

**Understanding IL-10 and the G-1082A Polymorphism**

Interleukin-10 (IL-10) is a crucial signaling molecule within the immune system, primarily recognized for its powerful ability to dampen inflammatory responses. It achieves this by inhibiting the production of other cytokines that promote inflammation, thereby helping to keep inflammation in check. The G-1082A polymorphism, also known as -1082G>A, represents a specific alteration in the genetic code located within the regulatory region (promoter) of the IL-10 gene. These particular genetic variant influences how actively the IL-10 gene is expressed, which in turn dictates the quantity of IL-10 protein produced by the body.

**Implications for Cardiovascular Health:**

- **Inflammation Control:** Individuals possessing certain genotypes linked to reduced IL-10 production (for instance, those carrying the 'A' allele) may experience diminished capacity to regulate inflammation effectively. There is strong scientific consensus that ongoing, mild inflammation contributes significantly to the development and worsening of diseases such as atherosclerosis (hardening of the arteries), the formation of arterial plaques, coronary artery disease, and acute myocardial infarction (heart attacks).
- **Cardiac Remodeling:** Research indicates a correlation between this specific polymorphism and an elevated risk of developing left ventricular hypertrophy, a condition where the heart's main pumping chamber thickens.

- **Blood Pressure Regulation:** Investigations are also underway to explore the connection between variations in the IL-10 gene and an individual's susceptibility to developing high blood pressure (arterial hypertension).

In essence, the IL-10 G-1082A gene polymorphism serves as a genetic indicator that can help assess an individual's predisposition to various cardiovascular ailments, largely by influencing the delicate balance of inflammatory processes within the body.

The intricate network of cytokines acts as a central orchestrator of the body's internal stability (homeostasis), with their functions governed by the expression of their respective genes. Genetic factors, encompassing different versions of genes (allelic variants), complex interactions between genes (epistatic influences), and how genes are expressed, are thought to play a significant role in the onset and progression of numerous diseases, including coronary heart disease (CHD). These genetic insights are vital for accurate diagnosis and for tailoring effective treatment strategies. It's worth noting that many studies examining IL-10 gene polymorphisms in relation to CHD have often involved diverse populations, without specifically categorizing participants by gender or age. Furthermore, the precise interplay between various genetic determinants of both pro-inflammatory and anti-inflammatory cytokines and dyslipidemia (abnormal lipid levels) in the development of CHD among working-age men remains an area requiring further investigation.

This gene follows an **autosomal dominant** inheritance pattern, affecting men and women equally. IL-10 serves as a "braking system" for the immune response by:

- Inhibiting T-helper cells and γ-interferon.[2]
- Reducing the activity of macrophages.
- Suppressing the production of pro-inflammatory cytokines like **TNF-α, IL-6, and IL-1β**.[3]
- Promoting the survival and growth of B cells.

The specific combination of alleles directly dictates how much anti-inflammatory cytokine the body produces:

| Genotype | IL-10 Production Level | Clinical Association |
|---|---|---|
| **A/A** | Low / Normal | Often linked to a higher inflammatory state. |
| **A/G** | Elevated / Moderate | Intermediate regulatory capacity. |
| **G/G** | Very High | Strongest anti-inflammatory response. |

## Clinical Significance in Heart Disease

Polymorphisms at the 1082 G/A position are closely linked to the development of **atherosclerosis, Acute Coronary Syndrome (ACS), and Acute Myocardial Infarction (AMI)**. Research suggests that mutant alleles at this position can predict poor cardiovascular outcomes. In working-age men, identifying these variants early allows for better risk stratification and the prevention of severe cardiac events.

The cytokine system acts as a central hub for maintaining bodily balance (homeostasis).[4] While genetic factors like SNPs and gene expression are clearly fundamental to CHD progression, current research often overlooks specific demographics.

There is a significant gap in our understanding of how these genetic determinants—both pro-inflammatory (like IL-1β) and anti-inflammatory (like IL-10)—interact with **dyslipidemia** specifically in **working-age men**. Addressing this gap is essential for moving toward truly personalized diagnostic and treatment strategies.

# CHAPTER 2.

# Clinical features of CHD in working-age individuals, risk factor stratification, and genetic architecture

## Individuals clinical features of ischemic heart disease in working-age

Ischemic Heart Disease (IHD) stands as a primary cause of death worldwide, responsible for as much as half of all fatalities. A worrying development is its increasing prevalence in adults under 45, with the underlying arterial plaque buildup potentially starting by age 20. It's particularly noteworthy that men in this younger demographic face a 1.4 to 1.5 times greater risk of developing IHD compared to women. Ischemic heart disease (IHD) continues to be a major contributor to fatalities, responsible for a quarter to half of all deaths [221]. Alarmingly, both illness and death rates are on the rise in individuals under 45, with the initial signs of atherosclerosis now frequently appearing around the age of 20. Research consistently indicates that men under 45 experience IHD at a rate 1.4 to 1.5 times higher than women in the same age bracket [84].

For individuals of working age, IHD presents with distinct clinical patterns. The most telling signs of myocardial ischemia in working-age men are derived from their medical background and the specific type of chest discomfort. Angina episodes in this group are typically preceded by a brief period of ischemic disease. International studies reveal that a mere 24% of working-age men sought medical care for severe angina attacks. Furthermore, a significant majority, 69%, had no prior history of angina before their condition manifested [14, 41]. It's been observed that unusual chest pain in younger patients can be linked to spasms in the coronary arteries, inadequate blood flow in the heart's microcirculation, or autonomic nervous system imbalances, rather than being directly caused by narrowed coronary arteries [167]. A key characteristic of the disease progression in young patients is a

heightened likelihood of experiencing another heart attack or succumbing to sudden cardiac death.

Here are the points rewritten in different words, maintaining the original meaning:

- For younger people, a heart attack (MI) related to coronary heart disease frequently happens during strenuous physical exertion, such as demanding work, athletic training, competitions, or strenuous outdoor activities.
- Medication for individuals under 45 diagnosed with coronary artery disease is typically prescribed using standard treatment protocols.
- Following a heart attack, complications like heart failure, subsequent heart attacks, and angina are less frequent in individuals under 45 compared to older patients.
- When coronary artery disease is confirmed or suspected in younger individuals, specialized diagnostic procedures, including coronary angiography, are essential.
- Should coronary artery blockages be found, a proactive approach to restoring blood flow to the heart muscle is recommended, utilizing methods like balloon angioplasty or bypass surgery.
- If signs of coronary artery disease appear in younger patients with healthy or minimally affected coronary arteries, thorough investigations are needed to uncover underlying systemic illnesses or non-atherosclerotic causes of artery damage.

In summary, applying knowledge from research to everyday medical practice can aid in identifying individuals at higher risk of developing this condition sooner, thereby enhancing the accuracy of diagnosis, treatment effectiveness, early preventative measures, and the outlook for cardiovascular complications.

## Stratification of risk factors for coronary heart disease in working-age individuals

Coronary artery disease is a long-term illness stemming from a variety of causes. In numerous nations, shifts in how people live are a major contributor to the

onset of coronary artery disease in younger individuals. These lifestyle changes encompass poor eating habits, characterized by excessive intake of simple sugars and unhealthy fats, alongside insufficient consumption of produce, fish, and dietary fiber. This is often combined with a lack of exercise, persistent stress, and exhaustion, all of which can foster conditions like abnormal blood lipid levels, metabolic syndrome, excess body weight, and diabetes.

Furthermore, it's observed that younger employees frequently undertake extra and extended work hours, maintain a consistently fast-paced existence, and are more susceptible to ongoing workplace stress and depression. These pressures can, in turn, lead to habits like smoking, overeating, and the consumption of alcohol and energy drinks. Regrettably, even when screening for these changeable risk factors, it doesn't always succeed in pinpointing working-age men who, despite these risks, might later develop the condition. This reality fuels the ongoing quest for novel risk factors and their interconnectedness.

For working-age patients with coronary heart disease, smoking often transitions into a lifestyle habit, recognized as either a nicotine addiction or a disease state [87]. Extended cigarette use elevates the likelihood of acute myocardial infarction (AMI) by threefold [183, 185]. Smoking a pack or more daily increases the risk of sudden cardiac death (SCD) by five times relative to non-smokers. However, discontinuing smoking leads to a sharp decline in the risk of developing coronary heart disease (CHD). The risk of cardiovascular disease (CVD) drops by 36% after quitting, reaching the level of non-smokers within five years and positively influencing the disease's outcome [18, 180, 183].

Smokers imperil their own lives and those of others. Exposure to secondhand smoke increases the risk of CHD by 25–30%. The act of inhaling cigarette smoke negatively influences coagulation factors, platelet behavior, and other elements involved in atherothrombosis [133]. Smoking has detrimental effects on fibrinolysis, inflammation, and the function of blood vessels, thereby driving the development of atherosclerosis and increasing the propensity for subsequent thrombotic complications [180].

The way IHD appears in adults of working age is markedly different from that seen in older individuals, frequently hindering prompt diagnosis:

- **Reduced Health-Seeking Behavior:** Younger people are less inclined to seek medical attention for chest discomfort, and healthcare providers may have a lower inclination to suspect cardiac problems in this age group.
- **Unconventional Symptoms:** Patient histories and pain descriptions seldom match the typical indicators of ischemia. Around 69% of young men have no prior experience with angina before their initial significant cardiac event.
- **Sudden Occurrence:** Heart attacks (MI) in younger people often happen during periods of strenuous physical activity, such as athletic pursuits, demanding manual labor, or high-stress endeavors.
- **Root Causes:** Atypical pain is frequently associated with spasms in the coronary arteries, impaired function of small blood vessels, or imbalances in the nervous system, rather than the usual narrowing of arteries.

For cardiologists, treating younger patients necessitates a distinct strategy:
• Focused Diagnostic Procedures: When ischemic heart disease (IHD) is suspected, invasive methods such as coronary angiography become crucial.
• Proactive Revascularization Measures: Upon identifying plaques, intensive interventions like balloon angioplasty or coronary artery bypass grafting (CABG) are recommended.
• Exploring Non-Atherosclerotic Etiologies: If the coronary arteries appear normal or only minimally affected, it is important to evaluate for systemic conditions or rare coronary abnormalities.
• Improved Prognosis After Infarction: Younger patients who survive a heart attack generally have a lower incidence of recurrent events and heart failure compared to older individuals.

Risk Factor Assessment. The emergence of IHD in younger populations is complex and largely driven by contemporary lifestyle changes. Smoking cessation strategies require systematically identifying smokers, determining the degree of addiction, and preparing individuals for cessation,

providing advice on quitting smoking, lifestyle changes, and nicotine replacement therapy. Adherence to prescribed treatment is key. Hypertension is considered one of the important risk factors, which contributes to early disability in the young population. It is difficult to accurately assess the prevalence of hypertension in young people [178]. According to N.T. Vatutin (2017), hypertension is common among young people in up to 14.2% of cases, with higher prevalence rates noted among men. prevalence and accounts for 22.2% [28]. A number of risk factors can contribute to increased blood pressure, such as smoking, physical inactivity, poor diet, stressful situations, and these risk factors are closely related to lifestyle. The risk of developing hypertension can be 6 times more common with an unhealthy diet with the consumption of fatty and salty foods, alcohol, etc. With the development of hypertension before the age of 35, a relationship is observed between increasing age 44 9 32 and activation of the SAS [162]. Between the ages of 35 and 45, the development of hypertension is significantly influenced by clinical signs of metabolic syndrome (MS), which lead to sympathicotonia, an increase in circulating blood volume and total peripheral vascular resistance and ED. This creates a "vicious circle" of excessive increase in blood pressure and ED, accelerating the development of atherosclerotic processes [31, 58], subsequently leading to cardiovascular catastrophes [179].

It is observed that diabetes mellitus is less common in working-age individuals already suffering from coronary heart disease. However, for those with type 2 diabetes, the risk of dying from coronary heart disease is considerably higher, between two and six times that of individuals without this condition [19]. In type 2 diabetes mellitus, LDL concentrations increase sharply [72], becoming denser with a high cholesterol content and being more susceptible to peroxidation. In the liver, apo B and E receptors poorly recognize LDL and are very slowly cleared from the bloodstream. These LDLs are more actively phagocytosed by monocytes /macrophages and accumulate in the vascular wall, stimulating atherosclerosis in the coronary arteries [19, 160].

Amongyoungpatients with coronary artery disease, individuals with a family history of coronary heart disease (CHD) are more common, occurring in 41 to 64% of cases [6, 133]. In the presence of coronary heart disease (CHD) in first-degree relatives is considered 9 33 9 9 ON [25, 44], and the risk of developing CHD in such cases increases by 1.5-1.7 times.

This familial predisposition appears to weaken with increasing degrees of relation. ARIC studies further support the hereditary nature of CHD, indicating it's a factor in 90% of cases among those who lead healthy lives. The risk is particularly elevated, tripling for offspring, when a parent experiences early-onset coronary artery atherosclerosis. The presence of CHD in one's family history, especially at an earlier age, signals the need for proactive measures like genetic screening, lifestyle counseling, and medication. However, the precise biological pathways through which CHD is inherited are still being investigated. Beyond genetics, excess body weight and obesity are strongly linked to CHD and independently contribute to the premature development of coronary atherosclerosis in adults.

The risk of developing coronary heart disease increases in men with a waist circumference greater than 94 cm, and a waist-to-hip ratio greater than 1.0 is considered an accurate indicator of central obesity. The causes of excess weight can 34 be hereditary predisposition. Calorie control and regular exercise are the cornerstones of maintaining a normal weight [172, 201]. The influence of nervous stress on the development of coronary heart disease is a compelling risk factor, and the prevalence of nervous stress in Europe ranges from 25 to 33% [138], and in the Russian Federation – 19.3% [201].

The confluence of intense occupational stress, neuro-emotional strain, irregular work patterns, and disrupted sleep-wake cycles precipitates clinical manifestations of anxiety and depression. These mental health challenges are associated with an increased susceptibility to coronary heart disease and a higher risk of mortality. The negative impact of psychoemotional stress lies in its tendency to solidify adverse behavioral patterns, such as smoking, alcohol consumption, and excessive intake of simple carbohydrates, in individuals following stressful experiences.

Psychologically induced stress triggers adrenergic stimulation, which augments myocardial oxygen demand and intensifies the development of myocardial ischemia. Furthermore, psychological stress induces vascular constriction, affecting coronary vessels that may already harbor atherosclerotic plaques, thereby compromising myocardial oxygen delivery. Under stressful conditions, catecholamines promote enhanced blood coagulation, facilitating thrombus formation, which is crucial for the development of atherothrombosis or the destabilization of pre-existing atherosclerotic plaques.

Their professional roles are inherently linked to acute and chronic stressors, elevated neuro-emotional tension, irregular work schedules, and disrupted sleep patterns, all of which contribute to a heightened risk to their lives and health. Alcohol consumption plays a dual role in the risk of developing CHD. Small amounts of alcohol (1–2 drinks, 10–12 grams of pure alcohol) have a beneficial protective effect by stimulating HDL production and reducing its catabolism [49, 113]. Large amounts of alcohol (>2 drinks) adversely affect the human body, contributing to elevated blood pressure, impaired cerebral circulation, aggravating coronary heart disease, atrial fibrillation, and diabetes [48, 188], and weakening the effects of antihypertensive and anti-ischemic therapy [97, 184, 208].

A family history of alcohol consumption also plays a significant role in the development of alcoholism. 31 Energy drink consumption is a new addition to the ranks of unhealthy habits, along with alcohol, tobacco, and drugs. Small amounts of energy drinks speed reaction times, increase aerobic and anaerobic endurance, prevent drowsiness, enhance information processing, and improve mood and well-being [130]. Health problems associated with energy drink consumption are primarily associated with excess caffeine, the dose of which in energy drinks ranges from 150to 320mg/L, and this dose is the upper tolerable daily level [29, 129]. Large doses of caffeine found in energy drinks deplete nerve cells, increase spinal cord reflex excitability, and stimulate the respiratory and vasomotor centers of the brain [94, 131].

One of the important risk factors for the development of coronary heart disease is poor nutrition. Poor nutrition is considered when a patient consumes foods high in trans fats and table salt [45] and few vegetables and fruits (less than 3 servings per day), fish products, fiber, as well as fast and excessive eating [40, 149, 212]. A lifestyle characterized by regular intake of processed items, baked goods, sugary fizzy beverages, and refined starches, combined with a lack of physical activity, is a significant driver of weight accumulation and obesity. By removing foods high in cholesterol and prioritizing those rich in fiber, such as leafy greens and fruits, along with seafood, individuals can achieve better regulation of their carbohydrate and fat metabolism and improve overall bodily balance.

Recently, much attention has been paid to patients with low physical activity (LPA). In individuals with LPA, the risk of developing coronary heart disease increases by 1.5-2.4 times, compared with individuals leading a physically active lifestyle. According to the WHO criteria, LPA is defined as work in a sedentary position for more than 5 hours a day and/or if active leisure time is less than 10 hours per week [68]. In the United States, 7 out of 10 adults are currently unable to perform even moderate physical activity [150], while in the Russian Federation, 61.2% of students have non-functional physical activity [132], and its prevalence increases with age [68].

Engaging in regular physical activity, whether it's 150 minutes per week of moderate effort or 75 minutes per week of vigorous effort, or a blend of the two, offers substantial advantages. These include a notable decrease in deaths related to heart and blood vessel conditions, a reduction in blood pressure, weight management, enhanced cholesterol levels (specifically by boosting "good" HDL cholesterol), support for quitting smoking, and improved blood clotting processes.

Brisk walking for half an hour daily reduces the risk of developing cardiovascular disease by 18%, while running for an hour weekly reduces the risk by 42%. For patients with coronary heart disease, light physical activity such as jogging, swimming, cycling, aerobics, sports dancing, Nordic walking, etc. are recommended

[150, 166]. Physical exercise should be performed at least 4-5 times per week, lasting 30-40 minutes, with warm-up and cool-down periods. When subjected to a regimen of systematic, quantified physical activity and dietary management, individuals can achieve a reduction in excess body weight and mitigate the risk of developing coronary heart disease and its sequelae [46]. Accordingly, a comprehensive study of all the aforementioned critical risk factors associated with the early manifestation of coronary heart disease in younger patients will broaden our knowledge of the disease's etiology, pathogenesis, and specific manifestations. Such an understanding will be paramount for enhancing early diagnostic capabilities, therapeutic interventions, and the formulation and deployment of preventive programs for this patient population.

**Modern Behavioral Risk Factors:**

- **Dietary Habits:** High intake of trans fats and simple carbohydrates, combined with low fiber and fruit consumption.
- **Occupational Stress:** Long working hours, high-paced environments, and chronic fatigue often lead to "maladaptive coping," such as smoking, overeating, or excessive consumption of alcohol and energy drinks.
- **Sedentary Lifestyle:** Physical inactivity directly contributes to the development of metabolic syndrome, obesity, and diabetes.

**The Framingham Perspective:** While classic factors—hypertension, smoking, and heredity—remain critical, traditional screening does not always capture the risk in working-age men. This underscores the need to identify new biomarkers and genetic combinations to predict disease before it manifests. Protective factors, such as moderate physical activity and a diet high in HDL-promoting foods, remain the primary defense against early-onset IHD.

In working-age individuals, coronary heart disease is driven by a complex interplay of conventional and modern environmental factors. Research indicates that approximately **85% to 90%** of these patients possess at least one traditional risk factor, which serves as the primary catalyst for early-onset atherosclerosis.

### Traditional Risk Factors

These are the established pillars of cardiovascular risk that contribute to the structural degradation of the coronary arteries:

- **Biological & Genetic:** Male gender, advancing age, and a strong family history (heredity) including specific genetic predispositions.
- **Metabolic:** Hypertension, Diabetes Mellitus (DM), Dyslipidemia (DLP), and obesity.
- **Behavioral & Psychological:** Active and passive smoking, physical inactivity, chronic stress, and clinical depression.

### Additional and Modern Risk Factors

Recent studies have identified a secondary tier of "non-traditional" triggers that are increasingly prevalent in the modern workforce. These factors often act as acute triggers for cardiac events in younger populations:

- **Substance Use:** Abuse of alcohol, frequent consumption of energy drinks, and the use of stimulants like cocaine.
- **Occupational & Social:** Professional demands, irregular work schedules, high-pressure organizational conditions, and broader socio-economic influences.
- **Environmental & Lifestyle:** * **Dietary:** Low consumption of essential nutrients found in fruits and vegetables.
- **External:** Air pollution, rapid urbanization, and sensitivity to meteorological or seasonal changes.
- **Biochemical:** Elevated levels of Lipoprotein (a).
- **Physical Extremes:** Excessive or unaccustomed physical exertion (often contrasting with general physical inactivity).

### Conclusion

The convergence of these factors creates a "perfect storm" for the working-age population. Unlike older patients, where aging is the dominant driver, younger patients are more susceptible to the **cumulative effect** of lifestyle and occupational stressors [181, 205].

Extensive clinical research confirms that the development of coronary heart disease (CHD) in younger populations is a complex synergy of demographic, behavioral, and molecular factors. For men under 45, the risk is particularly high, with mortality rates in the working-age population being up to 6.2 times higher than in women.

### Traditional and Lifestyle Risk Factors

In men aged 39–49, the incidence of coronary atherosclerosis is triple that of women. Several primary drivers have been identified:

- **Smoking:** Found in 60%–90% of CHD patients under 45. It acts as a primary catalyst, increasing the risk of CHD fivefold and sudden cardiac death (SCD) fivefold for heavy smokers. It causes endothelial dysfunction (ED), accelerates LDL oxidation, and impairs blood coagulation.
- **Hypertension:** Affects up to 22.2% of young men. Early-onset hypertension (before age 35) is often linked to an overactive sympathoadrenal system (SAS), creating a cycle of high blood pressure and vascular damage.
- **Diabetes Mellitus:** While less common in the young, it accelerates atherosclerosis significantly. Patients with type 2 diabetes face a 2–6 times higher mortality risk due to denser, more toxic LDL particles and impaired platelet function.
- **Obesity:** Central obesity (waist >94 cm in men) is an independent predictor of early plaque formation. Even a 10% increase in body weight can significantly raise plasma cholesterol levels.

### Psychoemotional and Environmental Triggers

The modern "working-age" environment introduces specific pressures that differ from older demographics:

- **Occupational Stress:** High-pressure roles (drivers, law enforcement, IT) involve irregular sleep and chronic neuro-emotional tension. This leads to catecholamine surges that demand more oxygen for the heart while simultaneously constricting vessels.

- **Substance Use:** Beyond tobacco, the abuse of alcohol and high-caffeine energy drinks (150–320 mg/L) can trigger arrhythmias and hypertension, depleting nerve cells and overstimulating the vasomotor centers.
- **Physical Inactivity:** Defined as sitting for >5 hours a day. Transitioning to moderate activity (150 min/week) can drastically improve lipid profiles and lower blood pressure.

**Genetic Architecture of CHD**

The emerging field of **Genetic Cardiology** allows for "molecular diagnosis" before symptoms appear. By studying **Candidate Genes**—polymorphisms in DNA sequences that affect proteins, receptors, and inflammatory markers—clinicians can determine an individual's specific predisposition.

Key findings in genetic research include:

1. **Heredity:** A family history of early CHD (e.g., a father with an MI before 55) triples the risk for offspring.
2. **SNPs and GWAS:** Genome-wide association studies (GWAS) identify Single Nucleotide Polymorphisms (SNPs) that involve lipid metabolism, inflammation, and thrombosis.
3. **Personalized Prevention:** Unlike general mutations, these polymorphisms often require an "environmental trigger" (like smoking or stress) to manifest as disease.

