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Global dynamics of mortality from cardiovascular diseases in different regions of the world

Possibilities of immunological diagnostics of chronic heart failure in patients with rheumatoid arthritis

An innovative approach to assessing residual risk using advanced glycation end product autofluorescence in patients with coronary heart disease based on various lipid-lowering therapy regimens

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Contents

Editor's Welcome

Dear colleagues!

We are pleased to present to you the 46th issue of the International Heart and Vascular Disease Journal, which features editorial, original, and review articles.

In the "Leading article" section, we offer a comprehensive review article analyzing the dynamics of cardiovascular disease (CVD) mortality across 12 regions of the world from 1990 to 2022. The article also discusses differences in CVD mortality based on countries' economic development and the impact of various risk factors. While there has been a global decline in CVD mortality, the reduction is significantly more pronounced in economically developed regions compared to low-income countries. Public health policy must focus on the most impactful risk factors in specific country groups.

In the "Original Articles" section, two studies are presented. The first investigates the relationship between the autofluorescence index and residual risk based on different cholesterol-lowering regimens in patients with coronary heart disease (CHD). This prospective study involved 120 patients with CHD who underwent a cascade cholesterol inhibition therapy (monotherapy, dual, and triple therapy). The authors suggest that determining the autofluorescence index in clinical practice may serve as a convenient non-invasive tool for indirect assessment of residual risk in CHD patients and for tailoring lipid-lowering therapy. The second study assesses the impact of COVID-19 on the cardiovascular system of athletes and the dynamics of cardiovascular parameters during physical activity after recovery. A total of 62 marathon runners aged 43.8 ± 3.5 years, with training history ranging from 3 to 7 years, were examined. Despite a mild course of illness, changes in the cardiovascular system during physical activity peaked at 2–3 months post-COVID and persisted for at least six months. These findings are important for decision-making regarding return to training and competition.

The "Review Articles" section features three contributions. The first article presents modern categories of immunological markers of direct myocardial damage, secondary angiogenesis, myocardial fibrosis, and general vascular risk. These markers have significant potential for evaluating the course of chronic heart failure in the context of rheumatoid arthritis.

The second review explores the effectiveness of echocardiographic screening and discusses various indicators that may predict the development of CVD. These include assessments of systolic and diastolic function, as well as detection of hypertrophy and cardiac dilation. The article compares screening strategies, their clinical relevance, and implications for asymptomatic patients. The third review highlights the prevalence, risk factors, early predictors, and diagnostic features of childhood hypertension in South Africa. The prevalence ranges from 1.3% to 32.6%, with a particularly steep rise among adolescents. Family history of hypertension, low birth weight, and rapid weight gain during infancy and early childhood are the most important early predictors. Addressing childhood hypertension in South Africa requires committed engagement from the healthcare system, with a focus on prevention, early detection, and effective management.

We invite everybody to collaborate with the journal. Our team is waiting for your original papers, review articles, discussions, and opinions about problems, treatment and prophylaxis recommendations.

Mekhman N. Mamedov
Editor-in-Chief
President of the "Cardioprogress" Foundation

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Review of international medical news

The prognostic significance of rare genetic variants in patients with atrial fibrillation (AF) was evaluated using data from 44,182 individuals enrolled in the UK Biobank and the All of Us Research Program.

The analysis revealed that pathogenic or likely pathogenic variants in cardiomyopathy-associated genes (CMP-PLP) were twice as prevalent among patients with AF compared to the general population, and five times more common in those with early-onset AF (before 45 years of age).

The authors concluded that genetic testing in patients with AF—particularly those with early onset—could help identify individuals at high risk of developing cardiomyopathy and heart failure.

According to the Journal of the American Medical Association

A South Korean research team found that vaccination against herpes zoster significantly reduces the risk of cardiovascular diseases (CVD). Use of the live attenuated vaccine was associated with a 23 % reduction in CVD incidence.

The authors noted that herpes zoster virus may contribute to vascular damage, inflammation, and thrombus formation, ultimately increasing CVD risk, which can be mitigated through vaccination.