**Summary Table: Impact of Modifiable Factors**

| Factor | Impact on CHD Risk | Key Mechanism |
|---|---|---|
| **Smoking** | 5x higher risk | Endothelial damage & LDL oxidation |
| **Diabetes (Type 2)** | 2–6x mortality risk | Dense LDL & extensive myocardial necrosis |
| **Physical Activity** | 18% reduction (brisk walking) | Improved HDL & hemostasis |
| **High Stress** | 2x mortality risk | Adrenergic stimulation & vasoconstriction |

## Genetic Architecture of Coronary Heart Disease in Young Adults

The field of genetic cardiology is a recent development in medicine, dedicated to understanding the origins and progression of coronary heart disease (CHD) through the lens of genetic variations. This area of research illuminates the underlying biological mechanisms of CHD, paving the way for earlier detection, more tailored therapies, and preventative strategies that can ultimately lower mortality rates and enhance patient well-being. The sequencing of the human genome has uncovered a spectrum of genetic predispositions to CHD, which is characterized by the buildup of plaque in the coronary arteries. Extensive research into the molecular genetics of CHD has demonstrated a growing understanding of the complex gene network involved, highlighting significant links between variations in specific genes and an increased likelihood of developing conditions like CHD, high blood pressure, irregular heartbeats, heart muscle disease, and inflammation of the heart. It is now widely accepted that both external influences, such as environmental exposures and unhealthy habits, and internal genetic predispositions, stemming from variations in gene alleles, contribute to the development of CHD.

In clinical settings, this involves molecular analysis of genes identified as conferring predisposition or being candidate genes. These molecular genetic investigations identify gene mutations and polymorphisms (genotyping) linked to CHD risk. Gene mutations, which are changes in the DNA sequence, can cause significant functional impairments in the proteins they code for, leading to disease. These mutations are relatively uncommon, occurring in less than 5% of the population. Candidate genes, on the other hand, refer to genes whose altered protein products arise from genetic variations within that gene. Investigating variations within specific genes, known as candidate gene polymorphisms, involves examining alterations in the DNA sequence. These alterations typically have a subtle impact on the proteins they code for, such as enzymes, receptors, or components of crucial biological systems like blood clotting, inflammation, and ion transport [174].

The understanding of how multiple genes contribute to cardiovascular disease (CVD) often stems from genome-wide association studies (GWAS). These studies aim to identify single nucleotide polymorphisms (SNPs) that might be linked to CVD development. More recently, the candidate gene approach has gained traction. This method focuses on genes believed to be central to the disease's underlying mechanisms, even if the link between the specific genetic variation and CVD is less pronounced [140, 147]. A wealth of research highlights the role of particular genetic polymorphisms in the onset and instability of atherosclerotic plaque (ASP) across diverse populations. These polymorphisms are often found in genes regulating inflammation, lipid metabolism, and blood clotting [139, 146]. Consequently, by analyzing genetic polymorphisms, we can gauge not only an individual's susceptibility to coronary heart disease (CHD) but also their likelihood of disease progression. This proactive assessment of individual genetic risk, even at the earliest signs of illness, is now a key focus [146, 147]. Therefore, a forward-looking evaluation of candidate gene polymorphisms implicated in the development and progression of CHD within the Central Asian (CA) population could pave the way for tailored strategies to treat and prevent this condition, even in individuals of working age.

# CHAPTER 3.
# Results of domestic and foreign studies on the prevalence of risk factors in patients with ischaemic heart disease in young patients

Coronary heart disease (CHD) remains the world's leading cause of death, accounting for up to 50% of annual mortalities. A particularly alarming trend is the rising impact on the working-age population, specifically men. CHD continues to be the primary driver of yearly fatalities globally, responsible for a substantial portion of deaths, ranging from 25% to 50%. Specifically, CHD contributes to over 7 million deaths annually, representing 12.8% of all cases. Alarmingly, both mortality and morbidity rates are on the rise among younger adults, with men being disproportionately affected. Given that younger individuals form the bulk of the working-age population, the impact of disability and death in this demographic presents a critical medical and societal challenge.

A key contributor to CHD is atherosclerosis of the coronary arteries, a condition characterized by a fluctuating progression that can lead to sudden complications like AMI and/or acute coronary syndrome (ACS). The initial, preclinical phase is silent, but during this time, the inner lining of the coronary arteries is damaged, leading to the formation of fatty streaks and the growth of atherosclerotic plaques. This process triggers a chain of events, including endothelial dysfunction, dyslipidemia, and inflammation within the plaque. Early clinical manifestations of coronary plaque typically arise from its rupture or erosion, exposing its contents to the bloodstream and initiating atherothrombosis. When coronary arteries become completely blocked and collateral circulation is insufficient, heart muscle tissue dies, resulting in acute myocardial infarction. In cases of partial blockage and coronary artery spasms, myocardial ischemia occurs, leading to myocardial infarction presenting as new-onset, progressive, variant, or early post-infarction angina. The dynamic nature of atherosclerotic plaques involves periods of stability, where the fibrous cap thickens and the lipid core shrinks, interspersed with periods of instability. During these exacerbations, inflammation intensifies, hemorrhages occur within the plaque, the

fibrous cap thins, the lipid core expands, and the plaque grows rapidly. Clinically, these alternating phases are reflected in the progression from stable angina to unstable angina.

Angina is primarily characterized by a constricting chest pain located behind the breastbone, or a sense of discomfort in the cardiac area. This discomfort can extend to the interscapular region, the left shoulder and arm, the back, the lower jaw, and the epigastrium. Such pain is typically exacerbated by physical activity, emotional strain, and elevated blood pressure, and is usually alleviated rapidly by rest or the administration of nitroglycerin. In individuals with coronary artery disease (CAD), a multitude of risk factors are commonly identified. These factors can either initiate CAD or play a role in its worsening, as certain risk factors contribute to the earlier onset of various complications. The understanding of the role these risk factors play in CAD development has undergone substantial expansion, leading to significant alterations in diagnostic and therapeutic approaches. The prevention of CAD in the working-age population is challenging due to a recent increase in the number of risk factors and their impact on a growing segment of the younger population. Moreover, each young patient presents with their own distinct set of risk factors, highlighting the imperative for personalized prevention strategies. Cardiologists frequently encounter patients with two, three, or even more co-existing risk factors, many of which are modifiable. For individuals with CAD, the presence of any number of risk factors leads to a considerably poorer prognosis compared to those without them. Consequently, the modification of these risk factors in patients with coronary artery disease must constitute a principal component of their treatment strategy, which should be individually devised for each patient.

## The Pathological Progression of CHD

The primary driver of CHD is coronary artery atherosclerosis, which follows a complex, "undulating" course. The disease typically moves through several distinct stages:

- **The Preclinical Stage:** This phase is asymptomatic. Behind the scenes, the vascular walls undergo primary damage, leading to the formation of lipid spots. A cascade of reactions—including endothelial dysfunction (ED), dyslipidemia (DLP), and localized inflammation—fuels the growth of atherosclerotic plaques.
- **Plaque Destabilization and Thrombosis:** Clinical symptoms often emerge suddenly when a plaque ruptures or erodes. When the plaque's internal contents meet blood cells, it triggers **atherothrombosis**.
  - **Complete Occlusion:** If the artery is totally blocked and blood flow cannot be rerouted (collateral insufficiency), myocardial tissue dies, resulting in an **AMI**.
  - **Incomplete Occlusion:** Partial blockages or spasms lead to ischemia, manifesting as various forms of unstable angina.

### The "Undulating" Cycle of Atherosclerosis

Atherosclerotic plaques do not grow linearly; they cycle between periods of stability and dangerous exacerbation:

| Period | Plaque Characteristics | Clinical Manifestation |
|---|---|---|
| **Remission (Stability)** | Thickening of the fibrous capsule; reduction in the size of the lipid core. | Stable Angina |
| **Exacerbation (Instability)** | Increased inflammation; internal hemorrhaging; thinning of the fibrous cap; rapid "explosive" plaque growth. | Unstable Angina / Acute Coronary Syndrome |

This cyclical nature explains why a patient may appear stable for long periods before experiencing a sudden, life-threatening cardiac event.

With angina, the main complaint of patients is squeezing pain behind the sternum or discomfort in the heart region, radiating to the interscapular region, left shoulder, left arm, back, lower jaw, and epigastric region. These pains intensify with physical exertion, emotional stress, and increased blood pressure, and quickly disappear after rest or taking nitroglycerin [127]. Among patients with coronary heart disease, risk factors are often encountered that may be the cause or play a role in the development or destabilization of coronary heart disease, since some risk

factors contribute to the earlier development of various complications. Modern perspectives on cardiovascular health emphasize that the list of risk factors (RFs) for coronary heart disease has grown considerably, leading to fundamental shifts in how the disease is diagnosed and managed. Preventing CHD in the working-age population is particularly challenging because the prevalence of these factors is rising among younger people, and each patient presents a unique clinical profile.

### The Complexity of Risk Factors

In clinical cardiology, it is common to find young patients presenting with a combination of two, three, or even more risk factors simultaneously. Most of these are modifiable, meaning they can be managed or reversed through intervention.

Key observations regarding risk in younger patients include:

- **The "Multiplier" Effect:** The prognosis for an individual with CAD worsens significantly with every additional risk factor present. A patient with multiple RFs faces a much higher danger of sudden cardiac events than one with a single factor.
- **Necessity of Individualization:** Because the specific combination of RFs varies from person to person, preventive strategies cannot follow a "one-size-fits-all" model.
- **Integrated Treatment:** Correcting and managing these risk factors is not just a secondary goal; it must be a central component of the primary treatment plan.

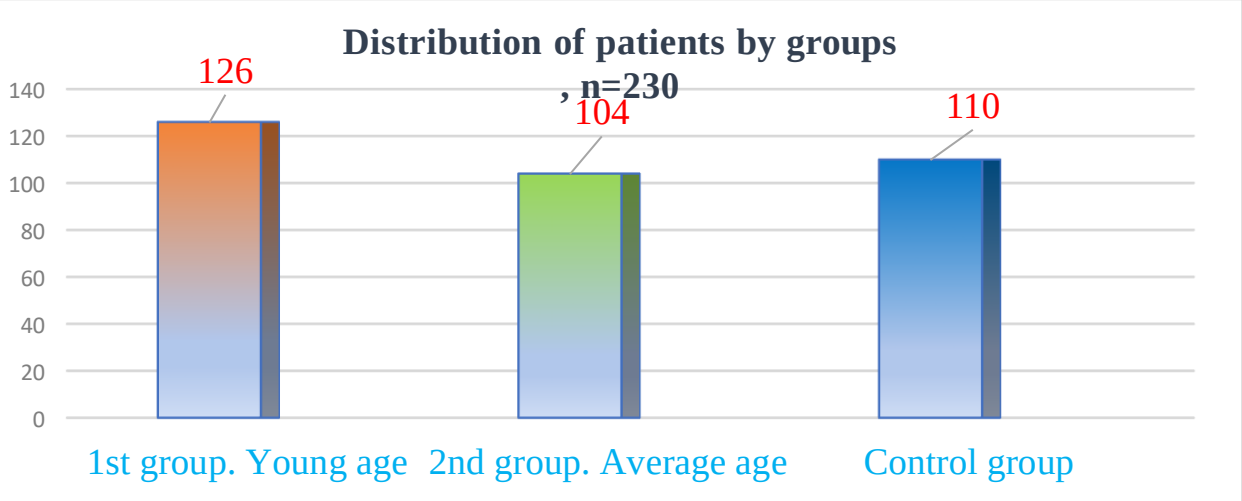
### Strategic Intervention

To improve long-term outcomes for working-age patients, medical tactics must transition from reactive treatment to proactive, personalized management. This involves identifying the specific cluster of RFs—such as smoking combined with high stress and genetic predisposition—and developing a tailored strategy to mitigate each one.

To improve the effectiveness of primary prevention, individuals with coronary heart disease (CHD) of working age should undergo in-depth preventive medical examinations at least twice a year, focusing on each individual's lifestyle and risk factors, and developing strategies to combat each modifiable risk factor. It is also necessary to consider the work environment, identify the causes of stressful and

depressive circumstances, and conduct individual outreach to prevent the development of acute coronary events.Clinical characteristics of patients

This study is based on the results of observation of patients with CHD hospitalized between 2018 and 2021 in the intensive care and emergency care departments No. 1 and 2 of the Samarkand Branch of the Republican Scientific Center for Emergency Medical Care (SB RESEC). The study involved 230 individuals diagnosed with coronary heart disease (CHD). These patients were categorized into two distinct age-based cohorts. The primary cohort comprised 126 men (54.8%) of working age suffering from CHD, with an average age of 38.8±5.29 years. The secondary, comparative cohort consisted of 104 elderly men (45.2%) also with CHD, whose mean age was 65.9±4.22 years (as depicted in Fig. 3.1). A separate control group was established, consisting of 110 healthy volunteers.




**Inclusion Criteria:**

- Participants had to be either young adult males between 18 and 44 years old, or older adult males aged 60 to 74.
- All individuals included must have had a confirmed diagnosis of coronary artery disease.
- Prior to enrollment, all participants were required to provide their informed consent to take part in the study.

**Exclusion Criteria:**

- Men within the specified age ranges (18-44 and 60-74) for whom a diagnosis of coronary artery disease or acute coronary syndrome (ACS) could not be established were not eligible.
- Individuals with significant co-existing health conditions were excluded. This included those who had experienced recent strokes, were suffering from acute exacerbations of chronic illnesses, had heart defects that significantly impacted blood flow, or had non-coronary related heart muscle conditions.
- Furthermore, participants with systemic or autoimmune disorders, active cancer, impaired liver or kidney function, mental health disorders, or a past history of head injuries were also disqualified.

When assigning patients to groups, the WHO age classification (2020) was used, which included: young age (18 to 44 years), middle age (45 to 59 years), elderly age (60 to 74 years), old age (75 to 89 years), and longevity (over 90 years). To determine the severity of unstable angina, the modified Braunwald classification adopted in 2000 was used. This classification defines unstable angina as having the following variants: new-onset angina (NOA), progressive angina (PA), variant (Prinzmetal) angina, and early post-infarction angina. The Killip classification was used to clarify the severity of acute heart failure (AHF), and the NYHA classification was used for chronic heart failure (CHF). All patients underwent a clinical and anamnestic assessment. For male patients diagnosed with coronary artery disease (CAD), a thorough medical history was gathered. This aimed to identify indicators of CAD, such as angina that occurs at rest or is unstable, and prior heart attacks. The assessment also sought to document the presence of contributing risk factors, including smoking, a family history of heart disease, sedentary lifestyle, stress, high blood pressure, diabetes, excess weight, consumption of energy drinks, and suboptimal dietary habits, as well as any other health conditions that might worsen the disease or its progression.

The clinical presentation of CAD patients included:

- Extended episodes of angina occurring while at rest, persisting for over 20 minutes, and showing little to no improvement with nitroglycerin.

- Individuals experiencing newly developed angina displayed symptoms that emerged within the preceding 28-30 days.
- Those with unstable angina exhibited a worsening of previously stable angina, or developed symptoms consistent with functional class III as defined by the Canadian Heart Association, or began experiencing angina attacks while at rest.

In evaluating patients with coronary artery disease (CAD), the primary clinical marker is retrosternal anginal pain. To ensure diagnostic precision, clinicians must perform a multi-dimensional assessment of this pain, focusing on its nature, triggers, and associated physical signs.

### Clinical Assessment of Anginal Pain

The characterization of anginal pain is based on several specific diagnostic criteria:

- **Location and Radiation:** Typically centered in the lower third of the sternum, with pain often radiating to the left clavicle, shoulder girdle, scapula, arm, neck, or lower jaw.
- **Triggers:** The relationship between the attack and physical activity (walking or exertion), environmental factors (cold weather), and psychological stressors. Additional triggers include elevated blood pressure, alcohol/energy drink consumption, or sleep disturbances.
- **Duration and Frequency:** Documenting the length of attacks in minutes and their frequency per day or week.
- **Pain Characteristics:** Describing the sensation (burning, pressing, or squeezing) and identifying associated symptoms such as shortness of breath, palpitations, nausea, weakness, or a sense of impending doom ("fear of death").
- **Relief Mechanisms:** Determining if the pain subsides with rest or the administration of nitroglycerin.

### Pain Intensity and Functional Limits

To quantify the patient's experience, the **Wong-Baker Scale** is utilized:

- **0:** No pain.

- **1–3:** Minimal pain.
- **4–6:** Moderate pain.
- **7–9:** Severe pain.
- **10:** Maximum possible pain.

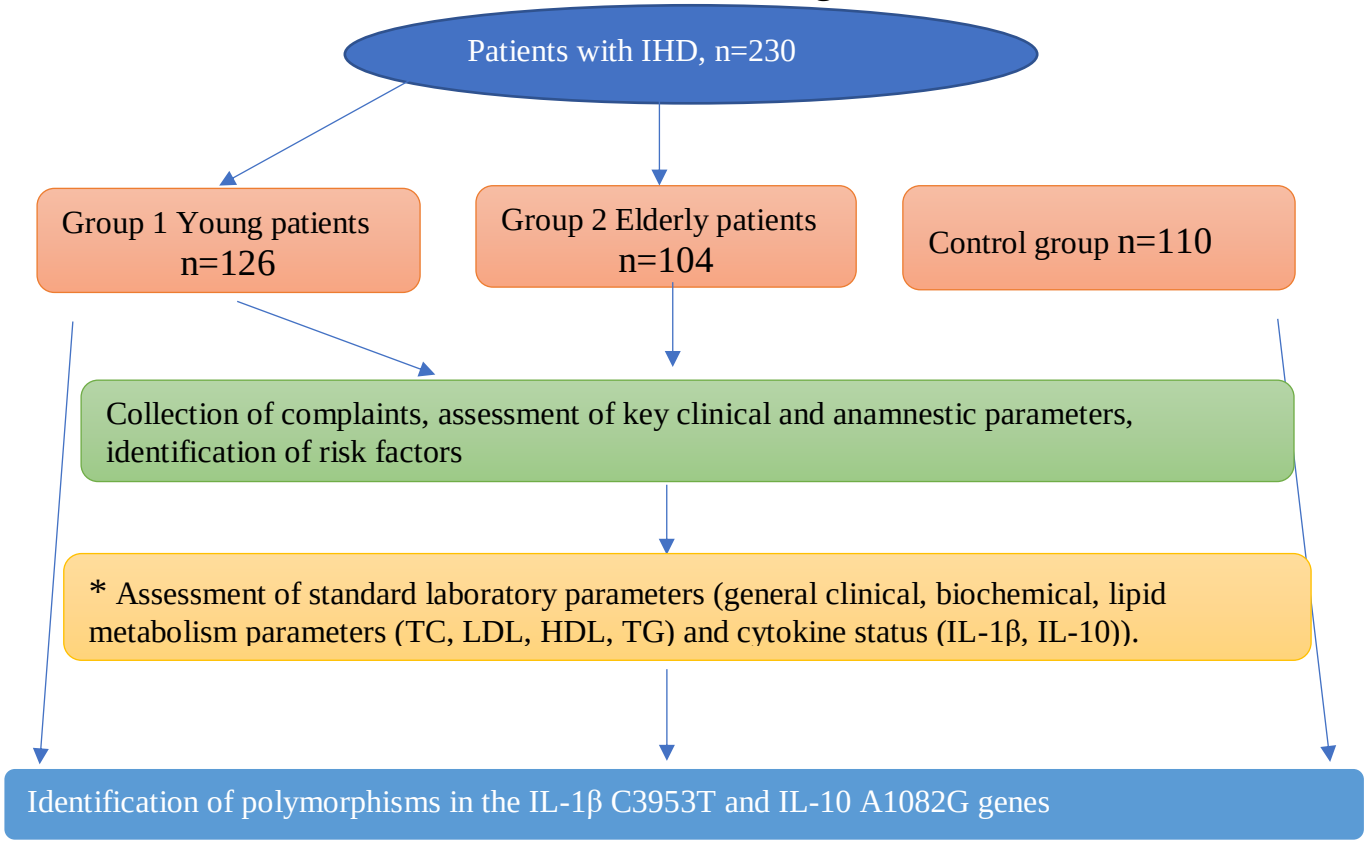
Clinicians also measure **exercise tolerance** by documenting the distance (in meters) or the number of floors a patient can climb before pain occurs.

### Physical Examination and BMI

Physical assessment follows standard protocols, including heart rate and blood pressure measurements (using the Korotkov method after a 5-minute rest). A critical component is the calculation of **Body Mass Index (BMI)** to assess obesity-related risks: BMI Classification (WHO Standards): Classification | BMI Range, Normal | 20.0 – 25.0, Overweight | 25.1 – 30.0 |, Obesity Grade I | 30.0 – 34.9 |, Obesity Grade II | 35.0 – 39.9 |, Obesity Grade III | 40.0 |

The objective of this comprehensive physical examination is twofold: to confirm myocardial ischemia and to rule out non-coronary (extracardiac) causes of chest pain.

**Research design**



Statistical analysis of the obtained data with assessment of the relationship between identified traditional risk factors, lipid metabolism disorders, cytokine imbalance, and polymorphisms in the IL-1ß C3953T and IL-10 A1082G genes

Figure 3.1. Research design

**Characteristics of patients in the study and comparison groups**

During the examination of patients by group, the following clinical, anamnestic, and hemodynamic data were revealed. Almost all patients examined had between 1 and 3 comorbidities. Hypertension was diagnosed in 58 (46%) young men, a lower rate than in the older age group, where this figure was 92 (88.5%) ($p<0.001$*). A history of diabetes was noted in 15 (11.9%) young men and 20 (19.2%) elderly patients ($p=0.07$). Overweight/obesity was diagnosed in 54 (42.9%) patients in Group 1, which was significantly lower than in Group 2, where it was observed in 92 (88.5%) patients ($p<0.001$*). Anemia was observed in 17 patients (13.5%) in group 1 and 16 (15.4%) in group 2 ($p=0.24$). A history of previous acute cerebrovascular accident was noted in 2 patients (1.6%) in group 1 and in 7 patients (6.7%) in group 2 ($p=0.01$*). PICS was observed in 15 patients (11.9%) in group 1 and in 29 patients (27.9%) in group 2 ($p=0.004$*). A history of chronic obstructive bronchitis (COPD) was observed in 1 patient (0.79%) in group 1 and in 2 patients (1.92%) ($p=0.31$) in group 2 (Fig. 3.2).