According to the European Heart Journal

The impact of anabolic steroid use on male cardiovascular health was assessed. The analysis showed that the risk of acute myocardial infarction increased threefold, while the incidence of percutaneous coronary intervention or coronary artery bypass grafting rose by approximately 2.95 times.

Additionally, the risks of venous thromboembolism and arrhythmia increased by 2.42 and 2.26 times, respectively.

The authors concluded that anabolic steroid use is associated with a significantly elevated risk of severe cardiovascular disease, with adverse effects potentially persisting for years after discontinuation.

According to the Journal of the American Medical Association and Circulation

A U.S. research team investigated the impact of diabetic hypoglycemia on the risk of acute ischemic stroke (AIS). The analysis revealed that the risk of AIS peaked on the day following a hypoglycemic episode (Relative Risk (RR) = 3.7), then gradually declined, remaining statistically significant at RR = 2.3 after 30 days.

The authors suggested that hypoglycemia may act as a trigger for AIS, temporarily increasing susceptibility to stroke and can be potentially used for its prediction and prevention.

According to the Stroke journal

Researchers proposed that preventing iron deficiency in women of reproductive age may reduce the incidence of cardiovascular abnormalities.

The study found that anemia (hemoglobin <110 g/L during the first 100 days of pregnancy) was present in 4.4 % of women whose children were born with congenital heart defects, compared to 2.8 % in the control group.

After adjusting for demographic and clinical factors, anemia was associated with a 47 % increased risk of congenital heart defects.

The authors concluded that the prophylactic use of iron supplementation may become a simple and cost-effective strategy of reducing congenital heart disease.

According to the BJOG

The first cardiac procedure using optical coherence tomography in Russia was performed in Yekaterinburg, using the only device of its kind currently operating in the country.

Optical coherence tomography provides real-time, high-resolution imaging of coronary arteries by transmitting light signals through a catheter. The resulting 3D images of the vessel wall and built-in AI algorithms help physicians assess the severity of lesions, presence of calcifications, and risk of plaque rupture during interventions.

According to the press service of the Ministry of Health of the Sverdlovsk Region

Researchers from Canada have evaluated the long-term risk of serious adverse renal outcomes in children and adolescents diagnosed with arterial hypertension (AH).

Data from 26,324 participants aged 3 to 18 years were analyzed.

The findings revealed a significantly higher incidence of severe kidney-related outcomes — including death, chronic kidney disease, or kidney failure — among hypertensive children and adolescents: 5.52 events per 1,000 person-years compared to 1.66 in normotensive peers.

The authors concluded that early detection and effective management of blood pressure in children may reduce the risk of chronic kidney disease and prevent long-term kidney function loss.

According to The Lancet Child & Adolescent Health journal

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Global dynamics of mortality from cardiovascular diseases in different regions of the world

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In most regions of the world, complications of cardiovascular diseases (CVD) are the leading cause of death in adults. There is currently a significant variability in the incidence of CVD mortality across countries.

The aim of this review is to analyze trends in CVD mortality across 12 world regions from 1990 to 2022, as well as to assess differences in CVD mortality depending on countries' economic development and the role of various risk factors (RF).

Methods. Data from the Global Burden of Disease, Injuries, and Risk Factors research group were used. CVD mortality was analyzed across eighteen specific CVD conditions. Each relevant epidemiological metric was assessed for 23 age groups, ranging from birth to 95 years and older; for males, females, and both sexes combined, from 1990 to 2022. The material for this article was gathered from peer-reviewed publications indexed in PubMed, eLIBRARY.RU, CyberLeninka, and other research platforms from 2016 to 2024.

Results. An analysis of age-standardized CVD mortality rates across different global regions revealed a range from 73.6 per 100,000 in the high-income Asia-Pacific region to 432.3 per 100,000 in Eastern Europe in 2022. Overall, between 1990 and 2022, there has been an average 38.5% reduction in CVD mortality across 12 global regions. The analysis also examined differences in CVD mortality by the level of a country's economic development and the role of various RF.