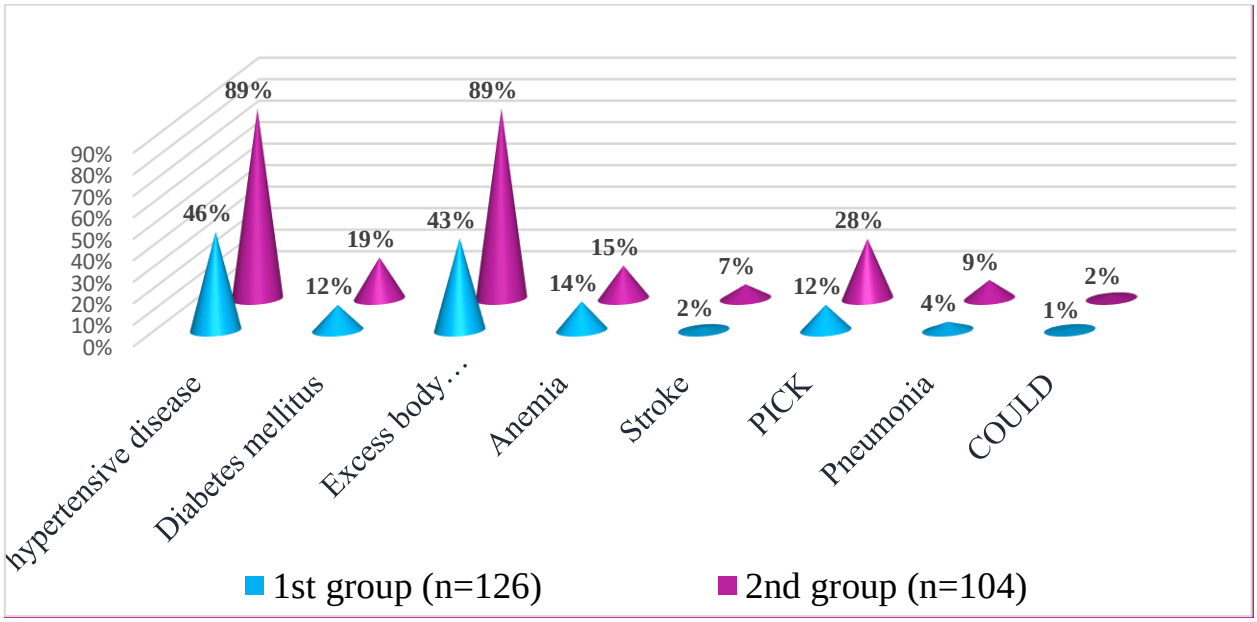


Fig. 3.2. Frequency of comorbidities in the study groups

Depending on the complications, the following were noted: episodes of cardiac asthma were detected in 50 patients (39.7%) in Group 1 and 93 patients (89.4%) in Group 2 ($p < 0.001$). Killip class 3 CHF was detected in 1 patient (0.79%) in Group 1 and 11 patients (10.6%) in Group 2 ($p = 0.02$)*. Killip class 4 CHF was detected in only 1 patient (0.79%) in Group 1. NYHA class II CHF was recorded in 10 patients (7.9%) in Group 1 and 4 patients (3.8%) in Group 2 ($p = 0.12$). NYHA class III CHF was diagnosed in 12 patients (9.5%) in Group 1 and 16 patients (15.4%) in Group 2 (p=0.006*) (Table 3.1).

**Table 3.1.**

**Clinical and hemodynamic parameters of patients with coronary artery disease**

| Indicators | Group 1 (n=126) | Group 2 (n=104) | Mann-Whitney-Wilcoxon test p-value. |
|---|---|---|---|
| Episodes of cardiac asthma | 50 (39,7%) | 93 (89,4%) | <0,001 |
| Killip Class 3 | 1 (0,79%) | 11 (10,6%) | 0,02* |
| Killip Class 4 | 1 (0,79%) | - | - |
| NYHA Class II CHF | 10 (7,9%) | 4 (3,8%) | 0,12 |
| NYHA Class III CHF | 12 (9,5%) | 16 (15,4%) | 0,006* |

The 2015 ESC Guidelines for Non-ST-Elevation Acute Coronary Syndrome, the 2014 RSC/ESC Guidelines (2015 Revision) for Unstable Angina, and the 2017 ESC Guidelines for ST-Elevation Myocardial Infarction all indicate that patients with coronary artery disease were treated with a standard array of medications. This included nitrates, beta-blockers, statins, ACE inhibitors or angiotensin II receptor antagonists (ARBs), anticoagulants, diuretics, antiplatelet agents (aspirin plus clopidogrel), and thrombolytic drugs. For patients specifically diagnosed with coronary heart disease (CHD), an additional treatment regimen was prescribed: levocarnitine and L-arginine hydrochloride at 100 ml daily for 5 days, in conjunction with their standard therapy. This was then followed by a month of levocarnitine

tablets (500 mg daily) and Tivortin syrup (5 ml, three times a day), as presented in Table 3.2.

In accordance with the 2015 ESC Guidelines for ACS (without persistent ST-segment elevation), the 2014 RSC/ESC protocols for Unstable Angina, and the 2017 ESC Guidelines for STEMI, patients followed a standardized pharmacological regimen. This traditional approach included:

- **Anti-ischemic and hemodynamic agents:** Nitrates, beta-blockers, ACE inhibitors, or Angiotensin II Receptor Antagonists (ARAII).
- **Antithrombotic therapy:** Anticoagulants, dual antiplatelet therapy (Aspirin + Clopidogrel), and thrombolytic agents where indicated.
- **Metabolic and lipid management:** Statins and diuretics.

### Specialized Combination Therapy

In addition to traditional treatment, a specific metabolic regimen involving **Levocarnitine and L-arginine hydrochloride** was implemented to support myocardial function and endothelial health:

This combined approach aims to enhance cellular energy metabolism and improve nitric oxide availability, which is particularly critical for patients with the endothelial dysfunction often seen in working-age men.

**Table 3.2.**

**Frequency of drug administration for CHD depending on the general condition of patients**

| Groups of drugs | Group 1 (n=126) | Group 2 (n=104) |
|---|---|---|
| | Frequency of use (%) | |
| Nitrates | 108 (85,7%) | 100 (79,4%) |
| β-blockers | 69 (54,8%) | 80 (76,9%) |
| ARBs | 32 (25,4%) | 33 (31,7%) |
| Antiplatelet agents | 83 (65,9%) | 94 (90,4%) |
| Statins | 80 (63,5%) | 75 (72%) |
| Diuretics | 19 (15,1%) | 29 (27,9%) |
| Cardiac glycosides | 10 (7,9%) | 18 (14,3%) |
| Anticoagulants | 79 (63%) | 84 (80,7%) |
| Streptokinase | 9 (7,1%) | 3 (2,9%) |
| Levocarnitine + L-arginine | 83 (65,9%) | 94 (90,4%) |

| | | |
|---|---|---|
| hydrochloride | | |

### Key medical features of the non-intervention group.

For the control group, 110 volunteers, all appearing healthy, were recruited. Their ages fell between 18 and 44 years, with a calculated average of 37.6 ± 5.3 years. Inclusion criteria for the control group included the absence of chronic coronary heart disease (CHD), normal blood pressure, and clinical and exercise testing data on coronary heart disease.

The average BMI was 23.6 ± 3.07 kg/m². Seventy-six (69.1%) individuals had normal body weight, 32 (29.1%) were overweight, and only two (1.8%) were classified as class I obese. Early-onset CHD was present in 53 (48.2%) men in the control group. Thirty-eight (34.5%) were smokers, with an average smoking prevalence index (SRI) of 0.33. Stressful conditions were observed in 50 (45.5%) individuals. Alcohol consumption was noted in 34 (30.9%) individuals, and energy drink consumption was noted in 52 (47%) individuals (Table 3.3).

Table 3.3.

**General characteristics of the control group**

| Name of indicators | Control group (n=110) |
|---|---|
| BMI, kg/m2 | 23,6±3,07 |
| Normal body weight, kg/m2 | 76 (69,1%) |
| Overweight, kg/m2 | 32 (29,1%) |
| Grade I obesity | 2 (1,8%) |
| Family history | 53 (48,2%) |
| Smoking | 38 (34,5%) |
| Smoking index | 0,33 |
| Stress | 50 (45,5%) |
| Alcohol consumption | 34 (30,9%) |
| Energy drink consumption | 52 (47,3%) |

An assessment of clinical and anamnestic features, and the frequency of risk factor occurrence, was conducted in patients with coronary artery disease and a comparative control group. Following this, patients underwent random assignment

to groups based on their presenting complaints, clinical evolution, and results from laboratory and instrumental evaluations. VSV was observed in 30 patients (23.8%) in Group 1, while this type of unstable angina was not observed in Group 2. PHF was detected in 51 patients (40.5%) in Group 1 and 58 patients (55.8%) in Group 2 (p = 0.02). There were no significant differences in the development of ST-segment elevation ACS (ST-ACS) between the groups, observed in 26 (20.6%) young patients and 27 (25.9%) older patients (p = 0.35). ACS with ST depression (AST-ACS) was detected in 12 patients (9.5%) in group 1 and 9 patients (8.7%) in group 2 (p=0.82). AMI with Q wave in group 1 was observed in 5 patients (3.7%), which was statistically less than in the older age group, where it was detected in 10 patients (9.6%) (p=0.09), and AMI without Q wave was observed only in 2 patients (1.6%) in group 1 (Fig. 3.3).

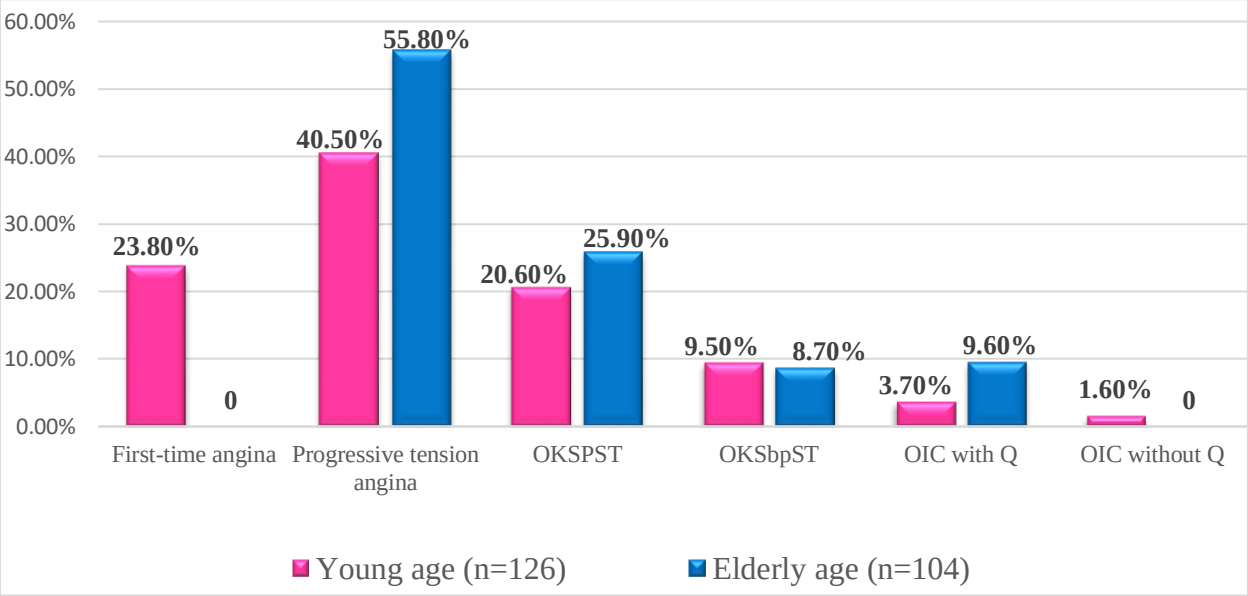



Fig. 3.3. Distribution of patients depending on the clinical course of coronary heart disease

Smoking, one of the main risk factors, was identified in 66 patients (52.4%) in group 1 and 49 (47.1%) in group 2 (p1>0.05), while in the control group, smoking was observed in 38 (34.5%) individuals (p2<0.001*). Hypertension in group 2 was 42.2% higher than in group 1, amounting to 92 (88.5%) and 58 (46.3%) patients, respectively (p1<0.001*), while in the control group, hypertension was observed in only 10 (9.1%) individuals (p2<0.001*). In group 1, diabetes was detected in 15

patients (11.9%), in group 2 - in 20 patients (19.2%) (p1<0.05*), and in the control group - in 6 patients (5.4%) (p2<0.05*). Overweight/obesity was noted in 54 patients (42.9%) in group 1, 92 patients (88.5%) in group 2 (p1<0.001*), and in the control group - in 25 patients (22.7%) (p2<0.0001*).

Among the patients engaged in labor activity, there were 80 men (63.5%) in group 1, 17 men (16.3%) in group 2 (p1<0.0001*), and 61 men (55.5%) in the control group (p2>0.05). 46 patients (36.5%) in the 1st group do not work, in the control group 49 (44.5%) persons (p2<0.01*), and in the 2nd group 87 (83.7%), (p1<0.0001*) patients do not work, this was due to the fact that most of them were people of retirement age. ON in the 1st group was noted in 66 (52.4%) patients, in the 2nd group in 35 (33.6%), (p1>0.05), in the control group in 53 (48.2%) persons (p2>0.05). Chronic stress in the 1st group was detected in 72 (57.1%), in the 2nd group in 44 (42.3%) patients (p1<0.01*), in the control group in 50 (45.5%) persons (p2<0.05*). Alcohol consumption was observed in 42 patients (33.3%) in Group 1, 35 (33.6%) in Group 2 (p1>0.05), and 34 (30.9%) in the control group (p2>0.05). Energy drink consumption was detected in 63 patients (50%) in Group 1, 10 (9.6%) in Group 2 (p1<0.0001*), and 52 (47.3%) in the control group (p2>0.05) (Table 3.4).

**Table 3.4**.

**Comparison of the prevalence of risk factors among patients with coronary heart disease and the control group**

| Risk factors | Group 1: young age (n=126) | Group 2: elderly age (n=104) | Control group (n=110) | Mann-Whitney-Wilcoxon test p-value. | |
|---|---|---|---|---|---|
| Smoking | 66 (52,4%) | 49 (47,1%) | 38 (34,5%) | p>0,05 | 1vs2: |
| | | | | p<0,001* | 1vs3: |
| Hypertension | 58 (46,3%) | 92 (88,5%) | 10 (9,1%) | p<0,001* | 1vs2: |
| | | | | p<0,001* | 1vs3: |
| Diabetes mellitus | 15 (11,9%) | 20 (19,2%) | 6 (5,4%) | p<0,05* | 1vs2: |
| | | | | p<0,05* | 1vs3: |
| Overweight/obesity | 54 (42,9%) | 92 (88,5%) | 25 (22,7%) | p<0,001* | 1vs2: |
| | | | | p<0,0001* | 1vs3: |
| Working | 80 (63,5%) | 17 (16,3%) | 61 (55,5%) | p<0,0001* | 1vs2: |

| | | | | | |
|---|---|---|---|---|---|
| | | | | p>0,05 | 1vs3: |
| Not working | 46 (36,5%) | 87 (83,7%) | 49 (44,5%) | p<0,0001* | 1vs2: |
| | | | | p<0,01* | 1vs3: |
| Burdened heredity | 66 (52,4%) | 55 (52,9%) | 53 (48,2%) | p>0,05 | 1vs2: |
| | | | | p>0,05 | 1vs3: |
| Stress | 72 (57,1%) | 44 (42,3%) | 50 (45,5%) | p<0,01* | 1vs2: |
| | | | | p<0,05* | 1vs3: |
| Alcohol consumption | 42 (33,3%) | 35 (33,6%) | 34 (30,9%) | p>0,05 | 1vs2: |
| | | | | p>0,05 | 1vs3: |
| Energy drink consumption | 63 (50%) | 10 (9,6%) | 52 (47%) | p<0,0001* | 1vs2: |
| | | | | p>0,05 | 1vs3: |

One of the important RF that contributes to the progression of coronary heart disease is stressful situations at work, at home or on the street. According to our study, severe stress was noted in 52 (41.3%) patients in group 1, and in 28 (26.9%) patients in group 2 (p1 < 0.001 *), in the control group, severe stress was found in 31 (28.2%) individuals (p2 < 0.01 *). Moderate stress was found in 34 (27%) patients in group 1, 16 (15.4%) patients in group 2 (p1 < 0.01 *), and in the control group, moderate stress was noted in 25 (22.7%) individuals (p2 < 0.05 *). The absence of stress in the 1st group was observed in 40 (31.7%) patients, in the 2nd group in 60 (57.7%) patients (p<0.001*), in the control group in 54 (49.1%) individuals (p2<0.01*), no stressful situations were noted (Fig. 3.4).

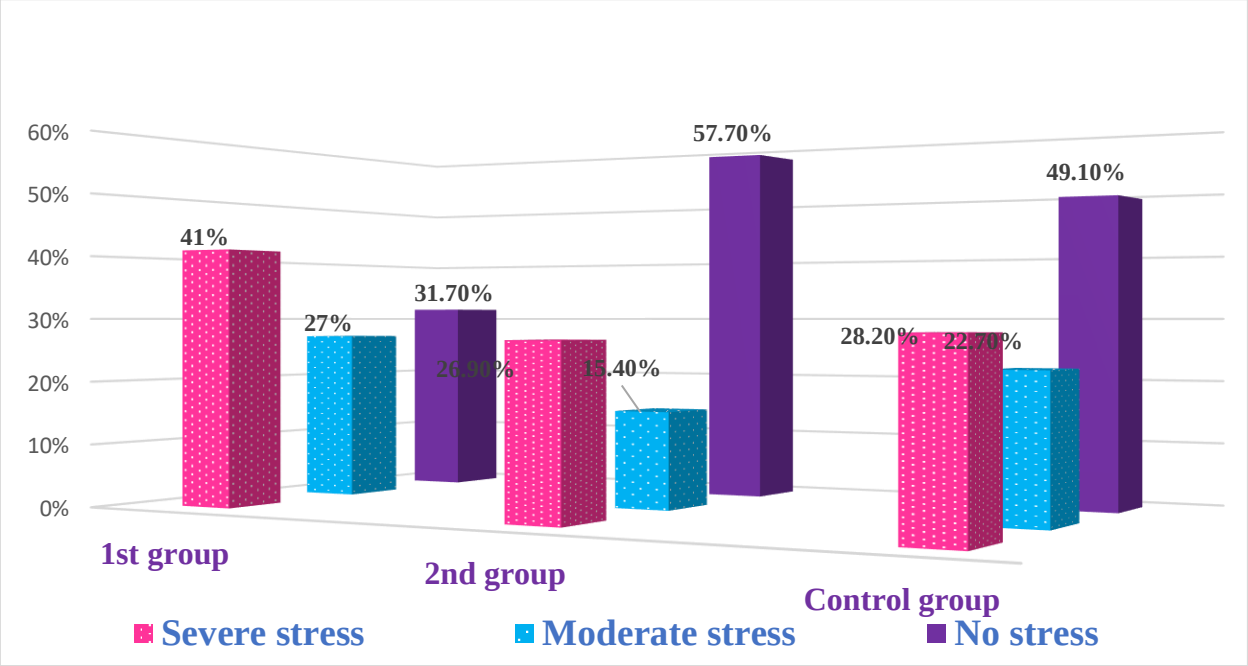



Fig. 3.4. Frequency of stress in patients with coronary heart disease

Paternal stress was observed in 23 patients (18.3%) in Group 1, 20 (19.2%) in Group 2 (p>0.05), and 24 (21.8%) in the control group (p>0.05). Maternal stress was detected in 29 patients (23%) in Group 1, 26 (25%) in Group 2 (p>0.05), and 14 (12.7%) in the control group (p<0.05*). Heredity from both parents was noted in 14 (11.1%) patients in the 1st group, in 11 (10.6%) patients in the 2nd group (p>0.05), and in 15 (13.6%) individuals in the control group (p>0.05) (Fig. 3.6).

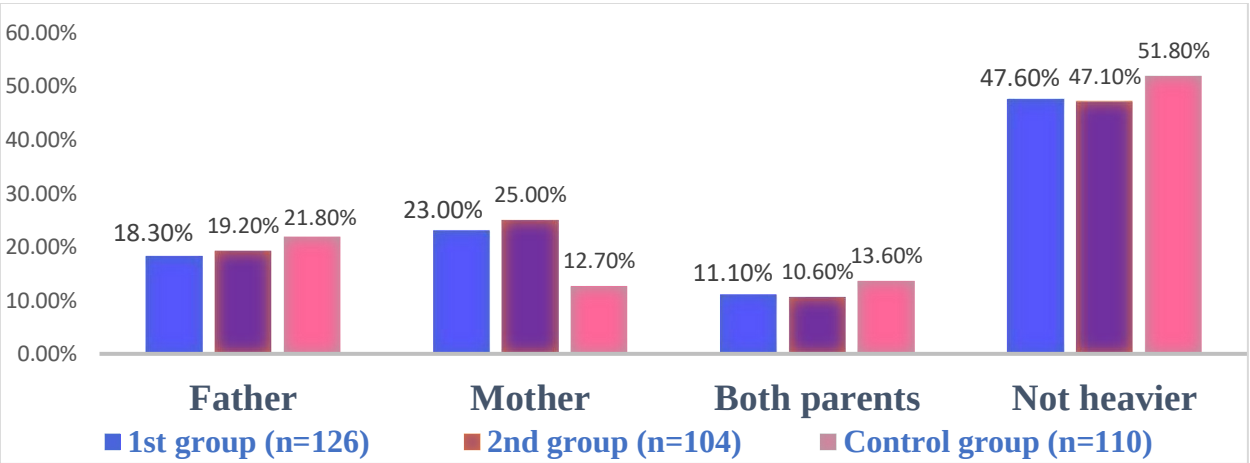



Figure 3.6. Difference in Family History between Patients with CHD and the Control Group

**Conclusion**

Ultimately, our investigation into the risk factors for CHD in these patient groups demonstrated a significant overlap between working-age and elderly patients. This shared profile of risk factors suggests that younger individuals may be predisposed to a more rapid and severe progression of CHD. The identified common and modifiable risk factors in young people – such as smoking, stress, weight issues, pulmonary hypertension, high blood pressure, poor nutrition, and substance use – are crucial areas for intervention.

The study results indicate that working-age patients with coronary heart disease (CHD) exhibit risk factor profiles remarkably similar to those of elderly populations. This similarity suggests that younger patients are predisposed to an earlier and potentially more aggressive progression of the disease if left unmanaged.

### *Key Modifiable Risk Factors*

A significant portion of the risk in younger demographics stems from factors that can be actively modified or managed. These include:

- **Prevalent Vices:** Widespread smoking, common alcohol consumption, and the growing phenomenon of energy drink usage.

- **Health Markers & Diet:** Elevated systemic and pulmonary blood pressure, poor nutritional habits, and a high prevalence of individuals carrying excess weight.

- **Mental Well-being:** Severe occupational and emotional stressors.

### *Strategic Clinical Implications*

The presence of various comorbidities further complicates the disease's course in younger patients, making early identification vital. Utilizing these risk factors as predictive markers allows modern cardiology to transition from reactive treatment to a **strategic, preventative management model**.

By aggressively addressing these factors through individualized treatment and lifestyle shifts, clinicians can significantly reduce the risk of adverse cardiovascular events. This proactive approach is essential not only for the patient’s long-term health but also for mitigating the socioeconomic impact caused by early disability and mortality in the active workforce.

**Is there anything else you would like me to do with this text? I can:**

- Synthesize all the paraphrased sections into a **single, final report**.
- Create a **PowerPoint outline** based on these findings.
- Draft a **set of clinical recommendations** for managing working-age men at high risk.

## Comparison of Clinical, Anamnestic, Laboratory, and Instrumental Parameters in Patients with IHD in Working-Age and the Elderly

### Clinical and Anamnestic Data

When interviewing all patients with IHD, attention was paid to the primary complaint of chest pain. The following data were revealed regarding the daily frequency of pain attacks. Angina attacks 3-5 times per day were observed in 17 patients (13.5%) in Group 1 and 7 patients (6.7%) in Group 2 ($p < 0.0001$). Angina attacks 6-8 times per day were observed in 85 patients (67.5%) in Group 1 and 82 patients (78.8%) in Group 2 ($p = 0.001$). Attacks more than 9 times a day were observed in 24 (19%) patients of the 1st group, in 15 (14.4%) patients of the 2nd group ($p>0.05$), (Fig. 3.8).