Conclusion. Over recent decades, there has been a global decline in CVD mortality, with more significant progress observed in regions with high levels of economic development compared to low-income countries. Public health policy should focus on the most impactful risk factors in specific country groups.

Keywords: mortality, cardiovascular diseases, regions, dynamics, risk factors, economic level.

Conflict of interests: none declared.

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Cardiovascular diseases (CVD) remain the leading cause of mortality among the adult population of both sexes worldwide. This trend was first recorded in the 1960s [1–3]. At the same time, the early 21st century has seen a rapid increase in mortality from cancer [4]. Despite a 34.9% global decrease in CVD mortality over the past 32 years, complications from cardiovascular diseases still represent the main cause of adult mortality in most countries, due to their high prevalence across different regions of the world. According to the literature, the current age-standardized prevalence of CVD ranges from 5,881.0 per 100,000 population in South Asia to 11,342.6 per 100,000 in Central Asia. As of 2023, coronary heart disease (CHD) has the highest age-standardized DALY (Disability-Adjusted Life Years) rate globally among all diseases — 2,275.9 per 100,000 people. Intracerebral hemorrhage and ischemic stroke follow as leading contributors to CVD-related DALYs [5].

The aim of this review is to analyze trends in CVD mortality across 12 world regions from 1990 to 2022, as well as to assess differences in CVD mortality depending on countries' economic development and the role of various risk factors (RF).

Methods

Overall, international analysts classify the world's countries into 21 regions. These regions consist of countries and territories that are geographically close and epidemiologically similar. For the preparation of this article, materials from the Global Burden of Disease, Injuries, and RF (GBD) study group were used. The GBD project generates time series of comprehensive health metrics, including prevalence, cause-specific mortality rate (CSMR), years of life lost (YLLs), years lived with disability (YLDs), and disability-adjusted life years (DALYs). Cardiovascular disease mortality was analyzed with reference to eighteen specific CVDs. Each epidemiological metric of interest was assessed for 23 age groups, ranging from birth to age 95 and older, for males, females, and both sexes combined, from 1990 to 2022. Age standardization was performed using the direct method with the standard age structure of the global population defined by GBD. This standard population size is based on the population structure of all settlements in countries with populations >5 million. The share of the population in each age group is calculated based on the specific settlement, and then these age proportions are averaged across all settlements [6, 7].

The material for this article was collected from peer-reviewed publications indexed in PubMed, eLIBRARY.RU, CyberLeninka, and other research platforms from 2016 to 2024. Keywords used for the search included: cancer, mortality, cardiovascular diseases, regions, trends, risk factors, economic level.

Results and Discussion

Cardiovascular diseases in Eastern and Central Europe

Over the observation period from 1990 to 2022, CVD mortality in Eastern Europe decreased by 24.3%. It is important to emphasize that age-standardized CVD mortality within the region varied by a factor of 2.6 — ranging from 215.0 to 553.0 per 100,000 population. Among all analyzed regions, Eastern Europe ranked first in CVD mortality, a position it has maintained consistently over the past 32 years [5].

In 2022, following CHD and stroke, alcoholic cardiomyopathy had the highest age-standardized DALY rate — 521.2 per 100,000 population. Among all risk factors (RF), the most significant was arterial hypertension (AH), particularly elevated systolic blood pressure (SBP)[1,2].

In 2022, the age-standardized mortality rate from cardiovascular disease (CVD) among Central

[1] Murray CJL Protocol for the Global Burden Of Diseases, Injuries, And Risk Factors Study (GBD). Accessed November 10, 2023. https://www.healthdata.org/sites/default/files/files/Projects/GBD/ March2020_GBD%20Protocol_v4.pdf

[2] Gibson G, Blumer V, Mentz RJ, Lala A. Universal Definition and Classification of Heart Failure: A Step in the Right Direction from Failure to Function. Accessed November 8, 2023. https://www. acc.org/Latest-in-Cardiology/Articles/2021/07/12/ 12/31/Universal-Definition-and-Classification-ofHeart-Failure

European countries ranged from 132.6 to 581.4 per 100,000 population, indicating a 4.4-fold difference. Over time, CVD mortality decreased by 47.0%, which is twice the reduction observed in Eastern Europe. Among all analyzed regions, Central Europe ranked 2nd in age-standardized CVD mortality in 1990 and 7th in 2022.