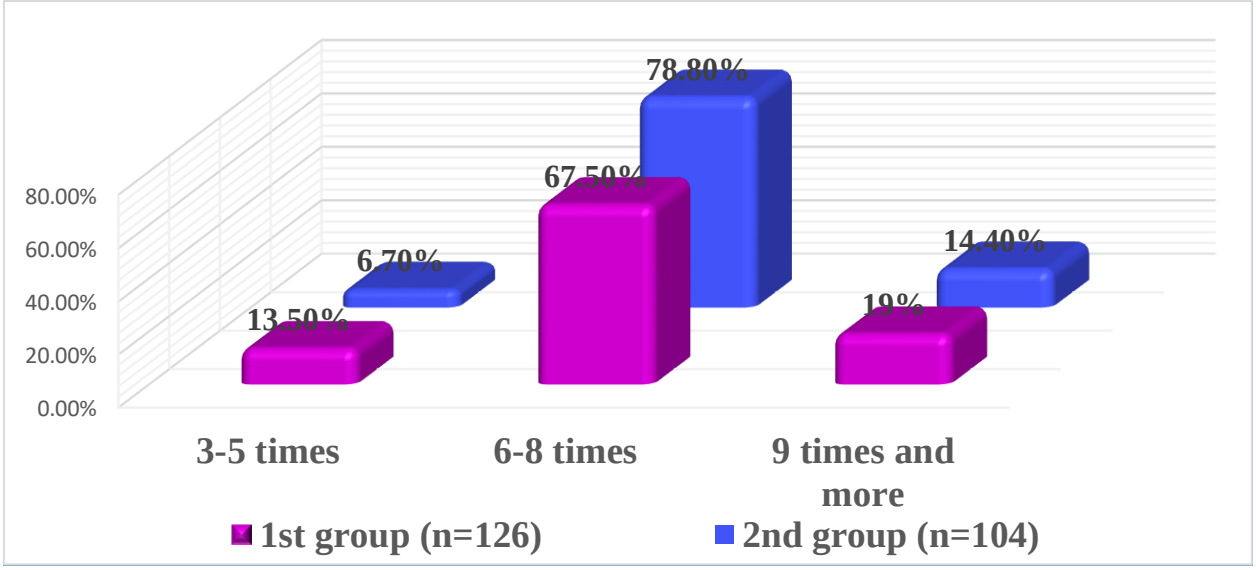



Fig. 3.8. Distribution of patients by frequency of angina attacks per day

When studying the intensity of angina pain using the 10-point Wong-Baker Grimace Scale, the following data were revealed. In patients with VSV, pain syndrome ranged from 1 to 3 points, and was observed in only 30 patients (23.8%) in Group 1. In patients with PSN, pain syndrome ranged from 4 to 6 points, and was

detected in 51 patients (40.5%) in Group 1 and 58 patients (55.8%) in Group 2 ($p < 0.05$). In patients with ACS, pain syndrome ranged from 7 to 9 points, and was observed in 38 patients (30.2%) in Group 1 and 36 patients (34.6%) in Group 2 ($p = 0.34$). Pain syndrome with an intensity of 10 points was observed in patients with AMI and this was noted in the 1st group in 7 (5.5%) patients, in the 2nd group in 10 (9.6%) patients (p=0.11), (Fig. 3.9).

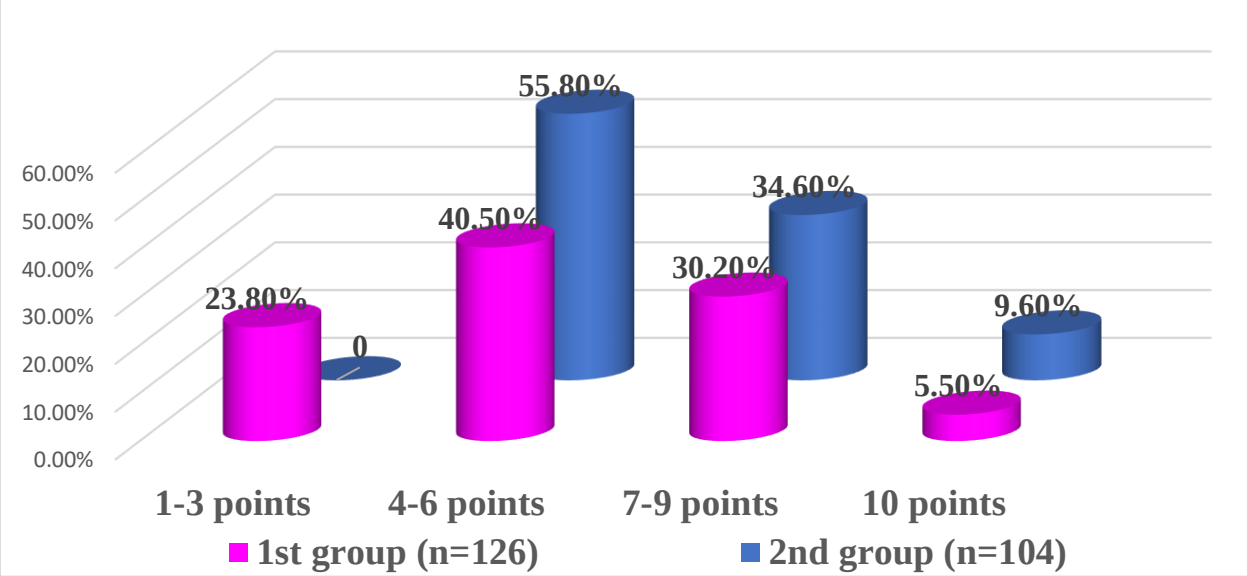



Figure 3.9. Distribution of patients by pain intensity on the 10-point Wong-Baker scale

**Laboratory data**

At the laboratory of comprehensive blood work was performed, including general clinical and biochemical assessments. The biochemical evaluation focused on liver function, with specific measurements of bilirubin (total and direct fractions), transaminases (ALT and AST), creatinine, urea, and residual nitrogen. The Malloy-Evelyn method was utilized on a biochemical analyzer to ascertain total and direct bilirubin levels in the serum. For liver transaminases, the Reitman-Frenkel method was applied using an automated biochemical analyzer. Serum creatinine was quantified through an enzymatic colorimetric approach on a biochemical analyzer.

Table 3.9 indicates that biochemical test results were statistically comparable between patients with coronary artery disease and the control group. Nevertheless, a significant finding pertains to elderly patients, who demonstrated a glomerular

filtration rate (GFR) 19.2 ml/min lower than their working-age counterparts, with values of 74.5 ± 10.2 ml/min and 93.77 ± 16.2 ml/min, respectively (p <0.0001*). The control group's GFR averaged 100.8 ± 18.3 ml/min, a figure not statistically different from other comparisons (p = 0.26).

**Table 3.9.**

**Biochemical data indicators in patients with coronary artery disease and the control group**

| Biochemical analysis indicators | Group 1 (n=126) | Group 2 (n=104) | Control group | Mann-Whitney-Wilcoxon test<br><br>p-value |
|---|---|---|---|---|
| Hb (g/l) | 95,5±12,7 | 91,14±15,37 | 112±14,2 | 1vs2: p=0,03*<br>1vs3: p<0,001* |
| ALT (mmol/l) | 0,77±0,41 | 0,71±0,27 | 0,38±0,15 | 1vs2: p=0,62<br>1vs3: p<0,01* |
| AST (mmol/l) | 0,57±0,34 | 0,54±0,26 | 0,21±0,14 | 1vs2: p=0,89<br>1vs3: p<0,01* |
| Total bilirubin (μmol/l) | 19,54±20,13 | 18,18±4,4 | 15,4±6,3 | 1vs2: p=0,10<br>1vs3: p=0,07 |
| Creatinine (mmol/l) | 104,13±25,60 | 116,6±49,28 | 108,2±29,5 | 1vs2: p=0,07<br>1vs3: p=0,11 |
| Urea (mmol/l) | 7,5±2,7 | 7,9±2,8 | 5,8±2,1 | 1vs2: p=0,78<br>1vs3: p=0,21 |
| Residual nitrogen (mmol/l) | 21,37±6,34 | 22,12±6,7 | 21,2+-5,4 | 1vs2: p=0,14<br>1vs3: p=0,17 |
| GFR (ml/min) | 93,77±16,2 | 74,5±10,2 | 100,8±18,3 | 1vs2: p<0,0001*<br>1vs3: p=0,26 |
| Glucose (mmol/l) | 5,12±1,82 | 5,84±2,60 | 5,04±2,0 | 1vs2: p<0,001*<br>1vs3: p=0,31 |
| PTI (%) | 98,9±7,41 | 96,4±8,04 | 92,9±9,2 | 1vs2: p=0,79<br>1vs3: p=0,36 |
| PTV (seconds) | 16,17±1,59 | 17,37±9,79 | 15,2±2,1 | 1vs2: p=0,28<br>1vs3: p=0,56 |

**Electrocardiographic data.**

Upon admission, all participants underwent an ECG examination using a Fukuda device to identify markers of myocardial ischemia or injury. For patients presenting with **unstable angina**, clinicians looked for pathological shifts such as

ST-segment elevation or depression, T-wave alterations, pathological Q waves, R-wave regression in leads V1–V4, cardiac rhythm disturbances, or the emergence of a new complete left bundle branch block.

### *1. ECG Criteria for Myocardial Ischemia*

**Diagnosing Myocardial Ischemia via ECG:**

To identify myocardial ischemia on an electrocardiogram (ECG), specific patterns were looked for. These included:

- **ST Segment Elevation:** A rise in the ST segment, measured at the J-point, of at least 0.2 millivolts (mV) in men within leads V1, V2, or V3, or greater than 0.1 mV in other leads, provided this elevation occurred in at least two adjacent leads.
- **ST Segment Depression:** A drop in the ST segment exceeding 1 millimeter (mm) in two or more neighboring leads.
- **T-Wave Abnormalities:** Inversion of the T wave by more than 1 mm in leads with a dominant R wave, as well as flattening, pseudo-normalization, or the appearance of tall, peaked T waves.

**ECG Indicators of a Confirmed Myocardial Infarction (AMI):**

For a definitive diagnosis of AMI, the following ECG findings were considered:

- The presence of any QR waves in leads V1 through V3 that lasted longer than 30 milliseconds (0.03 seconds).
- Abnormal Q waves measuring at least 1 mm deep in any two adjacent leads from the set including I, II, aVL, aVF, or V4 through V6.
- A reduction in R-wave amplitude in leads V1 through V4.

**24-Hour ECG Monitoring:**

To confirm diagnoses, assess heart rhythm irregularities, and detect silent ischemic events, 24-hour ECG monitoring was conducted using a Valenta Holter system. During this monitoring period, myocardial ischemia was identified by ST segment depression exceeding 2 mm that persisted for at least one minute.

Regarding the location of ischemic events as seen on the ECGs:

- **Anterior Wall:** Ischemic changes were detected in the anterior wall in 17 patients (13.5%) of the first cohort and 14 patients (13.5%) of the second cohort. The observed rates were comparable, with no statistically significant disparity between the groups (p = 0.99).
- **Posterior Wall:** The posterior wall of the left ventricle exhibited signs of ischemia in 28 patients (22%) from Group 1 and 19 patients (18.3%) from Group 2. This distribution also showed no statistically significant difference between the study groups (p = 0.45).
- **Anteroseptal Wall Ischemia:** This type of ischemia was found to be twice as frequent in Group 2, affecting 8 patients (7.7%) compared to 4 patients (3.2%) in Group 1, though this difference did not reach statistical significance (p = 0.14).
- **Lateral Wall Ischemia:** This was detected in a small number of patients: 3 (2.4%) in Group 1 and 2 (1.9%) in Group 2, with no significant difference (p = 0.81).

**Multi-Wall Ischemia:** Ischemia involving two or more walls of the heart was observed in a substantial proportion of patients: 52 (41.3%) in Group 1 and 42 (40.4%) in Group 2, with no significant difference between the groups (p = 0.79) (as depicted in Figure 3.

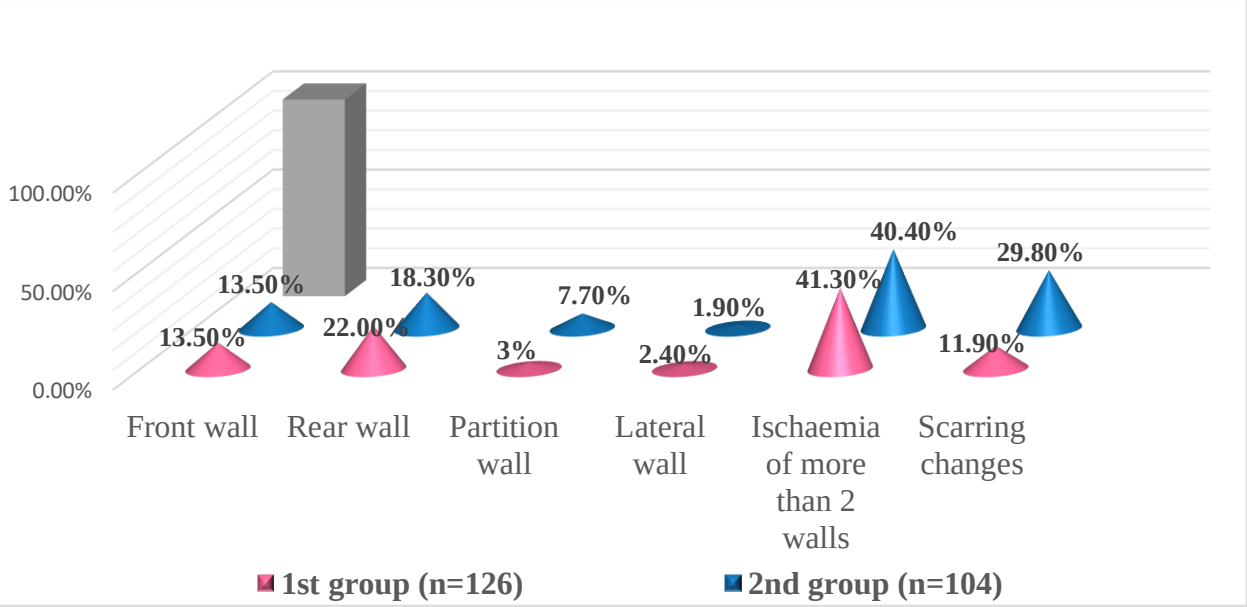


Fig. 3.10. Distribution of patients with coronary artery disease in working age and the elderly depending on ischemic damage to the left ventricular myocardium

T-wave inversion was observed in 81 (64.3%) patients in Group 1 and 58 (55.8%) in Group 2 ($p < 0.05$*). ST-segment elevation was observed in 26 (20.6%) patients in Group 1 and 27 (25.9%) in Group 2 ($p = 0.35$). ST-segment depression was observed in 12 (9.5%) patients in Group 1 and 9 (8.7%) in Group 2 ($p = 0.82$). The incidence of Q-wave MI was twice as high in patients in Group 2, occurring in 10 (9.6%) and 5 (3.7%) patients in Group 1, respectively ($p=0.09$). Non-Q-wave MI was detected only in Group 1 patients, occurring in 2 cases (1.6%).

Cicatricial changes were noted in 15 (11.9%) patients in Group 1 and in 31 (29.8%) patients in Group 2, $p<0.001$*. WPW syndrome was detected only in Group 1, in 3 (2.38%) patients (p=NA). Atrial fibrillation was observed in 3 (2.38%) young patients and in 5 (4.8%) elderly patients ($p>0.05$). Ventricular extrasystoles were observed in 3 patients (2.38%) in Group 1 and 1 patient (0.96%) in Group 2 ($p>0.05$). The incidence of heart blocks was similar in both groups, amounting to 6 (4.76%) and 6 (5.78%), respectively ($p>0.05$) (Table 3.10).

**Table 3.10.**

**ECG data in patients with coronary artery disease and the control group**

| Indicators | Group 1 (n=126) | Group 2 (n=104) | Mann-Whitney-Wilcoxon test p-value |
|---|---|---|---|
| T wave inversion | 81 (64,3%) | 58 (55,8%) | 1vs2:p=0,01* |
| ST segment elevation | 26 (20,6%) | 27 (25,9%) | 1vs2: p>0,05 |
| ST segment depression | 12 (9,5%) | 9 (8,7%) | 1vs2: p>0,05 |
| Myocardial infarction with Q wave | 5 (3,7%) | 10 (9,6%) | 1vs2: p=0,09 |
| Myocardial infarction without Q wave | 2 (1,6%) | - | 1vs2: NA |
| Cicatricial changes | 15 (11,9%) | 31 (29,8%) | 1vs2: 0,01* |
| WPW syndrome | 3 (2,38%) | - | 1vs2: NA |
| Atrial fibrillation | 3 (2,38%) | 5 (4,8%) | 1vs2: p>0,05 |
| Ventricular extrasystole | 3 (2,38%) | 1 (0,96%) | 1vs2: p>0,05 |
| Blockades | 6 (4,76%) | 6 (5,78%) | 1vs2: p>0,05 |

**Echocardiographic data.**

Within 1-2 days of hospitalization, patients underwent echocardiography using a Mindray system in M- and B-mode. In M-mode, measurements were taken through a parasternal approach along the LV axis in accordance with the Penn Convention Method. The following intracardiac hemodynamic parameters were calculated: LV end-systolic and diastolic diameter (ESD, EDD), LV end-systolic and diastolic volume (ESV, EDV), LV myocardial mass index (LVMI), interventricular septal thickness (IVST), LV posterior wall thickness (LVPPT) during diastole, LV ejection fraction (LVEF), presence of concentric myocardial hypertrophy, and pulmonary hypertension. Assessment of LV systolic function: LV EDS and LV EDD were determined using the standard method, followed by calculation of the degree of shortening of the anteroposterior diameter of the LV during systole.

LV ESV and LV EDV were calculated using the area-length method. The calculation was performed for at least three complexes, followed by calculation of LVEF.

LVEF and ESV were calculated using the formula of Teichholtz L. E. et al.:

$V = D \wedge 3 \times 7 / (2.4 + D)$,

where V is the volume (EDV or ESV) of the LV, D is the LV dimension (end-diastolic or end-systolic).

LVEF was estimated using the formula:

$EF = (EDV - ESV) / LVEF \times 100\%$,

where EF is the ejection fraction, %; EDV is the end-diastolic volume of the LV, ml; ESV is the end-systolic volume of the LV, ml. LV systolic dysfunction was diagnosed with LVEF <60%.

LV myocardial mass (LVMM) was calculated using the formula of R. Devereux and N. Reichek (1986):

LVMM = 1.04 x [(LV EDM + LVST + LVTP)3 - LV EDM3] - 13.6 (in grams),

where LVM is LV myocardial mass, g; LV EDM is LV end-diastolic diameter, cm; LVST is interventricular septal thickness, cm; LVPWT is the LV posterior wall thickness (cm).

Left ventricular myocardial mass index (LVMI) was calculated using the formula:

LVMI = LVM / body surface area,

where LVM is expressed in g/m², LVM is expressed in grams, and body surface area is expressed in m². An LVM greater than 125 g/m² for men and 110 g/m² for women was considered LV hypertrophy.

Body surface area was calculated taking into account height and weight using the formula:

Body surface area = 0.007184 x (height) x 0.725 x (body weight) x 0.425,

where height is expressed in centimeters, body weight is expressed in kilograms, and body surface area is expressed in m². The dimensions of the aortic root (Ao) (in mm) and the cardiac chambers – the left atrium (LA) (in mm) – were measured. The presence of areas of dyskinesia and akinesia, myocardial hypertrophy, compaction of the interventricular septum, papillary muscle dysfunction, and thrombi in the LV cavity were also recorded [203].

Echocardiography revealed the following changes in the study groups. LVEF in Group 1 averaged 54.6% ± 7.2, while in Group 2 it was reduced to 51% ± 9.3 ($p < 0.01$*). In the control group, LVEF averaged 56% ± 8.5 ($p = 0.48$). The end-ventricular volume (EVL) in group 1 averaged 138.7±37.6 ml, while in group 2 it was 150±48.03 ml ($p=0.09$), while in the control group it was 115±19.3 ml ($p<0.05$*). The ESV was 77.47±24.4 ml in group 1 and 85.1±35.6 ml in group 2 ($p=0.11$), while in the control group it was 53±12.2 ml ($p<0.001$*).

The LVEFT in both groups was almost the same, amounting to 1.22±0.27 mm in group 1 and 1.23±0.34 mm in group 2 ($p=0.59$), while in the control group the LVEFT averaged 0.8±0.17 mm ($p<0.001$*). The IVS was also almost identical in both groups, amounting to 1.18±0.27 mm in Group 1 and 1.22±0.18 mm in Group 2 ($p=0.03$). In the control group, the IVS averaged 0.8±0.13 mm ($p<0.001$*).

One hypokinesis zone was detected in 54 (40.5%) patients in Group 1 and 44 (42.3%) patients in Group 2 ($p=0.78$). Hypokinesis of more than two zones was

observed in 55 (44.4%) patients in Group 1 and 44 (42.3%) patients in Group 2 (p=0.83). Akinesia was detected in 32 patients (25.4%) in Group 1 and 42 patients (40.4%) in Group 2 (p=0.01*). No hypo- or akinetic zones were detected in the control group according to echocardiography (Table 3.11).

**Table 3.11.**

**Echocardiography parameters in patients with coronary heart disease of working age and the elderly and in the control group**

| Echocardiography parameters | Group 1 (n=126) | Group 2 (n=104) | Control group | Mann-Whitney-Wilcoxon test p-value |
|---|---|---|---|---|
| EF (%) | 55,0±7,0 | 51±9,3 | 56±8,5 | 1vs2: p<0,01*<br>1vs3: p=0,48 |
| LVDD (ml) | 138,7±37,6 | 150,5±48,3 | 115±19,3 | 1vs2: p=0,09<br>1vs3: p<0,05* |
| LVDD (ml) | 77,47±24,4 | 85,1±35,6 | 53±12,2 | 1vs2: p=0,11<br>1vs3: p<0,001* |
| LVEDD (cm) | 1,22±0,33 | 1,23±0,34 | 0,8±0,17 | 1vs2: p=0,59<br>1vs3: p<0,001* |
| LVEDD (cm) | 1,18±0,27 | 1,22±0,18 | 0,8±0,13 | 1vs2: p=0,03*<br>1vs3: p<0,001* |
| 1 area of hypokinesis | 51(40,5%) | 44(42,3%) | 0 (%) | 1vs2: p=0,78<br>1vs3: NA |
| 2 or more areas of hypokinesis | 56(44,4%) | 44(42,3%) | 0 (0%) | 1vs2: p=0,83<br>1vs3: p= NA |
| Area of akinesis | 32 (25,4%) | 42 (40,4%) | 0 (0%) | 1vs2: p=0,01*<br>1vs3: p= NA |
| *- statistically significant result | | | | |

## Cardiac-Specific Markers of Myocardial Necrosis in Patients with Acute Coronary Syndrome and Acute Myocardial Infarction

Using the qualitative rapid test Trop T (Troponin T) from Roche, cardiac troponin T was determined; an increase in its level above 0.1 ng/mL with the appearance of two white lines was considered positive. The Triage® MeterPro

enzyme immunoassay analyzer (BIOSITE, USA) was used to determine cardiac troponin I and the metabolic protein creatine phosphokinase (CPK-MB).

The following indicators were identified in blood tests for cardiac-specific biomarkers in patients with ACS and AMI. Creatinine phosphokinase (CPK) in patients in group 1 averaged 195±67.4 U/L, while in group 2 it was 202±48.0 U/L ($p>0.05$), CPK-MB in group 1 was 26.1±7.66 U/L, while in group 2 it was 26.6±4.79 U/L ($p>0.05$). Troponin I in group 1 averaged 0.135±0.095 ng/ml, while in group 2 it was 0.316±0.289 ng/ml ($p<0.05$). Troponin T levels averaged 0.012±0.098 ng/ml in Group 1 and 0.028±0.028 ng/ml in Group 2 ($p>0.05$) (Table 3.12).

**Table 3.12**

**Values of cardiac-specific markers of myocardial necrosis in patients with ACS and AMI in the study groups**

| Cardio-specific markers of myocardial necrosis | Group 1 (n=126) | Group 2 (n=104) | Mann-Whitney-Wilcoxon test p-value |
|---|---|---|---|
| CK (26-192 U/L) | 195±67,4 | 202 ±48,0 | p>0,05 |
| MB-CK (up to 24 U/L) | 26,1±7,66 | 26,6±4,79 | p>0,05 |
| Troponin I (0.16 ng/ml) | 0,135±0,095 | 0,316±0,289 | p<0,05 |
| Troponin T (0.010 ng/ml) | 0,012±0,098 | 0,028±0,028 | p>0,05 |

## Chapter Conclusion

The study findings reveal that both the working-age population (Group 1) and the elderly population (Group 2) face a significant disease burden, though their clinical profiles differ. A critical observation was the high frequency of angina attacks—occurring 6 to 8 times daily—which affected 67.5% of Group 1 and 78.8% of Group 2, underscoring the severe nature of their conditions. This investigation's findings reveal a concerning trend: patients with VSV and PSN demonstrated poorer outcomes than those with AMI across both working-age and elderly cohorts. The frequent occurrence of angina attacks, reported by a large majority in both Group 1 (67.5%) and Group 2 (78.8%) at 6-8 episodes per day, underscores the significant impact of these conditions. Left ventricular ejection fraction (LVEF) was 54.6% in

Group 1 and declined to 51% in Group 2. While hypokinesia involving more than two regions was slightly more prevalent in Group 1 (44.4%) compared to the elderly (42.3%), akinetic zones were notably more common in the elderly population (40.4%) than in Group 1 (25.4%).

**Left Ventricular Ejection Fraction (LVEF):** Group 1 maintained a higher average LVEF at 54.6%. In Group 2, this figure dropped by 3.6%, averaging 51%, reflecting the cumulative damage often seen in older hearts.

- **Wall Motion Abnormalities:** * **Hypokinesia:** Interestingly, hypokinesia involving more than two zones was slightly more prevalent in working-age patients (44.4%) than in the elderly (42.3%).
- **Akinesia:** Akinetic zones (areas with no movement) were less common in the young (25.4%) compared to the elderly (40.4%), where these non-functional areas were 15% more frequent.

# CHAPTER 5.

## Features of polymorphism of certain cytokine genes in patients with ischemic heart disease depending on cytokine status and DLP among Uzbeks

Over the past ten years, numerous investigations have highlighted a notable trend in many developed nations: the strategic implementation of initiatives focused on the prompt identification of detrimental risk factors (RFs) for coronary heart disease (CHD) and their subsequent timely mitigation has yielded a measurable decrease in both the occurrence and fatality rates associated with this condition [43]. Nevertheless, evaluating an individual's CHD risk extends beyond merely addressing modifiable RFs. Recent discoveries have brought to light novel genetic factors that significantly influence CHD's onset and progression. These genetic elements are instrumental in shaping cardiac and vascular structures, regulating immune-inflammatory responses, influencing lipid metabolism, endothelial dysfunction (ED), and numerous other biological pathways contributing to atherosclerosis, particularly in the working-age population [6, 44, 50, 139]. This imperative has spurred extensive genome-wide association studies (GWAS) for CHD globally. Yet, given the complex, multifactorial etiology of CHD, distinct ethnic populations exhibit unique genetic markers that correlate with an elevated risk of severe complications [64, 88].

Investigating molecular genetic indicators linked to the premature manifestation of coronary heart disease (CHD) in working-age males holds the potential for earlier detection and proactive measures against this condition in individuals with a genetic susceptibility. Such insights could, at minimum, postpone the disease's initial appearance or mitigate its severity, even if complete prevention isn't achievable. Consequently, pinpointing specific genes implicated in the genesis and progression of CHD among working-age men presents significant scientific and clinical value [44, 47, 89].

To uncover the precise genetic pathways driving atherosclerotic changes in coronary arteries and acute coronary events in CHD patients, researchers have examined the concentrations of pro- and anti-inflammatory interleukins alongside observable traits indicating a predisposition to CHD onset [98, 117]. Currently, over a hundred genetic variations have been identified within cytokine genes and their receptor counterparts. Further exploration of these polymorphic cytokine network structures, coupled with deciphering their regulatory mechanisms governing immune cell production and genetic control of immune responses, promises to facilitate disease prevention even in its nascent stages [98, 117].

## Molecular Genetic Testing Method: DNA Extraction

Venous blood samples (3-5 ml) were drawn from subjects via the cubital vein, utilizing Beckton-Dickinson vacutainer systems. These samples were then prepared for subsequent DNA isolation by immediate preservation with a 15% solution of tripotassium EDTA (Ethilendianine tetraacetic acid), which functions as both an anticoagulant and a preservative. For short-term storage prior to further processing, the blood could be maintained for up to 24 hours, provided the temperature did not exceed +4°C.

Genomic DNA was subsequently isolated through a two-stage cellular lysis procedure. The initial step involved the selective lysis of red blood cells. This was achieved by subjecting the entire whole blood volume to two rounds of centrifugation in Red Cell Lysis Buffer (RCLB) for 15-20 minutes at 1500 rpm. RCLB induces an osmotic shock, causing the red blood cells to swell and subsequently rupture. Following this, the supernatant, containing the remnants of the lysed red blood cells, was carefully decanted, and any residual supernatant was aspirated.

The remaining leukocyte pellet was then subjected to lysis using White Cell Lysis Buffer (WCLB), with the volume of WCLB adjusted according to the quantity of the leukocyte mixture. WCLB additionally functions as a long-term preservative for the resulting leukocyte lysates, even at ambient temperatures, allowing for indefinite

storage under these conditions. The specific formulations for both lysis buffers are detailed below:

RCLB WCLB

1 mM NH4HCO3

100 mM Tris-Cl (pH 7.6)

115 mM NH4Cl

40 mM EDTA (pH 8.0)

Autoclave

50 mM NaCl

0.05% Sodium acid

After autoclaving

0.2% SDS

**Enhanced Purification of Leukocyte Lysates and DNA Isolation**

Following the initial preparation, leukocyte mass lysates undergo further refinement using an alcohol-saline precipitation technique. This method, originally described by S. Miller and colleagues in 1988, has been adapted by the Stanford University laboratory. The process involves adding 150 µl of 5 M sodium chloride solution to 400 µl of the leukocyte lysate. This mixture is agitated on a shaker and then chilled on ice for a period of 10 to 20 minutes. Subsequently, it is subjected to centrifugation at 1200°C for 15 minutes.

The resulting supernatant is carefully transferred to a fresh Eppendorf tube. To this, 100% ice-cold ethanol is introduced. Gentle agitation of this mixture will precipitate the DNA, appearing as a quaternary chain. The solution is then centrifuged again at 1200 rpm for 15 minutes. The supernatant is discarded, and the pellet, a whitish residue at the bottom of the tube, is washed with 80% ethanol. This washing step is performed at 1200 rpm for 10 minutes. After decanting the supernatant, any residual alcohol is meticulously removed. The tube is left open to allow complete evaporation of the alcohol, which can take approximately 12 hours at room temperature or 2 hours in a thermostat set at 40-45°C.

Once the DNA is fully dried, a TE (Tris-EDTA) buffer, diluted with distilled water at a 1:3 ratio (TE to water) and adjusted to a pH of 8.0, is added to the tube. The purified DNA should be stored at -20 degrees Celsius.

## Methods for Detecting Allelic Variations in Polymorphic Cytokine Gene Loci

The identification of allelic variations within polymorphic cytokine gene loci is achieved through Polymerase Chain Reaction (PCR). This amplification process is carried out on a CorbettResearch Rotor-Gene-2000 thermal cycler. The reaction utilizes specific primers and a 10 µl PCR master mix (from NPO Litekh). This master mix contains 2 mM MgCl2, Cresol Red dye, and Taq DNA polymerase.

The amplified DNA fragments are then analyzed by electrophoresis on a 2% agarose gel containing ethidium bromide. This separation is performed at 150 V and 290 mA. The polymorphisms of interest are detected by amplifying specific segments of the target cytokine genes.

In many developed nations, the last decade has seen a measurable decline in coronary heart disease (CHD) incidence and mortality. This success is largely attributed to public health programs focused on the early detection and management of modifiable risk factors (RFs), such as smoking cessation, blood pressure control, and dietary improvements.

### The Shift Toward Genetic Risk Assessment

While correcting modifiable RFs remains a cornerstone of cardiology, researchers now recognize that these traditional assessments are incomplete. A new frontier has emerged focusing on **genetic risk factors**, which play a fundamental role in how the disease develops and progresses.

These genetic determinants are responsible for:

- **Vascular and Cardiac Remodeling:** Determining the structural changes in the heart and blood vessel walls in response to stress or injury.
- **Immune-Inflammatory Activity:** Controlling the intensity and duration of the body's inflammatory response within the arterial walls.

- **Lipid Metabolism:** Influencing how the body processes, transports, and clears cholesterol and triglycerides from the bloodstream.

### Why Individualized Risk Matters

Because these genetic factors vary significantly between individuals, two people with the same modifiable risk factors (e.g., both smokers with similar BP) may face vastly different outcomes based on their DNA. Genetic mapping allows clinicians to identify patients who may be "genetically primed" for aggressive plaque formation or early-onset AMI, even if their external lifestyle factors appear moderate.

In the search for a specific mechanism for the implementation of a genetic predisposition to the development of atherosclerotic changes in coronary arteries and the occurrence of acute coronary events in patients with coronary heart disease, an analysis of the levels of pro- and anti-inflammatory interleukins in association with phenotypic markers of predisposition to the initiation of coronary heart disease was conducted.

### Molecular Genetic Research Methodology

Below is the paraphrased technical description of the DNA extraction and analysis processes, suitable for a scientific report or monograph.

#### *1. Genomic DNA Extraction Method*

The isolation of genetic material was performed using venous blood (3–5 ml) collected in Beckton-Dickinson vacutainers, utilizing 15% tripotassium EDTA as an anticoagulant/preservative.

Cell Lysis Stages:

A two-step lysis protocol was employed to obtain high-quality genomic DNA:

- **Erythrocyte (Red Cell) Lysis:** Whole blood was processed using Red Cell Lysis Buffer (RCLB). This buffer induces osmotic shock, causing the red blood cells to swell and rupture. This was achieved through double centrifugation at 1500 rpm for 15–20 minutes.
- **Leukocyte (White Cell) Lysis:** After removing the supernatant, the remaining leukocyte mixture was treated with White Cell Lysis Buffer (WCLB).

This buffer serves a dual purpose: it breaks down the white cell membranes and acts as a stable preservative, allowing the lysates to be stored indefinitely at room temperature.

**Purification and Precipitation:**

Further purification followed the salt-alcohol precipitation method (modified from Miller et al., 1988):

1. **Protein Precipitation:** 5 M NaCl was added to the leukocyte lysate to precipitate proteins. The mixture was shaken and kept on ice before being centrifuged.
2. **DNA Precipitation:** The clear supernatant was mixed with 100% ice-cold ethanol, causing the DNA chains to become visible.
3. **Washing and Dissolution:** The DNA pellet was centrifuged, washed with 80% ethanol to remove residual salts, and dried. The purified DNA was finally dissolved in a Tris-EDTA (TE) solution (pH 8.0) and stored at -20°C.

*2. Identification of Cytokine Gene Polymorphisms*

To detect specific allelic variations in the IL-1β and IL-10 genes, the Polymerase Chain Reaction (PCR) method was utilized.

- **Amplification Process:** The reaction was executed on a CorbettResearch Rotor-Gene-2000 thermal cycler. The PCR mixture contained specific primers, Taq DNA polymerase, magnesium chloride ( MgCl_2 ), and Cresol Red dye.
- **Visualization and Detection:** The amplification products were analyzed using horizontal electrophoresis in a 2% agarose gel stained with ethidium bromide. The process was conducted at 150 V and 290 mA. The resulting DNA bands were visualized under UV light, allowing for the precise identification of genotypes based on the specific amplified regions of the target genes.

**Table 5.1**

**Primers and probes used to determine cytokine gene expression levels with their characteristics**

| Gen | Polymorphic locus | Cytogenetic localisation | Rs | Localisation | Structure of primers |
|---|---|---|---|---|---|
| *IL-1β* | C3953T | 2q13-2q21 | rs1143634 | Intron | 5′-TCC CTA CTG GTG TTG TCA TCAG-3′ и 5′-CTT GGG TGG ACA TGG TCC TG-3′ |
| *IL-10* | G1082A | 1q31-1q32 | rs1800896 | Intron | 5-CCT ATC CCT ACT TCC CCT-3' |

The IL-1β -3953 C/T and IL-10 -1082 G/A gene polymorphisms were determined by PCR. Amplification of 32 cycles was performed after a hot start and the first denaturation (94°C, 2 min), each of which included: denaturation (94°C, 30 sec), primer annealing (55°C, 1 min), and elongation (74°C, 1 min). PCR was performed using a 25 μl mixture containing 10 pmol of primer, 200 μM dNTPs, 1 μl (about 50 ng) of genomic DNA, and a PCR mixture from Interlabservice. At 370C, 8.5 μl of PCR product 306 bp in length. The samples were incubated with 0.5 mel (3 U) of Ava-I restriction enzyme, and 1 μl of 10x buffer was used for restriction. Restriction products were visualized by electrophoresis in a 2% agarose gel containing 1 μg/ml ethidium bromide. To identify polymorphisms in the human genome by PCR, the "SNP-express" diagnostic kit manufactured by NPF Litekh was used. Polymorphisms in proinflammatory cytokine genes were tested using the The kit was designed for 120 studies, which included a control group. The isolated DNA sample was analyzed in parallel, including amplification reactions with two pairs of allele-specific primers. The analysis results indicated three types of conclusions: Type 1 - normal homozygote; Type 2 - heterozygote; Type 3 - mutant homozygote. The "SNP-express" reagent included "normal" and "mutation" reaction mixtures, diluent, Taq polymerase, and mineral oil. Manufactured by NPF Litekh. The study was conducted in three stages: DNA extraction from leukocytes, amplification, and detection of amplification products.

Finally, the amplification products were sorted using electrophoresis. The method involved adding TAE buffer to the electrophoresis apparatus with distilled

water (pH 8.3). Agarose was used, with a reserve for evaporation. The prepared mixture is then melted in a microwave oven and 5 µl of 1% ethidium bromide is added. The melted agarose is poured into the plate. Using a bulldog clamp, the agarose gel is positioned on the comb plate, after which the solidified gel is removed. The electrophoretic chamber is connected to a power source with a voltage of 10-15 V/cm. The amplification product is separated for 15 minutes in the directions from the cathode (-) to the anode (+). The movement of the dye bands is monitored, monitoring the electrophoretic separation. The gel is transferred to the glass of a UV transilluminator, and the parameters are analyzed visually using a protective screen and software. When luminous orange-red bands appear under UV radiation with a wavelength of 310 nm, a DNA fragment is identified, where three variants can be identified: a normal homozygote, a heterozygote, and a mutant homozygote.

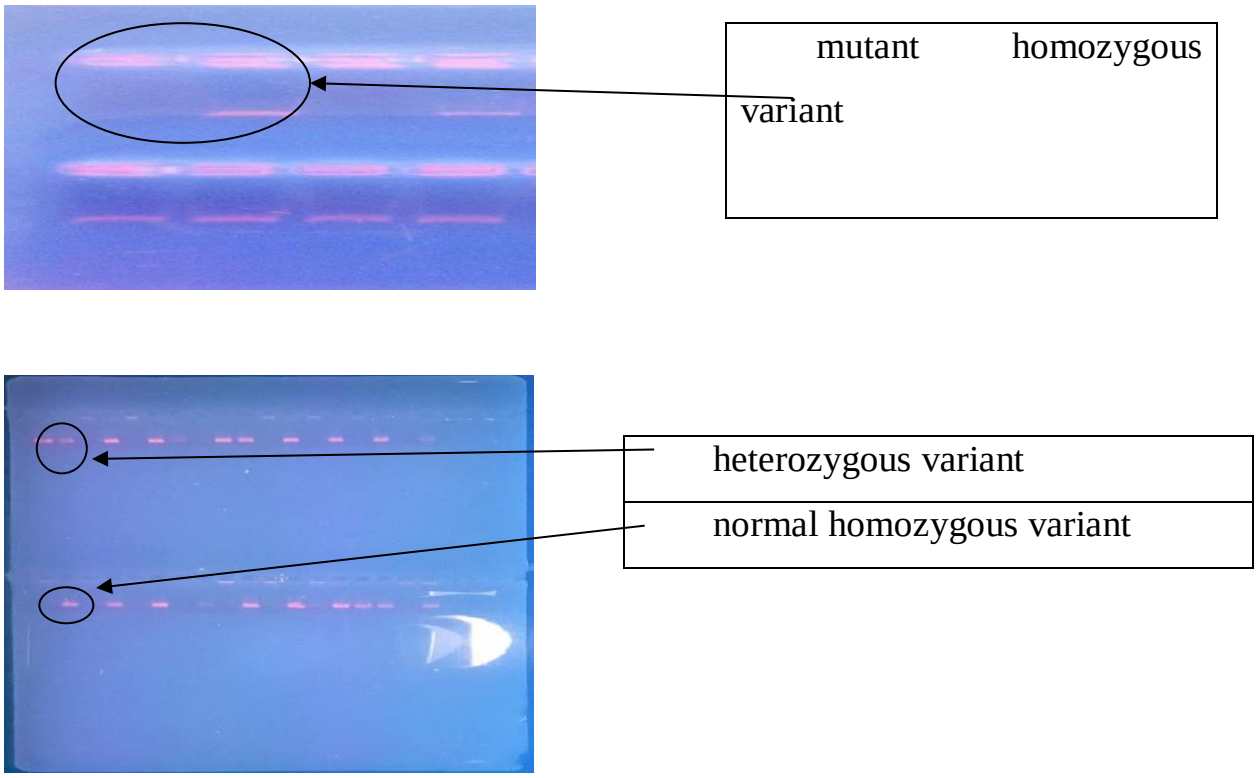



Fig. 5.1. Electropherogram of the -3953 C/T IL-1β gene under ultraviolet light (310 nm) after electrophoresis

The use of restriction fragment length polymorphism (RFLP) is shown in Figs. 5.2 and 5.3. Hydrolysis of the amplified fragment of the IL-1β gene with the restriction endonuclease Taq I reveals three fragments of 550 bp, 146 bp, and 404

bp. The presence of the 550 bp fragment that has not undergone hydrolysis indicates the presence of the T allele of the IL-1β gene +3953. In the presence of the C allele of the IL-1β gene +3953, the amplicon is cut into two fragments of 146 bp and 404 bp.

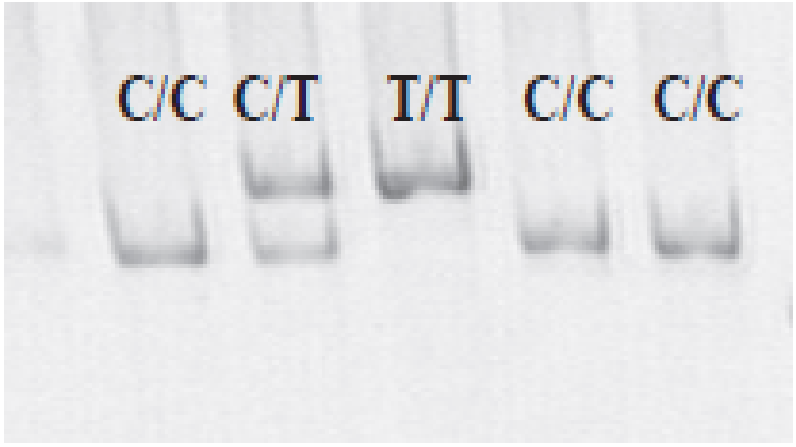



Fig. 5.2. Genotypes of the +3953C/T IL-1β SNP

The use of allele-specific PCR to determine genetic polymorphisms is shown in the diagram for determining the SNP at the -1082 G/A point in IL-10 (reagents manufactured by Litekh Scientific and Production Company, Moscow). Figure 2.2.4. shows the different genotype variants under numbers: No. 1, 4 – heterozygotes – samples containing the wild-type allele (-1082* G) and the allele with the substitution (-1082* A); No. 2 – homozygous for the wild-type allele (-1082 G/ G); No. 3 – homozygous for the allele with the substitution (-1082 A/A).

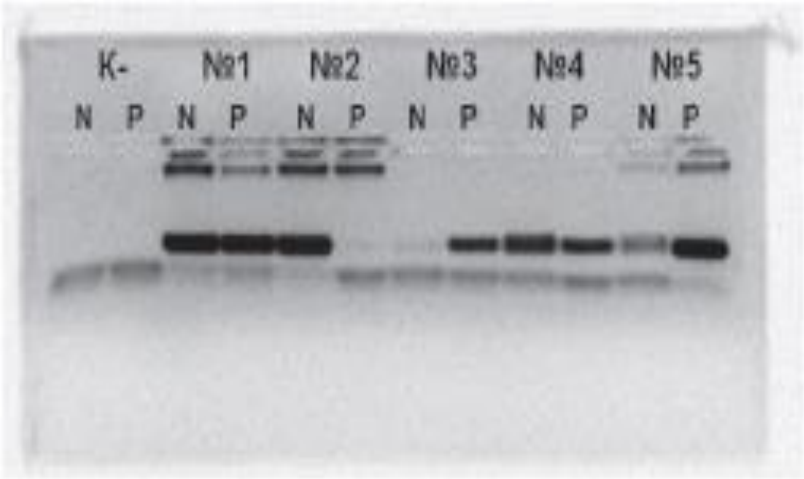



Figure 5.3. IL-10 SNP +1082G/A genotypes

## Statistical Methodology and Genetic Analysis of the IL-1β Gene

Our statistical workflow commenced with data stored in a Microsoft Excel 2019 database. The subsequent stages of data processing and analysis were conducted within the RStudio environment (version 3.5.2), employing specialized libraries, including Epidisplay and dplyr, for data manipulation tasks. Descriptive statistics were quantified as the mean (M) with its associated standard deviation (m). For the comparison of continuous variables, the selection of the appropriate statistical test was contingent upon the data's distributional properties: the Student's t-test was utilized for parametric data, whereas the Kolmogorov-Smirnov or Mann-Whitney U tests were applied to nonparametric data. A p-value of 0.05 served as the criterion for establishing statistical significance. Subsequent to the descriptive analysis, generalized logistic regression was employed to ascertain odds ratios (ORs) and their respective 95% confidence intervals. To assess differences in group frequencies for categorical variables, a two-tailed Fisher's exact test was applied. In our molecular genetic investigations, we quantified the frequencies of gene alleles and genotypes, as well as their combined occurrences, through direct counting. The association between gene and genotype frequencies was statistically assessed via odds ratios (ORs) with associated 95% confidence intervals (95% CI).

The χ2 criterion, derived from the Holdene formula (χ2= Wy2c) and applied with one degree of freedom (df=1), is utilized in conjunction with a factorial table to define the relationship between the values being compared. This leads to a modified final formula.

$$\chi^2 = \frac{\left[\frac{((a+0.5)x(d+0.5)^2}{(b+0.5)x(c+0.5)}\right]}{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$$

If at least one of the values a, b, c, d is equal to 1, then the reliability of differences in the frequency of occurrence of genes and haplotypes is calculated using χ2 with Yates' correction for sample continuity

$$\chi^2 = \frac{(axb+bxc)^2\ xN}{(a+b)x(c+d)x(a+c)x(b+d)}$$

A $\chi 2$ statistic exceeding 3.841 (corresponding to a p-value less than 0.05) suggests a statistically meaningful divergence in the observed frequencies between the groups being contrasted.

The prevalence of the -3953 C/T variant (rs1143634) within the IL-1β gene, examined in relation to cytokine and lipid profiles among working-age males diagnosed with coronary heart disease.

A central goal of our study was to explore the genetic landscape at the -3953 C/T position (rs1143634) of the IL-1β gene in individuals affected by coronary heart disease (CHD), with the ultimate aim of uncovering factors that signal a poor prognosis. To this end, we examined the distribution of alleles and genotypes for the -3953 C/T variant (rs1143634) of the IL-1β gene in both CHD patients and healthy controls from Uzbekistan. Our cohort included 130 CHD patients, comprising 70 younger and 60 older individuals, alongside 45 healthy Uzbek participants, all of whom were genotyped for the -3953 C/T polymorphism (rs1143634) of the IL-1β gene.

Table 5.2 highlights a significant finding: the T allele is 24% more common in working-age CHD patients than in their healthy counterparts. Conversely, the C allele demonstrates greater prevalence within the control group, a difference of 24% (statistically significant with a chi-squared value of 14.13 and a p-value below 0.0001).

Utilizing sophisticated statistical analysis and molecular genetic techniques, our research aimed to pinpoint markers for coronary heart disease (CHD) within the Uzbek population. Below is a paraphrased technical summary of the methodology and the specific findings regarding the **IL-1β gene polymorphism (-3953 C/T, rs1143634)**.

### *1. Statistical Data Processing*

Key Findings on Allele Distribution:

The study identified a significant disparity in allele frequencies between working-age patients and healthy controls:

- **T Allele (Risk Factor):** The T allele was found to be **24% more prevalent** in working-age men with CHD compared to the healthy control group. This suggests that the T allele serves as a genetic predictor for the early development of coronary atherosclerosis.
- **C Allele (Protective Factor):** Conversely, the C allele was more frequent in the healthy control group, appearing at a rate **24% higher** than in the CHD group 3.

## Clinical Implications

The significant association of the **T allele** with CHD in younger Uzbek men indicates that this specific polymorphism may drive a more aggressive immune-inflammatory response. This genetic predisposition, when combined with modifiable risk factors like smoking or stress, accelerates the destabilization of atherosclerotic plaques, leading to early-onset unstable angina and myocardial infarction.

**Table 5.2.**

| Polymorphism | Alleles | Frequency (%) | | χ2 | p | OR (95%CI) | RR (95%CI) |
|---|---|---|---|---|---|---|---|
| | | Patients with IHD of working age (n=70) | Control group (n=45) | | | | |
| IL-1β 3953 C/T rs1143634 | C | 80 (57,1%) | 73 (81,1%) | 14,13 | 0,0001 | 3,2206 (1,7238-6,017) | 1,4903 (1,2293-1,8066) |
| | T | 60 (42,9%) | 17 (18,9%) | | | | |

Analysis of Genotype Distribution for the IL-1β Gene (rs1143634)

*Genotype Frequency Comparison*

The distribution of the three possible genotypes (CC, CT, and TT) revealed significant statistical differences:

- **Homozygous TT (High-Risk Genotype):** This genotype was significantly more prevalent in the working-age CHD group, appearing **19.9% more frequently**

than in healthy controls. This confirms the TT variant as a major genetic marker for disease susceptibility.

- **Homozygous CC (Protective Genotype):** In contrast, the CC variant was found to be **28.1% less frequent** in the CHD group compared to the control group. This suggests that the CC genotype may offer a protective effect against the early development of atherosclerosis.
- **Heterozygous CT:** This variant showed a slight increase of **8.2%** in the CHD group compared to controls. However, with a p-value of 0.06, this difference did not reach the threshold for high statistical significance, though it suggests a potential trend toward increased risk.

| TT (Homozygous) | Higher | Lower | +19.9% |

| CC (Homozygous) | Lower | Higher | -28.1% |

| CT (Heterozygous) | Slightly Higher | Lower | +8.2% |

**Table 5.3.**

| Polymorphism | Genotypes | Frequency (%) | | $\chi 2$ | p | OR (95%CI) | RR (95%CI) |
|---|---|---|---|---|---|---|---|
| | | Patients with IHD of working age (n=70) | Control group (n=45) | | | | |
| IL-1β 3953 C/T rs1143634 | C/C | 27 (38,6%) | 30 (66,7%) | 3,49 | 0,06 | 2,2222 (0,9548-5,172) | 1,5789 (0,9504-2,6231) |
| | C/T | 26 (37,1%) | 13 (28,9%) | | | | |
| | T/T | 17 (24,3%) | 2 (4,4%) | 10,36 | 0,001 | 9.44 (1,99-44,7) | 5 (1,31 |

An examination of the IL-1β C/T 3953 gene polymorphism revealed distinct allele frequency patterns. Specifically, the T allele exhibited a 34.4% higher prevalence among elderly patients diagnosed with coronary heart disease compared to healthy controls. Conversely, the C allele was also observed to be more frequent within the control group, representing 34.4% of the allele pool. These differences were statistically highly significant ($\chi 2=25.75$; $p<0.001$).

**Table 5.4.**

| Polymorphism | Alleles | Frequency (%) | | $\chi 2$ | p | OR (95% CI) | RR (95%CI) |
|---|---|---|---|---|---|---|---|
| | | Patients with IHD of working age (n=60) | Control group (n=45) | | | | |
| IL-1β 3953 C/T rs1143634 | C | 56 (46,7%) | 73 (81,1%) | 25,75 | <0,0001 | 4,9076 (2,59-9,28) | 2,6963 (1,7214-4,2235) |
| | T | 64 (53,3%) | 17 (18,9%) | | | | |

The data revealed significant genetic shifts compared to the healthy control group, reflecting a strong association between these genotypes and the presence of the disease in older populations.

*Genotype Frequency Distribution*

The analysis of elderly patients (Group 2) showed the following trends compared to the control group:

- **Homozygous TT (High-Risk Variant):** The prevalence of the TT genotype was **15.6% higher** in elderly CHD patients ( $x22=18.7$ ; $p<0.0001$ ). This confirms that the risk-associated T allele remains a significant factor for CHD across different age groups.
- **Homozygous CC (Protective Variant):** The CC genotype was markedly less common in elderly patients, with a **53.4% lower frequency** compared to healthy individuals. This sharp decline reinforces the theory that the CC variant may serve as a protective marker against the development of coronary atherosclerosis.
- **Heterozygous CT:** The CT variant was **37.8% more frequent** in the elderly CHD group than in the control group ( $x22=11.5$ ; $p<0.0001$ ). Unlike the working-age group—where the CT increase was only a trend—the difference in the elderly population was highly statistically significant.

Table 5.5: Genotype Frequency Summary (Elderly vs. Controls)

| Genotype | Elderly CHD Patients | Healthy Controls | Difference | Statistical Significance |

| TT (Homozygous) | 15.6% More Frequent | Lower | +15.6% | $p < 0.0001$ |

| CC (Homozygous) | 53.4% Less Frequent | Higher | -53.4% | Highly Significant |

| CT (Heterozygous) | 37.8% More Frequent | Lower | +37.8% | $p < 0.0001$ |

*Synthesis of IL-1β Findings*

When comparing these results with the data from younger patients, a clear pattern emerges: the **T allele** (expressed in TT and CT genotypes) is a consistent driver of CHD risk. However, the elderly group shows a more pronounced accumulation of the heterozygous CT variant.

These findings suggest that while the **TT genotype** is a powerful predictor for early-onset disease in the young, both the **TT and CT variants** contribute heavily to the clinical manifestation of CHD as the population ages. This reinforces the need for genetic screening to identify individuals who are predisposed to chronic inflammatory damage of the coronary arteries.

**Table 5.5.**

**Frequency distribution of the polymorphic locus 3953 C/T (rs1143634) of the IL-1β gene**

| Polymorphism | Genotypes | Frequency (%) | | $\chi^2$ | p | OR (95%CI) | RR (95%CI) |
|---|---|---|---|---|---|---|---|
| | | Patients with coronary artery disease in old age (n=60) | Control group (n=45) | | | | |
| IL-1β 3953 C/T rs1143634 | C/C | 8 (13,3%) | 30 (66,7%) | 26,3 | <0,0001 | 11,5385 (4,2452-31,3617) | 3.2186 (1,9522-5,3065) |
| | C/T | 40 (66,7%) | 13 (28,9%) | | | | |
| | T/T | 12 (20%) | 2 (4,4%) | 18,07 | <0,0001 | 22.5 (4,1602-121,689) | 5.5263 (1,5158-20,148) |

## Comparative Analysis of IL-1β Allele Frequencies: Working-Age vs. Elderly Patients

This section evaluates the distribution of the **rs1143634 (3953 C/T)** allele frequencies specifically between the two groups of patients diagnosed with coronary heart disease (CHD): the working-age cohort (Group 1) and the elderly cohort (Group 2).

### *Allele Frequency Comparison*

The data reveals subtle but noteworthy shifts in the genetic landscape as the age of disease manifestation increases:

- **T Allele (Pro-inflammatory Marker):** The T allele was found to be **10.4% more prevalent** in the elderly patient group compared to the working-age group. This indicates a high accumulation of the risk-associated allele in older populations with established CHD.
- **C Allele (Potential Protective Marker):** Conversely, the C allele was more common in the working-age group, appearing at a rate **10.4% higher** than in the elderly group.
- **Statistical Significance:** The comparison yielded a x22 value of 2.84 and a p-value of 0.09. Since the p-value is greater than 0.05, these specific differences between the two CHD groups do not reach the threshold for high statistical significance, suggesting that the allele distribution is relatively consistent across age groups once the disease has manifested.

Table 5.6: Allele Frequency Comparison (Working-Age vs. Elderly)

| Allele | Working-Age Patients (Group 1) | Elderly Patients (Group 2) | Difference | Statistical Significance |
|---|---|---|---|---|
| T Allele | Lower | Higher | +10.4% in Elderly | x2 = 2.84 |
| C Allele | Higher | Lower | +10.4% in Young | p = 0.09 |

### *Summary of Genetic Findings*

While the T allele is a strong predictor of CHD when compared to healthy controls, the data in Table 5.6 suggests that the genetic "burden" of the **T allele** is slightly higher in the elderly population. In working-age patients, although the T allele is

prevalent, the presence of the **C allele** is more frequent than in their older counterparts, highlighting the complex interplay between genetic predisposition and the age of disease onset.

**Table 5.6.**

**Distribution of 3953 C/T (rs1143634) allele frequencies of the IL-1β gene in working-age and elderly patients with coronary heart disease.**

| Polymorphism | Alleles | Frequency (%) | | χ2 | P | OR (95%CI) | RR (95%CI) |
|---|---|---|---|---|---|---|---|
| | | Patients with IHD of working age (n =70) | Patients with coronary artery disease in old age (n=60) | | | | |
| IL-1β 3953 C/T rs1143634 | C | 80 (57,1%) | 56 (46,7%) | 2.84 | 0.09 | 1,5238 (0,933-2,4888) | 1,2535 (0,9632-1,6312) |
| | T | 60 (42,9%) | 64 (53,3%) | | | | |

Comparison of IL-1β Genotype Frequencies: Working-Age vs. Elderly Patients

This section provides a comparative analysis of the **rs1143634 (3953 C/T)** genotype distributions between working-age patients (Group 1) and elderly patients (Group 2) already diagnosed with coronary heart disease (CHD).

*Genotype Frequency Distribution*

The data reveals how the genetic profile of the IL-1β gene differs between these two clinical cohorts:

- **Homozygous TT (High-Risk Genotype):** The prevalence of the TT variant was slightly higher in the elderly group (**+4.3%**) compared to the working-age group. However, with a p-value of 0.11 ( x22=2.53 ), this difference is not statistically significant, suggesting that the homozygous risk genotype is present at similar levels across both age groups in CHD.

- **Homozygous CC (Protective Genotype):** The protective CC variant was significantly less frequent in the elderly, appearing at a rate **25.3% lower** than in the working-age CHD patients.
- **Heterozygous CT:** The most striking difference was observed in the heterozygous CT variant, which was **29.6% more frequent** in the elderly population compared to the younger patients. This difference was highly statistically significant ( x22=13.07 ; p=0.0003 ).

Table 5.7 Summary: Genotype Comparison (Elderly vs. Working-Age)

| Genotype | Working-Age CHD (Group 1) | Elderly CHD (Group 2) | Difference | Statistical Significance |
|---|---|---|---|---|
| TT (Homozygous) | 4.3% Lower | 4.3% Higher | +4.3% | Not Significant ( p=0.11 ) |
| CC (Homozygous) | Higher | Lower | -25.3% | Significant |
| CT (Heterozygous) | Lower | Higher | +29.6% | Highly Significant ( p=0.0003 ) |

*Clinical Interpretation*

The data suggests that as the patient population ages, the genetic "protective" influence (the CC genotype) diminishes, and the "risk" associated with the T allele becomes increasingly dominated by the **heterozygous CT variant**.

In younger, working-age patients, the disease may be more strongly driven by the homozygous TT state or a combination of moderate genetic risk and severe external stressors. In contrast, in the elderly, the presence of at least one T allele (as seen in the increased CT frequency) appears to be a more common marker of the chronic inflammatory state associated with long-term coronary heart disease.

| Polymorphism | Genotypes | Patients with IHD of working age (n=70) | Patients with coronary artery disease in old age (n=60) | $\chi 2$ | p | OR (95%CI) | RR (95%CI) |
|---|---|---|---|---|---|---|---|
| IL-1β 3953 C/T rs1143634 | C/C | 27 (38,8%) | 6 (10%) | 13,07 | 0,0003 | 5,1923 (2,0471-13,1697) | 2.6515 (1,3996-5,0233) |
| | C/T | 26 (37,1%) | 40 (66,7%) | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | T/T | 17 (24,3%) | 14 (23,3%) | 2, 53 | 0, 11 | 2,3824 (0,8082-7,0224) | 1.8103 (0,8577-3,8213) |

Our investigation explored the prevalence patterns of alleles and genotypes for the IL-1β gene's -3953G/A (rs1143634) polymorphism. This analysis was conducted across patient cohorts experiencing various forms of unstable angina and healthy controls, with consideration for the specific clinical presentation of their coronary heart disease. Examining the allele frequencies for the IL-1β gene polymorphism C/T 3953 (rs1143634) showed a notable difference: the T allele appeared significantly more frequently within the unstable angina patient group compared to the seemingly healthy individuals (21.1% versus 18.9%). Conversely, the C allele was observed more often in the control group, representing 81.1% and 78.9% of alleles, respectively ($\chi 2=0.08$; $p=0.77$) (refer to Table 5.8).

**Table 5.8:**

**Allele Frequency Distribution of IL-1β Gene 3953 C/T (rs1143634) in VSV Patients and Healthy Subjects**

| Polymorphism | Alleles | Frequency (%) | | $\chi 2$ | p | OR (95%CI) | RR (95%CI) |
|---|---|---|---|---|---|---|---|
| | | Patients with VBS (n = 19) | Control group (n=45) | | | | |
| IL-1β 3953 C/T rs1143634 | C | 30 (78,9%) | 73 (81,1%) | 0, 08 | 0, 77 | 1,1451 (0,4465-2,9365) | 1,0423 (0,7752-1,4013) |
| | T | 8 (21,1%) | 17 (18,9%) | | | | |

Within the VSV patient cohort, the homozygous T/T genotype at the -3953 position of the IL-1β gene polymorphism was observed with an 11.4% greater frequency than in the control group ($\chi 2=0.18$; $p=0.22$). Concurrently, the homozygous C/C variant showed a 7% increased prevalence, while the heterozygous C/T variant was 18.4% less common in patients compared to controls ($\chi 2=-0.18$; $p=0.14$). These findings are detailed in

Table 5.9,

which illustrates the frequency distribution of the IL-1β gene's 3953 C/T polymorphism (rs1143634) across VSV patients and healthy subjects.

| Polymorphism | Genotypes | Frequency (%) | | χ2 | p | OR (95%CI) | RR (95%CI) |
|---|---|---|---|---|---|---|---|
| | | Patients with VBS (n = 19) | Control group (n=45) | | | | |
| IL-1β 3953 C/T rs1143634 | C/C | 14 (73,7%) | 30 (66,7%) | - | | | |
| | C/T | 2 (10,5%) | 13 (28,9%) | 0.18 | 0.14 | 0,3297 (0,0654-1,663) | 0.419 (0,1075-1,634) |
| | T/T | 3 (15,8%) | 2 (4,4%) | +0.18 | 0.22 | 3,2143 (0,4815-21,4552) | 1,8857 (0,8171-4,3516) |

As presented in Table 5.10, the T allele is observed with a frequency of 45.5% in patients diagnosed with PSN, a notably higher incidence than the 18.9% recorded in healthy individuals. Conversely, the C allele demonstrates a greater prevalence within the control group (81.1%) compared to the PSN patient group (54.5%), a difference that is statistically significant ($\chi2 = 10.43$; $p = 0.001$).

**Table 5.10.**

**Distribution of 3953 C/T (rs1143634) allele frequencies of the IL-1β gene in patients with PSN and healthy individuals.**

| Polymorphism | Alleles | Frequency (%) | | χ2 | p | OR (95%CI) | RR (95% CI) |
|---|---|---|---|---|---|---|---|
| | | Patients with PSN (n =22) | Control group (n=45) | | | | |
| IL 1β 3953 C/T rs1143634 | C | 24 (54,5%) | 73 (81,1%) | 10,43 | 0,001 | 3,5784 (1,6173-7,9179) | 1,638 (1,1341-2,3658) |
| | T | 20 (45,5%) | 17 (18,9%) | | | | |

Genotype polymorphism data (Table 5.11) indicated that patients with PSN exhibited a higher frequency of the homozygous T/T variant at the IL-1β gene's -3953 position by 22.8% relative to the control group. In contrast, the homozygous C/C variant was less frequent by 30.3%, and the heterozygous C/T variant was more frequent by 7.5% in the PSN group when compared to controls.

**Table 5.11.**

**Frequency distribution of the 3953 C/T polymorphism locus (rs1143634) of the IL-1β gene in patients with PSN and healthy individuals**

| Polymorphism | Genotypes | Frequency (%) | | χ2 | p | OR (95%CI) | RR (95%CI) |
|---|---|---|---|---|---|---|---|
| | | Patients with PSN (n =22) | Control group (n=45) | | | | |
| IL-1β 3953 C/T rs1143634 | C/C | 8 (36,4%) | 30 (66,7%) | 1,99 | 0,158 | 2,3077 (0,7116-7,4832) | 1,8095 (0,795-4,1185) |
| | C/T | 8 (36,4%) | 13 (28,9%) | | | | |
| | T/T | 6 (27,2%) | 2 (4,4%) | +0,44 | 0,006 | 11,25 (1,8967-66,7281) | 3,5625 (1,7095 - 7,4242) |

IL-1β SNP carriage rates also differed between ACS patients and healthy individuals. Among patients, the minor T allele was prevalent, with a frequency of 33.2%, while the major C allele was found at a low frequency, also 33.2%, compared with the control group ($\chi2=17.12$; $p<0.001$) (Table 5.12).

**Table 5.12.**

**Distribution of 3953 C/T (rs1143634) allele frequencies of the IL-1β gene in ACS patients and healthy individuals.**

| Polymorphism | Alleles | Frequency (%) | | χ2 | p | OR (95% CI) | RR (95% CI) |
|---|---|---|---|---|---|---|---|
| | | Patients with ACS (n = 24) | Control group (n=45) | | | | |
| IL 1β 3953 C/T rs1143634 | C | 23 (47,9%) | 73 (81,1%) | 16,29 | <0,0001 | 4,6675 (2,1522-10,1226) | 1.8787 (1.2802-2.757) |
| | T | 25 (52,1%) | 17 (18,9%) | | | | |

Within the cohort of patients diagnosed with Acute Coronary Syndrome (ACS), a comparison with the control group indicated that the homozygous T/T genotype at the -3953 locus of the IL-1β gene was 20.6% more prevalent ($\chi2=+0.54$; $p=0.001$). In contrast, the homozygous C/C genotype exhibited a 45.9% lower frequency, and the heterozygous C/T genotype was 25.3% more frequently observed than in the control population ($\chi2=9.15$; $p=0.002$). Table 5.13 provides a detailed breakdown of

the frequency distribution for the 3953 C/T polymorphism (rs1143634) of the IL-1β gene in both ACS patients and healthy controls. Additionally, the study investigated the mean LDL-C levels as a function of the various allele variants of the IL-1β gene's -3953 C/T polymorphism among working-age individuals with coronary heart disease and a control group. When we analyzing the distribution of the C and T alleles in patients with elevated and target LDL levels, we found that the T allele was present in 43.2% of cases ($\chi2 = 13.74$; $p = 0.00021$), while in patients with target LDL levels, the T allele was present in 40.9% ($\chi2 = 4.81$; $p = 0.028$) (Table 5.14).

**Table 5.14.**

**A comparative analysis of the IL-1 gene's -3953 C/T allele (rs1143634) frequencies in working-age individuals, distinguishing between those with coronary heart disease and healthy controls, and exploring the impact of varying blood LDL cholesterol levels on these distributions.**

| Genotypes | Frequency (%) | | χ2 | P | OR | Lower, g, 95% CI | Upper, g, 95% CI |
|---|---|---|---|---|---|---|---|
| | Patients with elevated LDL-C levels (≥4.0 mmol/L) (n=59) | Control group (n=45) | | | | | |
| C | 67 (56,8%) | 73 (81,1%) | | | 0,3059 | 0,1611 | 0,581 |
| T | 51 (43,2%) | 17 (18,9%) | 13,74 | 0,00021 | 3,2687 | 1,7213 | 6,207 |
| Genotypes | Frequency (%) | | χ2 | P | OR | Lower, g, 95% CI | Upper, g, 95% CI |
| | Patients with normal LDL levels (≥4.0 mmol/L) (n=11) | Control group (n=45) | | | | | |
| C | 13 (59,1%) | 73 (81,1%) | | | 0,3364 | 0,1237 | 0,9148 |
| T | 9 (40,9%) | 17 (18,9%) | 4,81 | 0,028 | 2,9729 | 1,093 | 8,0849 |

LDL levels were also studied in relation to different allele variants of the IL-1β gene -3953 C/T (rs1143634) among elderly patients with coronary heart disease. When distributing the C and T alleles in patients with elevated and target LDL levels,

it was found that 56.7% of patients with high LDL levels had the T allele ($\chi2$=29; p<0.0001), while in patients with target LDL levels, this figure was also 31.2% ($\chi2$=-0.11; p=0.21) (Table 5.15).

**Table 5.15.**

**Distribution of IL-1β gene allele frequencies -3953 C/T (rs1143634) in elderly patients with coronary heart disease and healthy individuals depending on the level of LDL in the blood**

| Genotype | Frequency (%) | | $\chi2$ | P | OR | Lower, g, 95% CI | Upper, g, 95% CI |
|---|---|---|---|---|---|---|---|
| | Patients with elevated LDL levels (≥4.0 mmol/L) (n=52) | Control(n=45) | | | | | |
| C | 45 (43,3%) | 73 (81,1%) | 29 | <0,0001 | 0,1776 | 0,0923 | 0,342 |
| T | 59 (56,7%) | 17 (18,9%) | | | 5,6301 | 2,9244 | 10,8391 |
| Genotype | Frequency (%) | | $\chi2$ | P | OR | Lower, g, 95% CI | Upper, g, 95% CI |
| | Patients with elevated LDL levels (≥4.0 mmol/L) (n=52) | Control (n=45) | | | | | |
| C | 11 (68,8%) | 73 (81,1%) | -0,11 | 0,21 | 0,5123 | 0,1572 | 1,67 |
| T | 5 (31,2%) | 17 (18,9%) | | | 1,9519 | 0,5988 | 6,3622 |

Beyond the established diagnostic approaches, a correlation was identified between specific cytokine levels and the -3953 C/T (rs1143634) polymorphic locus within the IL-1β gene. Individuals possessing the heterozygous C/T or homozygous T/T genotypes at this IL-1β gene locus exhibited significantly elevated IL-1β concentrations, specifically 6.6 pg/ml and 13 pg/ml higher, respectively, when compared to those with the homozygous C/C genotype (both comparisons yielded p-values less than 0.0001). Furthermore, patients carrying the heterozygous C/T or homozygous T/T genotypes of the IL-1β gene 3953 C/T (rs1143634) displayed reduced levels of the anti-inflammatory cytokine IL-10, with decreases of 1.5 pg/ml and 1.9 pg/ml, respectively, relative to individuals with the homozygous C/C

genotype at the same locus (p <0.0005 and p <0.0001, respectively). These findings are detailed in Table 5.16.

**Table 5.16.**

**Concentrations of certain cytokines depending on the polymorphism of the -3953C>T locus (rs1143634) of the IL-1β gene in patients with coronary heart disease of working age.**

| Indicators of cytokine concentration | IL-1β T/C genotype 3953 | | | P-value |
|---|---|---|---|---|
| | C/C | C/T | T/T | |
| | 1 | 2 | 3 | |
| IL-1β пг/мл | 63,4±5,86 | 70±6,2 | 76,4±7,2 | 1vs2: <0,0001*; 1vs3: <0,0001* |
| IL-10 пг/мл | 13,7±1,6 | 12,2±1,39 | 11,8±1,29 | 1vs2: <0,0005*; 1vs3: <0,0001* |

Cytokine Imbalance and Genetic Polymorphisms in CHD

The following sections summarize the relationship between genetic variants, cytokine levels, and the risk of coronary heart disease (CHD) in both working-age and elderly populations.

*IL-10 Gene Polymorphism (rs1800896) Analysis*

The study also investigated the **IL-10 -1082 G/A** polymorphism, which governs the production of the body's primary anti-inflammatory cytokine. Analysis focused on 70 young patients, 60 elderly patients, and 45 healthy controls of Uzbek ethnicity.

Allele Distribution Findings (Table 5.17):

The distribution of the G and A alleles showed a significant divergence between CHD patients and healthy individuals:

- **G Allele (Risk Factor in this population):** Found to be **25.5% more frequent** in working-age CHD patients compared to the control group.

- **A Allele (Protective Factor):** Conversely, the A allele was **25.5% more common** in healthy individuals than in patients ( x22=14.25 ; p=0.0001 ).

Table 5.17: Allele Frequencies of IL-10 (-1082 G/A)

| Allele | Working-Age CHD Patients | Healthy Controls | Statistical Significance |

| G Allele | 25.5% Higher | Lower | Significant Risk Factor |

| A Allele | Lower | 25.5% Higher | x22 = 14.25 ; p = 0.0001 |

This data suggests that in the Uzbek population, the **G allele** of the IL-10 gene may be associated with a "maladaptive" anti-inflammatory response, contributing to the high probability of developing coronary heart disease at a working age.

**Table 5.17.**

**Distribution of 1082 G/A (rs1800896) allele frequencies of the IL-10 gene in working-age patients with coronary heart disease and healthy individuals.**

| Polymorphism | Alleles | Frequency (%) | | χ2 | p | OR (95%CI) | RR (95% CI) |
|---|---|---|---|---|---|---|---|
| | | Patients with coronary heart disease of working age (n=70) | Control(n=45) | | | | |
| IL-10 1082 G/A rs1800896 | G | 87 (62,1%) | 33 (36,6%) | 14,25 | 0,0001 | 0,3527(0,2039-0,6102) | 0,5307 (0,77 - 0,747) |
| | A | 53 (37,8%) | 57 (63,3%) | | | | |

An investigation into the IL-10 gene's 1082 G/A locus polymorphism (rs1800896) revealed significant differences in genotype frequencies among working-age coronary heart disease patients compared to a control cohort. Specifically, the homozygous G/G genotype at IL-10 position -1082 was observed with a 29.8% higher prevalence ($\chi2=14.69$; $p<0.0001$) in the patient group. Similarly, the homozygous A/A variant showed a 21.3% increased frequency. Conversely, the heterozygous G/A variant was found to be 8.5% less common in

patients, though this difference did not reach statistical significance ($\chi 2=2.44$; $p=0.11$). (Refer to Table 5.18 for detailed data).

**Table 5.18.**

**This study aimed to delineate the allelic and genotypic frequencies of the IL-10 G/A 1082 (rs1800896) polymorphic locus within working-age coronary heart disease patient and healthy control populations**

| Polymorphism | Genotypes | Frequency (%) | | $\chi 2$ | p | OR (95%CI) | RR (95% CI) |
|---|---|---|---|---|---|---|---|
| | | Patients with IHD of working age (n =70) | Control group (n =45) | | | | |
| IL-10 1082 G/A rs1800896 | A/A | 10 (14,3%) | 16 (35,6%) | 2,44 | 0,11 | 2,112 (0,8203-5,4376) | 1,4277 (0,9343-2,1816) |
| | G/A | 33 (47,1%) | 25 (55,6%) | | | | |
| | G/G | 27 (38,6%) | 4 (8,8%) | 14,69 | 0,0001 | 10,8 (2,902-40,1924) | 4,7692 (1,8193-12,5026) |

Based on Table 5.19, the G allele of the IL-10 gene (rs1800896) is observed with a higher frequency in elderly patients diagnosed with coronary heart disease compared to healthy individuals, specifically being 24.2% more prevalent in the patient group. Conversely, the A allele also exhibits a greater occurrence within the control group, representing 24.2% of alleles in that cohort ($\chi 2=12.02$; $p=0.0005$). This data reflects the distribution of 1082 G/A allele frequencies.

| Polymorphism | Alleles | Frequency (%) | | $\chi 2$ | p | OR (95% CI) | RR (95%CI) |
|---|---|---|---|---|---|---|---|
| | | Patients with coronary artery disease in old age (n = 60) | Control group (n =45) | | | | |
| IL-10 1082 G/A rs1800896 | G | 73 (60,8%) | 33 (36,6%) | 12,02 | 0,0005 | 0,3727 (0,2121-0,6552) | 0,568 (0,4073-0,7922) |
| | A | 47 (39,2%) | 57 (63,3%) | | | | |

Statistical analysis of elderly patients with coronary heart disease, in contrast to the control group, indicated a significant increase in the homozygous G/G variant at the -1082 position of IL-10 (11.2% more frequent; $\chi2=15.23$; $p<0.0001$). The homozygous A/A variant was notably less frequent by 32.3%, and the heterozygous G/A variant was observed to be 21.1% more frequent ($\chi2=10.22$; $p=0.001$) (Table 5.20).

| Polymorphism | Genotypes | Frequency (%) | | $\chi2$ | p | OR (95%CI) | RR (95% CI) |
|---|---|---|---|---|---|---|---|
| | | Patients with coronary artery disease in old age (n = 60) | Control group (n =45) | | | | |
| IL-10 1082 G/A rs1800896 | A/A | 4 (3,3%) | 16 (35,6%) | 10,22 | 0,001 | 6,24 (1,8696-20,8269) | 2,048 (1,4056-2,9839) |
| | G/A | 39 (76,7%) | 25 (55,6%) | | | | |
| | G/G | 17 (20%) | 4 (8,8%) | 15,23 | <0,0001 | 17 (3,6265-79,6917) | 4,2 (1,693-10,4192) |

A study into the allele frequencies of the IL-10 gene polymorphism (specifically 1082 G/A (rs1800896)) among patients with coronary heart disease differentiated by age group yielded specific findings. The G allele was identified as being 1.3% more common in working-age patients with coronary heart disease than in elderly patients with the condition. Conversely, the A allele demonstrated a 1.3% higher frequency in elderly patients with coronary heart disease when compared to working-age patients. These results, summarized in Table 5.21, did not demonstrate statistical significance ($\chi2 = 0.11$; $p = 0.74$*).

| Polymorphism | Alleles | Patients with IHD of working age (n =70) | Patients with IHD in old age (n =60) | $\chi2$ | p | OR (95%CI) | RR (95% CI) |
|---|---|---|---|---|---|---|---|
| | G | 87 (62,1%) | 73 (60,8%) | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| IL-10 1082 G/A rs1800896 | A | 53 (37,8%) | 47 (39,2%) | 0,05 | 0,82 | 0,9462 (0,5733 - 1,5616) | 0,9707 (0,7424- 1,2694) |

An examination of the allele frequencies for the IL-10 gene's 1082 G/A (rs1800896) polymorphism revealed a notable difference between younger and older coronary heart disease (CHD) patients. Specifically, working-age CHD patients exhibited an 18.6% higher prevalence of the G/G genotype at the -1082 position compared to their older counterparts. Similarly, the A/A genotype was 11% more common in the younger group. Conversely, the G/A heterozygous genotype was found to be 29.6% less frequent in working-age CHD patients than in those at an advanced age ($\chi 2=3.07$; $p=0.079$) (Table 5.22).

Table 5.22.

Distribution of the 1082 G/A (rs1800896) polymorphism of the IL-10 gene across different age groups of coronary heart disease patients.

| Polymorphism | Genotypes | Patients with IHD of working age (n =70) | Patients with IHD in old age (n =60) | $\chi 2$ | p | OR (95%CI) | RR (95% CI) |
|---|---|---|---|---|---|---|---|
| IL-10 1082 G/A rs1800896 | A/A | 10 (14,3%) | 4 (3,3%) | 3,07 | 0,079 | 0,3385 (0,0971-1,1799) | 0,5275 (0,2243-1,2404) |
| | G/A | 33 (47,1%) | 39 (76,7%) | | | | |
| | G/G | 27 (38,6%) | 17 (20%) | 0,47 | 0,49 | 0,6353 (0,1716-2,3516) | 0,7395 (0,2982-1,8337) |

The research aimed to characterize the distribution of genetic variation, specifically allele and genotype frequencies, pertaining to the IL-10 gene polymorphism -1082 G/A (rs1800896) among patients afflicted with diverse types of unstable angina and a cohort of healthy controls. This characterization was

contingent upon the clinical manifestation of coronary heart disease. A notable observation from the allele frequency assessment of the IL-10 G/A polymorphism was the statistically significant enrichment of the G allele within the working-age unstable angina patient population relative to the apparently healthy individuals (42.1% versus 36.6%). The A allele, unlike the G allele, was more common in the control group, accounting for 63.3% and 57.9%, respectively ($\chi2$=0.33; p=0.56) (Table 5.23).

**Table 5.23.**

Table 5.23 presents the distribution of allele frequencies for the 1082 G/A (rs1800896) variation within the IL-10 gene, comparing individuals diagnosed with VSV of working age to a healthy cohort.

| Polymorphism | Alleles | Frequency (%) | | $\chi2$ | p | OR (95%CI) | RR (95% CI) |
|---|---|---|---|---|---|---|---|
| | | Patients with VBS (n=19) | Control group (n = 45) | | | | |
| IL-10 1082 G/A rs1800896 | G | 16 (42,1%) | 33 (36,6%) | 0,33 | 0,56 | 0,7961 (0,3672-1,7256) | 0,9334 (0,7355-1,1846) |
| | A | 22 (57,9%) | 57 (63,3%) | | | | |

Analysis of genotype polymorphism (see Table 5.24) indicated that the homozygous G/G form of the IL-10 gene's -1082 G/A (rs1800896) polymorphism was found at a 1.7% higher rate in VSV patients than in the control population. The homozygous A/A variant showed a 9.3% decrease in frequency among patients, and the heterozygous G/A variant was 7.6% more common in the VSV group relative to controls. (Statistical values: $\chi2$=+0.09; p=1.0 for G/G, and $\chi2$=0.48; p=0.48 for A/A and G/A).

**Table 5.24.**

| Polymorphism | Genotypes | Frequency (%) | | $\chi2$ | p | OR (95%CI) | RR (95% CI) |
|---|---|---|---|---|---|---|---|
| | | Patients with VBS (n = 19) | Control group (n = 45) | | | | |
| IL-10 1082 G/A rs1800896 | A/A | 5 (26,3%) | 16 (35,6%) | 0,48 | 0,48 | 1,536 (0,4546-5,1895) | 1,1276 (0,813- |
| | G/A | 12 (63,2%) | 25 (55,6%) | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | 1,564) |
| | G/G | 2 (10,5%) | 4 (8,8%) | +0,09 | 1,0 | 1,6 (0,2226-11,4985) | 1,1429 (0,6183-2,1123) |

The investigation into the G/A allele frequencies of the IL-10 gene polymorphism indicated that the G allele was significantly more prevalent in the PSN patient cohort, exceeding the frequency in apparently healthy individuals by 30.4%. In parallel, the A allele demonstrated a 30.4% higher frequency within the control group relative to the PSN group ($\chi2$=18.058; p<0.001) (Table 5.25).

Table 5.25.

Distribution of 1082 G/A (rs1800896) allele frequencies of the IL-10 gene in patients with PSN and healthy individuals

| Polymorphism | Alleles | Frequency (%) | | $\chi2$ | p | OR (95%CI) | RR (95% CI) |
|---|---|---|---|---|---|---|---|
| | | Patients with ACS (n = 22) | Control group (n = 45) | | | | |
| IL-10 1082 G/A rs1800896 | G | 27 (61,4%) | 33 (36,6%) | 7,29 | 0,006 | 0,3645 (0,1734-0,7663) | 0,714 (0,5503-0,9265) |
| | A | 17 (38,6%) | 57 (63,3%) | | | | |

Table 5.26 presents genotype polymorphism data indicating significant differences in IL-10 gene variants at position -1082 between PSN patients and controls. Specifically, the G/G homozygous genotype was 27.6% more frequent in the PSN group ($\chi2$=0.52; p=0.007), while the A/A homozygous genotype was 22% less frequent. The heterozygous G/A genotype showed a modest increase in frequency of 5.6% in PSN patients compared to controls ($\chi2$=0.16; p=0.33).

**Table 5.26.**

**Frequency distribution of the 1082 G/A (rs1800896) genotype of the IL-10 gene in patients with PSN and healthy individuals**

| | | Frequency (%) | $\chi2$ | p | OR | RR |
|---|---|---|---|---|---|---|

| Polymorphism | Genotypes | Patients with ACS (n = 22) | Control group (n = 45) | | | (95%CI) | (95% CI) |
|---|---|---|---|---|---|---|---|
| IL10 1082 G/A rs1800896 | A/A | 3 (13,6%) | 16 (35,6%) | | | | |
| | G/A | 11 (50%) | 25 (55,6%) | +0,16 | 0,33 | 2,3467 (0,5658-9,7328) | 1,2126 (0,9062-1,6227) |
| | G/G | 8 (36,4%) | 4 (8,8%) | +0,52 | 0,007 | 10,6667 (1,9085-59,6174) | 2,5263 (1,1088-5,7562) |

A comparison of G/A allele frequencies for the IL-10 gene polymorphism showed a marked disparity between working-age ACS patients and healthy individuals. The G allele was found to be substantially more prevalent in the patient group (72.9%) than in the control group (36.6%). In contrast, the A allele was more frequently detected in the control group (63.3%) compared to the ACS patients (27.1%), a finding that reached statistical significance ($\chi2=16.46$; $p<0.0001$) (Table 5.27).

| Polymorphism | Alleles | Frequency (%) | | $\chi2$ | p | OR (95%CI) | RR (95% CI) |
|---|---|---|---|---|---|---|---|
| | | Patients with ACS (n = 24) | Control group (n = 45) | | | | |
| IL10 1082 G/A rs1800896 | G | 35 (72,9%) | 33 (36,6%) | 16,46 | <0,0001* | 0,215 (0,0998-0,4633) | 0,596 (0,4553-0,78) |
| | A | 13 (27,1%) | 57 (63,3%) | | | | |

An investigation into genotype polymorphism (Table 5.28) demonstrated a significantly elevated prevalence of the homozygous G/G variant at position -1082 of the IL-10 gene polymorphism within the ACS patient cohort, registering a 45.4% increase compared to the control group ($\chi2=15.25$; $p<0.0001$). Conversely, the homozygous A/A variant was observed 28.3% less frequently, and the heterozygous G/A variant 18.1% less frequently, when contrasted with the control group, though these latter differences were not statistically significant ($\chi2=0.18$; $p=0.29$).

| Polymorphism | Genotypes | Frequency (%) | | χ2 | p | OR (95%CI) | RR (95% CI) |
|---|---|---|---|---|---|---|---|
| | | Patients with ACS (n = 24) | Control group (n = 45) | | | | |
| IL10 1082 G/A rs1800896 | A/A | 2 (8,3%) | 16 (35,6%) | +0,18 | 0,29 | 2,88 (0,5499-15,0821) | 1,2089 (0,9326-1,5671) |
| | G/A | 9 (37,5%) | 25 (55,6%) | | | | |
| | G/G | 13 (54,2%) | 4 (8,8%) | 15,25 | <0,0001 | 26 (4,0945-165,101) | 3,7778 (1,5789-9,039) |

When distributing the G and A alleles in patients with elevated and target LDL levels, it was found that 61% of patients with high values from the target LDL level had the G allele ($\chi2 = 12.11$; $p = 0.0005$), while in patients with the target LDL level, this figure was 68.2% ($\chi2 = 7.17$; $p = 0.007$) (Table 5.29).

**Table 5.29.**

| Genotypes | Frequency (%) | | χ2 | P | OR | Lower, g, 95% CI | Upper, g, 95% CI |
|---|---|---|---|---|---|---|---|
| | Patients with elevated LDL levels (≥4.0 mmol/L) (n=59) | Control group (n=45) | | | | | |
| G | 72 (61%) | 33 (36,7%) | 12,11 | 0,0005 | 0,5679 | 0,4077 | 0,7912 |
| A | 46 (39%) | 57 (63,3%) | | | 0,3699 | 0,21 | 0,6516 |
| Genotypes | Frequency (%) | | χ2 | P | OR | Lower, g, 95% CI | Upper, g, 95% CI |
| | Patients with normal LDL levels (≥4.0 mmol/L) (n=11) | Control group (n=45) | | | | | |
| G | 15 (68,2%) | 31 (34,4%) | 7,17 | 0,007 | 0,7719 | 0,6262 | 0,9515 |
| A | 7 (31,8%) | 59 (65,6%) | | | 0,2702 | 0,1 | 0,7303 |

In elderly patients with coronary heart disease, the distribution of G and A alleles in patients with elevated and target LDL levels revealed that 66.3% of patients

with high LDL levels had the G allele ($\chi2$ = 13.28; p = 0.0002), while in patients with target LDL levels, the G allele was found in 50% of cases ($\chi2$ = 1.32; p = 0.25) (Table 5.30).

**Table 5.30.**

**Distribution of IL-10 gene allele frequencies -1082 G/A (rs1800896) in elderly patients with coronary heart disease and healthy individuals depending on blood LDL levels**

| Genotypes | Frequency (%) | | $\chi2$ | P | OR | Lower, g, 95% CI | Upper, g, 95% CI |
|---|---|---|---|---|---|---|---|
| | Patients with elevated LDL levels (≥4.0 mmol/L) (n=49) | Control group (n=45) | | | | | |
| G | 62 (66,3%) | 33 (36,7%) | | | 0,5668 | 0,4118 | 0,7801 |
| A | 36 (33,7%) | 57 (63,3%) | 13,28 | 0,0002 | 0,3362 | 0,1857 | 0,6087 |
| Genotypes | Frequency (%) | | $\chi2$ | P | OR | Lower, g, 95% CI | Upper, g, 95% CI |
| | Patients with normal LDL levels (≥4.0 mmol/L) (n=11) | Control group (n=45) | | | | | |
| G | 11 (50%) | 33 (36,7%) | | | 0,8947 | 0,7325 | 1,0928 |
| A | 11 (50%) | 57 (63,3%) | 1,32 | 0,25 | 0,5789 | 0,2263 | 1,4811 |

IL-10 Gene Polymorphism and Cytokine Dynamics

The final genetic analysis focused on the **IL-10 -1082 G/A (rs1800896)** polymorphism, which plays a pivotal role in regulating the body's anti-inflammatory response. The results indicate that specific genotypes at this locus significantly influence the systemic inflammatory environment in CHD patients.

*2. Chapter Conclusion: IL-10 Allele Distribution*

The **G allele** of the IL-10 gene emerged as a primary genetic risk factor for the Uzbek population studied:

- **Prevalence vs. Controls:** The G allele was **25.5% more common** in working-age CHD patients and **24.2% more common** in elderly patients than in healthy individuals.
- **Lipid Status Interaction:** The presence of the G allele was even more pronounced in patients with dyslipidemia. In those with elevated LDL levels, the G allele was **61% more frequent** in working-age patients and **66.3% more frequent** in elderly patients compared to healthy controls.

### *3. Clinical and Strategic Implications*

The study confirms that carriers of the **G/G and G/A genotypes** are genetically predisposed to a cytokine imbalance characterized by high inflammation and low anti-inflammatory protection. This imbalance accelerates atherosclerotic progression and worsens the clinical outlook.

**Key Strategic Takeaways:**

- **Pathogenic Identification:** Early screening for the G allele of the rs1800896 gene allows for the identification of patients at high risk for aggressive disease.
- **Individualized Therapy:** Recognizing this genetic predisposition enables clinicians to implement personalized treatment plans designed to stabilize coronary heart disease more effectively.
- **Prognostic Improvement:** By tailoring interventions to a patient's genetic profile, the transition from unstable to stable CHD can be accelerated, reducing the likelihood of major adverse cardiovascular events (MACE).

# CHAPTER 6.

## Determination of the efficacy of levocarnitine and L-arginine hydrochloride pharmacotherapy in patients with ischaemic heart disease depending on the polymorphism of IL-1β 3953 C/T (rs1143634) and 1082 G/A (rs1800896) genes of the IL-10 gene



Consequently, current therapeutic strategies for CHD aim to achieve two primary objectives: alleviating symptoms and preventing disease progression [123]. Modern medications are expected to meet stringent criteria, including high efficacy, user-friendliness, and minimal adverse effects [101]. However, the pharmacological response to the same drug can vary considerably among CHD patients, influenced by individual genetic makeup. This inter-individual variability in drug response is shaped by a combination of clinical and genetic factors, such as age, gender, and hepatic and renal function, with the degree of influence differing across various drugs [89].

Pharmacogenetic testing offers a means to identify genetic predispositions in patients that lead to altered drug responses. The main purpose of this testing is to pinpoint specific genotypes, particularly those involving single nucleotide polymorphism (SNP) variations, that are linked to modified pharmacological outcomes [55, 122]. By utilizing pharmacogenetic testing, clinicians can assess the potential efficacy and safety of a treatment, facilitating the selection of the most appropriate first-line therapeutic agent. This approach can lead to a reduction in the number and dosage of medications required for effective treatment. Pharmacogenetic testing is generally considered valuable when the prevalence of polymorphisms in the gene under investigation exceeds 20% [56, 57].

A patient's genetic profile, characterized by single-nucleotide polymorphisms (including substitutions, insertions, and deletions) within genes encoding proteins involved in drug pharmacokinetics and pharmacodynamics, can significantly

contribute to their individual pharmacological response. Identifying these genetic variations through pharmacogenetic testing enables the prediction of drug responses, allowing for personalized drug selection, dosage adjustments, and, in some cases, tailored patient management strategies [17].

Specifically, this chapter investigates the therapeutic efficacy of a regimen involving levocarnitine + L-arginine hydrochloride. Patients received 100 ml/day of this combination for 5 days, followed by levocarnitine tablets at 500 mg/day and Tivortin syrup, 5 ml three times daily, for one month. This study was conducted on IHD patients exhibiting different allelic variants of the IL-1β 3953 C/T (rs1143634) gene.

Current clinical strategies prioritize two primary objectives: the immediate **alleviation of symptoms** and the long-term **prevention of morbidity and cardiovascular events**.

### *The Requirements for Modern Therapy*

To ensure patient compliance and clinical success, prescribed medications must meet rigorous standards:

- **High Efficacy:** Demonstrable improvement in cardiac function and symptom reduction.
- **Convenience:** Dosing regimens that are easy for the patient to follow.
- **Safety:** A profile with minimal side effects to prevent treatment discontinuation.

### *Genetic Determinants of Drug Response*

A major hurdle in standardizing CHD treatment is that different patients often exhibit vastly different pharmacological responses to the same medication. This variability is driven by a combination of clinical and genetic factors:

- **Pharmacogenetics:** An individual's unique genotype dictates how their body metabolizes and responds to specific drugs.
- **Clinical Variables:** Age, gender, and the functional status of the liver and kidneys significantly alter drug concentration and effectiveness.

The degree of influence these factors have varies depending on the specific drug class (e.g., statins vs. antiplatelet agents). Understanding these individual differences is essential for transitioning from a "one-size-fits-all" approach to **personalized cardiology**, where therapy is tailored to the patient's genetic profile to maximize benefits and minimize risks.

Genetic characteristics of patients associated with altered pharmacological response can be identified through pharmacogenetic testing. The primary goal of pharmacogenetic testing is to identify specific genotypes based on SNP polymorphisms associated with altered pharmacological response [55, 122]. Pharmacogenetic testing allows for the determination of the efficacy and safety of therapy and the selection of the most effective drug as a first-line therapeutic agent, thereby reducing the number and dose of medications required for adequate treatment. Pharmacogenetic testing is considered appropriate when the frequency of polymorphisms in the gene under study is greater than 20% of cases [56, 57].

The genetic characteristics of a patient's genome are represented by single-nucleotide polymorphisms (substitutions, insertions, and deletions) in genes encoding proteins involved in the pharmacokinetics and pharmacodynamics of drugs, which can determine the genetic contribution to an individual's pharmacological response. Identification of such substitutions using pharmacogenetic testing allows us to predict the pharmacological response to drugs and, individually, select the drug and its dosage regimen, and sometimes determine patient management tactics [17].

Therapy Efficacy in Working-Age Patients with IHD, Taking into Account Blood Pro- and Anti-inflammatory Cytokine Levels Depending on the 3953 C/T (rs1143634) Allelic Variant of the IL-1β Gene

We studied the efficacy of levocarnitine + L-arginine hydrochloride (levocarnitine + L-arginine hydrochloride) at a dose of 100 ml/day for 5 days, followed by levocarnitine tablets at a dose of 500 mg/day and Tivortin syrup, 5 ml 3 times daily for 1 month, in patients with IHD associated.

**Table 6.1.**

**The difference in LDL levels before and after the administration of levocarnitine and L-arginine hydrochloride depending on the 3953 T/C (rs1143634) polymorphism of the IL-1β gene in patients with coronary heart disease**

| Gen | Genotype | LDL level before treatment (mmol/l) | LDL level after treatment (mmol/l) | Difference in LDL level (mmol/l) |
|---|---|---|---|---|
| IL-1β T/C 3953 | 1 C/C, n=27 | 4,44±0,72 | 3,5±0,71 | 0,94±0,72 |
| | 2-C/T, n=26 | 4,54±0,66 | 3,66±0,76 | 0,89±0,71 |
| | 3-T/T, n=17 | 4,83±0,8 | 4,06±0,5 | 0,77±0,73 |
| | P-value | 1vs2: >0,05<br>1vs3: <0,001* | 1vs2: >0,05<br>1vs3: <0,001* | 1vs2: <0,05*<br>1vs3: <0,001* |

During a month-long treatment, out of 38 patients, 14 (36.8%) with the C/C genotype, 15 (39.5%) with the C/T genotype, and 9 (23.7%) with the T/T genotype of the IL-1β gene achieved the target value (≤4.0 mmol/L). Thirty-two patients (C/C - 40.6%; C/T - 34.4%; T/T - 25%) had elevated LDL-C levels (≥4.0 mmol/L) despite the therapy and did not achieve the target LDL-C level; there were more of them among patients with the T/T genotype (Table 6.2).

**Table 6.2.**

**Achievement of target LDL-C values depending on the 3953 T/C (rs1143634) polymorphism of the IL-1β gene**

| Genotype | Achieved target LDL-C (≤4.0 mmol/L), n=38 | Did not achieve target LDL-C (≥4.0 mmol/L), n=32 |
|---|---|---|
| C/C | 14 (36,8%) | 13 (40,6%) |
| C/T | 15 (39,5%) | 11 (34,4%) |
| T/T | 9 (23,7%) | 8 (25%) |

### Therapeutic Response and Genetic Polymorphisms

This section analyzes the impact of the **IL-1β -3953 C/T (rs1143634)** polymorphism on the efficacy of a specialized treatment regimen involving **Levocarnitine and L-arginine hydrochloride**. The study highlights that a patient's genetic makeup significantly dictates their response to metabolic therapy.

*3. Clinical Conclusion (Table 6.3)*

The data confirms that the **T/T genotype** represents a "low-responder" group. These patients are less sensitive to metabolic therapy and maintain a more aggressive inflammatory profile than those with the C/C or C/T variants.

**Summary of Treatment Responsiveness:** | Genotype | Initial Inflammation | IL-10 Increase | Therapeutic Sensitivity | | :--- | :--- | :--- | :--- | | **C/C (Homozygous)** | Lower | Highest (+7.66) | High Responder | | **C/T (Heterozygous)** | Higher | Moderate (+6.87) | Moderate Responder | | **T/T (Homozygous)** | Highest | Lowest (+6.23) | Low Responder |

These findings underscore the necessity of **genotype-guided therapy**. Patients with the T/T variant may require higher doses, longer treatment durations, or additional anti-inflammatory agents to achieve the same cardioprotective results as those with the C/C genotype.

**Table 6.3.**

**The level of cytokine status indicators before and after the administration of levocarnitine + L-agrinin hydrochloride depending on the 3953 T/C (rs1143634) polymorphism of the IL-1β gene**

| Cytokine status indicators | IL-1 T/C genotype 3953 | | | | | |
|---|---|---|---|---|---|---|
| | C/C, n=31 | | C/T, n=22 | | T/T, n=44 | |
| | Before | After | Before | After | Before | After |
| IL-1 β pg/ml | 63,4±5,86 | 28,91±6,59 | 70,1±6,24 | 40,7±11,69 | 76,45±7,26 | 52,88±14,7 |
| | <0.001* | | <0.001* | | <0.001* | |
| IL-10 pg/ml | 13,7±1,67 | 21,36±1,66 | 12,23±1,39 | 19,1±2,0 | 11,75±1,3 | 17,98±1,13 |

| | | | |
|---|---|---|---|
| | <0.001* | <0.001* | <0.001* |

Chapter Conclusion

## Impact of Metabolic Therapy on Lipid and Cytokine Profiles by Genotype

The final phase of the study evaluated how the **IL-1β (rs1143634)** and **IL-10 (rs1800896)** polymorphisms influenced the success of a combination therapy (Levocarnitine + L-arginine hydrochloride) alongside standard background treatment.

### *1. IL-1β Polymorphism and Lipid-Cytokine Dynamics*

While all patients initially presented with high LDL cholesterol, their response to treatment was clearly differentiated by their IL-1β genotype:

- **Lipid Response:** None of the groups reached the ideal target LDL levels. However, the **homozygous C/C genotype** showed the most significant reduction in LDL (**0.94 ± 0.72 mmol/L**), followed by the C/T (**0.89 mmol/L**) and the T/T variant (**0.77 mmol/L**).
- **Cytokine Response:** The **C/C genotype** demonstrated superior "positive dynamics." In these patients, the pro-inflammatory IL-1β dropped by **28.9 ± 6.59 pg/ml**, and the protective anti-inflammatory IL-10 rose to **21.6 ± 1.66 pg/ml**.
- **Endothelial Function:** Interestingly, the inclusion of Levocarnitine and L-arginine was particularly effective in correcting **endothelial dysfunction** in carriers of the "at-risk" T allele (C/T and T/T). This suggests that metabolic therapy can partially offset the genetic predisposition to severe vascular pathology by improving vessel wall health.

### *2. IL-10 Polymorphism and Treatment Outcomes (rs1800896)*

The study further explored how the **IL-10 1082 G/A** locus affected the outcomes of the same therapeutic regimen:

- **Baseline LDL Levels:** Before treatment, patients with the **homozygous G/G genotype** (the risk variant) had statistically higher LDL levels compared to those with A/A or G/A genotypes.
- **Differential Reduction:**

- **A/A (Protective):** Achieved the greatest LDL reduction (**1.02 ± 0.34 mmol/L**).
- **G/A (Heterozygous):** Showed a moderate reduction (**0.88 ± 0.79 mmol/L**).
- **G/G (Risk):** Showed the least improvement (**0.68 ± 0.74 mmol/L**).

### Clinical Conclusion on Therapy Effectiveness

**Table 6.4.**

| Gen | Genotype | LDL level before treatment (mmol/l) | LDL level after treatment (mmol/l) | Difference in LDL level (mmol/l) |
|---|---|---|---|---|
| IL-10 G/A 1082 (rs1800 896) | G/G, n=27 | 4,42±0,69 | 3,74±0,8 | 0,68±0,74 |
| | G/A, n=40 | 4,53±1,79 | 3,65±0,8 | 0,88±0,79 |
| | A/A, n=3 | 4,47±0,34 | 3,45±0,34 | 1,02±0,34 |
| | P-value | 1vs2: <0,05*<br>1vs3: <0,01* | 1vs2: <0,05*<br>1vs3: <0,05* | 1vs2: <0,01*<br>1vs3: <0,01* |

G/G genotype were more difficult to treat, with only 10 patients achieving the target level, while 6 patients with the A/A genotype and 18 patients with the G/A genotype of the IL-10 gene achieved the target values (Table 6.5).

**Table 6.5.**

**Achievement of LDL target values depending on the 1082 G/A (rs1800896) polymorphism of the IL-10 gene**

| Genotype | Achieved target LDL-C (≤1.8 mmol/L), n=38 | Did not achieve target LDL-C (≥1.8 mmol/L), n=32 |
|---|---|---|
| A/A | 6 (15,8%) | 4 (16,5%) |
| G/A | 18 (47,4%) | 15 (15,3%) |
| G/G | 10 (26,3%) | 13 (18,8%) |

### Therapeutic Response and the IL-10 Gene Polymorphism (rs1800896)

The study further investigated how the **IL-10 1082 G/A** polymorphism influences the success of metabolic therapy using **Levocarnitine and L-arginine hydrochloride**. The results confirm that an individual's genetic capacity for anti-inflammatory signaling directly affects their clinical recovery.

- **Response to Treatment:** After the administration of the combination therapy, IL-1β levels showed a downward trend across all genotypes.

- **Persistent Inflammation:** Similar to the IL-1β gene study, these levels failed to return to healthy target values, particularly in the G-allele carriers, indicating that the genetic drive toward inflammation is difficult to fully suppress.

### *2. Anti-inflammatory Response (IL-10)*

The therapy's ability to increase protective IL-10 levels was significantly moderated by the patient's genotype:

- **A/A (Homozygous):** Showed the strongest response, with IL-10 levels rising by **6.99 ± 0.7 pg/ml**.
- **G/A (Heterozygous):** Showed a moderate response, increasing by **6.59 ± 0.5 pg/ml**.
- **G/G (Homozygous):** Showed the weakest response, increasing by only **6.41 ± 0.7 pg/ml**.

### *3. Clinical Conclusion (Table 6.6)*

The data identifies the **G/G genotype** as a "resistant" or "low-responder" group. These patients exhibit a diminished ability to upregulate their anti-inflammatory defenses in response to Levocarnitine and L-arginine.

**Summary of Treatment Responsiveness for IL-10 rs1800896:** | Genotype | Baseline Inflammation | IL-10 Increase | Treatment Sensitivity | | :--- | :--- | :--- | :--- | | **A/A (Homozygous)** | Lower | **Highest (+6.99)** | High Responder | | **G/A (Heterozygous)** | Higher | Moderate (+6.59) | Moderate Responder | | **G/G (Homozygous)** | **Highest** | **Lowest (+6.41)** | Low Responder |

## Synthesis of Metabolic Therapy Results

When looking at both the IL-1β and IL-10 findings, a clear pattern emerges for personalized cardiology:

- **Genetic Resilience:** Patients with "protective" genotypes (IL-1β **C/C** and IL-10 **A/A**) respond efficiently to standard metabolic support.
- **Genetic Vulnerability:** Patients with "risk" genotypes (IL-1β **T/T** and IL-10 **G/G**) maintain a state of "cytokine resistance." For these individuals, the

combination of Levocarnitine and L-arginine is vital to address endothelial dysfunction, but they likely require more intensive or prolonged therapeutic protocols to achieve stabilization of coronary heart disease.

| Cytokine status indicators | Генотип IL-10 1082 C/T | | | | | |
|---|---|---|---|---|---|---|
| | G/G, n=31 | | G/A, n=53 | | A/A, n=1 | |
| | Before | After | Before | After | Before | After |
| IL-1 β пг/мл | 75,04±7,25 | 52,21±12,07 | 66,34±6,35 | 31,6±9,03 | 61,79±3,86 | 26,2±3,1 |
| | <0,001* | | <0,001* | | <0,001* | |
| IL-10 пг/мл | 11,58±1,15 | 17,99±0,99 | 13,36±1,56 | 19,95±2,41 | 13,98±0,79 | 20,97±1,24 |
| | <0,001* | | <0,001* | | <0,001* | |

Chapter Conclusion

## Summary of Therapeutic Outcomes and Genetic Influence (IL-10 rs1800896)

The final analysis of the study confirms that while the combination of **Levocarnitine and L-arginine hydrochloride** is a rational and effective treatment for coronary heart disease (CHD), its clinical success is significantly influenced by the patient's **IL-10 (1082 G/A)** genotype.

### *1. Lipid Profile Correction and Goal Achievement*

Despite receiving intensive background therapy combined with metabolic support, achieving target LDL levels proved difficult for many, with results varying by genotype:

- **G/G (Risk Genotype):** Responded most poorly to treatment. Only **11 patients** reached their target LDL levels.
- **G/A (Heterozygous):** Showed moderate success, with **14 patients** achieving target levels.
- **A/A (Protective Genotype):** Demonstrated the best response, with **17 patients** reaching their clinical targets.

### *2. Cytokine Dynamics and Anti-inflammatory Recovery*

The treatment's impact on systemic inflammation was most pronounced in carriers of the A allele:

- **IL-1β Reduction:** Patients with the **A/A** and **G/A** genotypes showed a substantial decrease in pro-inflammatory markers (by **35.59 ± 1.4 pg/ml** and **34.74 ± 2.3 pg/ml**, respectively).
- **IL-10 Increase:** In contrast, patients with the high-risk **G/G genotype** showed a much smaller increase in anti-inflammatory protection, with IL-10 levels rising by only **3.7 ± 0.5 pg/ml**.

### *3. Clinical Benefits of Levocarnitine + L-Arginine*

The study concludes that the inclusion of Levocarnitine and L-arginine is a "rational selection" for all CHD patients, regardless of genotype.

**Neuroprotection:** Supporting the nervous system's role in cardiovascular regulation.

- **Improved Perfusion:** Enhancing blood flow to vital organs.
- **Risk Reduction:** Lowering the probability of developing major cardiovascular complications (CVO).

### Final Conclusion of the Monograph

The research establishes that identifying the **IL-1β (rs1143634)** and **IL-10 (rs1800896)** polymorphisms is a powerful tool for modern cardiology. While certain genotypes are "resistant" to standard and metabolic therapies, the use of targeted treatments like Levocarnitine and L-arginine helps bridge the gap.

By integrating **genetic testing** into clinical practice, physicians can transition to a **personalized medicine** model—identifying high-risk "low-responders" early and adjusting their treatment intensity to prevent disability and death in both working-age and elderly populations.

# CONCLUSION

## Summary of Findings: Clinical and Genetic Determinants of CHD

The following sections provide a comprehensive paraphrase of the study's findings regarding the epidemiology, risk factors, and molecular-genetic influences on coronary heart disease (CHD), as well as the efficacy of metabolic correction.

In many regions, CHD accounts for over 50% of all cardiovascular deaths. Alarmingly, approximately 20% of these deaths occur during a person's working age. This "rejuvenation" of the disease—where unstable angina and myocardial infarction are increasingly diagnosed in younger adults—poses a severe threat to the socio-economic stability of society by depleting its active labor force.

### *2. The Synergy of Traditional and Genetic Risk Factors*

While modifiable risk factors (smoking, hypertension, obesity) are critical across all age groups, their role in working-age men is particularly complex.

- **Dyslipidemia and BMI:** Obesity (BMI $\geq 30$ kg/m²) doubles the mortality risk from CHD. In this study, working-age patients (Group 1) exhibited higher triglyceride levels (3.11 mmol/L) and LDL levels (4.5 mmol/L) compared to the elderly (Group 2). High concentrations of these atherogenic lipoproteins were directly linked to the early onset of acute coronary syndromes (ACS).
- **The Genetic Frontier:** Beyond lifestyle, the decoding of the human genome has identified non-modifiable genetic risks. Identifying polymorphic variants in cytokine genes allows for the early detection of individuals "primed" for aggressive atherosclerosis.

### *4. Anti-inflammatory Genetic Markers: IL-10 (rs1800896)*

The **1082 G/A** polymorphism of the **IL-10** gene was analyzed for its role in regulating the body's protective responses.

- **The G Allele Risk:** The **G allele** was found in 25.5% more working-age CHD patients than in healthy individuals.
- **Lipid Correlation:** In patients with elevated LDL, the G allele was significantly more prevalent (found in 24.3% of young and 29.6% of elderly patients), further linking genetic status to lipid metabolism disorders.

### *5. Personalized Pharmacotherapy and Metabolic Correction*

The study highlights that drug efficacy is not universal but depends on the patient's genotype. Pharmacogenetic testing can identify "low responders" and optimize first-line therapy.

- **Levocarnitine + L-arginine Hydrochloride:** This combination was used to target endothelial dysfunction.
- **Genotype-Specific Results: * IL-1β:** Carriers of the **C/T and T/T variants** showed a better response to this metabolic therapy than the normal C/C group, indicating its value in correcting severe vascular pathology.
- **IL-10:** Patients with the **A/A genotype** achieved better LDL reduction and cytokine balance (IL-1β decreased by 35.59 pg/ml) compared to those with the **G/G variant**, who responded more poorly.
- **Overall Value:** Despite genotype variations, the inclusion of Levocarnitine and L-arginine proved to be a rational choice for all groups due to its antioxidant, antihypoxant, and neuroprotective properties, which improve organ perfusion and reduce cardiovascular event risks.

Our findings suggest that the prevalence of these traditional risk factors is comparable between working-age and older men. Among the modifiable risk factors, dyslipidemia, often linked to excess weight, plays a crucial role in elevating the risk of CHD. Epidemiological data reveals a substantial proportion of men aged 35-44 are obese. Studies consistently show that a Body Mass Index (BMI) of 25 kg/m² or higher significantly increases the likelihood of developing CHD, hypertension, and diabetes. A BMI exceeding 30 kg/m² is associated with a 1.5 to 2-fold increase in CHD mortality compared to individuals with a normal weight. Each unit increase in BMI corresponds to a 10% rise in coronary complications, and a rise in BMI from 20 to 30 kg/m² can lead to a 10-20 mg/dL increase in LDL cholesterol. Our analysis of lipid metabolism disorders within our study groups revealed that Group 1 had LDL levels of 4.5 mmol/L, while Group 2 had 4.32 mmol/L. Triglyceride levels were notably higher in Group 1 at 3.11 mmol/L compared to Group 2 at 2.21

mmol/L. Statistically significant differences in lipid profiles were observed between clinical presentations of unstable angina and myocardial infarction (AMI).

Elevated levels of atherogenic lipoproteins and related indicators of atherogenic coefficient have been implicated in the premature onset of Acute Coronary Syndrome (ACS) and Acute Myocardial Infarction (AMI), highlighting the importance of addressing these imbalances [217, 218]. Early identification of specific polymorphic variants within cytokine genes linked to the early development of CHD could enable targeted preventative measures for individuals with a genetic susceptibility, allowing them to mitigate modifiable risk factors and potentially avert the manifestation of adverse genetic predispositions.

When comparing patient groups based on the clinical presentation of CHD, the T allele was consistently more common across all groups than in the control cohort. In patients experiencing unstable angina (NBC) with elevated LDL levels.

The G allele of the IL-10 gene is more common in people with coronary heart disease (CHD) across all age groups. It appears 25.5% more often in working-age CHD patients and 24.2% more often in elderly CHD patients compared to healthy individuals. This increased prevalence of the G allele was seen in all patient subgroups, regardless of how their CHD presented, when compared to controls.

Specifically, among CHD patients with high LDL cholesterol, the G allele of the IL-10 gene (G1082T, rs1800896) was found more frequently. It was 24.3% more common in working-age individuals and 29.6% more common in elderly individuals compared to the control group. Having the G/G or G/A genotypes for this IL-10 gene variant (G1082T, rs1800896) seems to make individuals more prone to cytokine imbalances and the progression of atherosclerosis. This increased susceptibility, in turn, worsens the course of the disease, requiring closer monitoring and more aggressive treatment to improve outcomes for CHD patients.

When it comes to treatment, how well a CHD patient responds to a particular medication depends on their genetic makeup. Pharmacogenetic testing can identify these genetic traits that are linked to different responses to drugs. This testing helps evaluate how effective and safe a treatment will be, allowing for the selection of the

best initial therapy. This personalized approach can lead to fewer medications and lower doses being needed for successful management.

Our study found that levocarnitine and L-arginine hydrochloride were more effective in CHD patients who had either the heterozygous C/T or homozygous T/T variants of the IL-1β (T511C) rs16944 gene, compared to those with the normal C/C genotype. This suggests a potential for targeted improvement of endothelial dysfunction, a key factor in severe vascular diseases. The treatment strategy used clearly boosted the effectiveness of drug therapy for CHD, particularly in the working-age population.

In contrast, CHD patients with the G/A and G/G genotypes of the IL-10 gene did not reach their target LDL levels even when treated with levocarnitine + L-arginine hydrochloride. Patients with the G/G genotype showed a poorer response, with only 11 achieving target LDL, compared to 17 with the A/A genotype and 14 with the G/A genotype. Cytokine measurements indicated more favorable changes in patients with the homozygous A/A genotype, including a significant reduction in IL-1β and an increase in IL-10. Therefore, the overall effectiveness of levocarnitine + L-arginine hydrochloride pharmacotherapy was limited in certain IL-10 genotypes.

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## TABLE OF CONTENTS

## FOR NOTES

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# CLINICAL AND GENETIC FEATURES OF IHD DESTABILIZATION IN WORKING-AGE PATIENTS AND WAYS TO CORRECT THEM

Monograph