Cardiovascular Diseases in Central Asia

Mortality from CVD in the countries of Central Asia and the South Caucasus is among the highest globally. In 2022, age-standardized mortality rates in this region ranged from 331.8 to 542.3 per 100,000 population. Over the period of observation, mortality decreased by 16.5%. It is worth noting that out of the 21 global regions, Central Asia ranked 4th in 1990 and 2nd in 2022 in terms of age-standardized CVD mortality, and 1st in age-standardized CVD prevalence. After CHD and all subtypes of stroke, hypertensive heart disease had the highest age-standardized DALY rate in 2022—337.4 per 100,000 people [5].

Cardiovascular Diseases in Western Europe

In Western European countries, age-standardized CVD mortality rates ranged from 80.2 to 199.9 per 100,000 in 2022 — a 2.5-fold difference. Over the observation period, CVD mortality declined by 60.2%. Western Europe has some of the best outcomes among the 21 global regions, ranking 15th in 1990 and 19th in 2022 for age-standardized CVD mortality. High SBP accounted for the largest number of age-standardized CVD parameters — 977.2 per 100,000 [5].

Cardiovascular Diseases in North America

In 2022, age-standardized CVD mortality rates in high-income North American countries ranged from 99.4 to 191.6 per 100,000 — a 1.9-fold difference. Over the 32-year observation period, CVD mortality declined by 45.9%. This region ranked 17th both in 1990 and 2022 in terms of age-standardized CVD mortality. As in Western Europe, high SBP contributed the most to age-standardized CVD burden.

Cardiovascular Diseases in Australia

In 2022, age-standardized CVD mortality rates in Australia ranged from 92.0 to 122.5 per 100,000, with a relatively small variation (1.3-fold difference). Between 1990 and 2022, CVD mortality decreased by 65.5%. In 2022, the region had one of the best outcomes, ranking 20th out of 21 global regions, compared to 16th in 1990. High SBP accounted for the highest number of age-standardized CVD parameters — 777.3 per 100,000 [5].

Cardiovascular Diseases in Asia-Pacific Countries

In 2022, age-standardized CVD mortality rates in high-income Asia-Pacific countries ranged from 72.7 to 252.6 per 100,000 population — a 3.55-fold difference. From 1990 to 2022, CVD mortality declined by 64.2%. Among the 21 high-income global regions, Asia-Pacific countries ranked 20th in 1990 and 21st in 2022 for age-standardized CVD mortality — the best ranking. In this region, after CHD and stroke, aortic aneurysm had the highest age-standardized DALY rate in 2022 at 79.6 per 100,000. Among all RF, high SBP contributed the most to the age-standardized burden [5].

Cardiovascular Diseases in Southeast Asia

In Southeast Asia, age-standardized CVD mortality rates in 2022 ranged from 123.2 to 406.2 per 100,000 — a 3.3-fold variation. Over the 32-year period, CVD mortality declined slightly by 16.9%. The region ranked 8th in 1990 and 6th in 2022 for age-standardized CVD mortality. Following CHD and all stroke subtypes, hypertensive heart disease had the highest age-standardized DALY rate in 2022 — 458.5 per 100,000 [5].

Cardiovascular Diseases in North Africa and the Middle East

In 2022, age-standardized CVD mortality rates in North Africa and the Middle East ranged from 132.5 to 578.7 per 100,000 population — a 4.4-fold difference. Between 1990 and 2022, CVD mortality declined by 31.6%. This region ranked 3rd in 1990 and 5th in 2022 for age-standardized CVD mortality. After CHD and stroke, hypertensive heart disease showed the highest age-standardized DALY rate in 2022 — 654.8 per 100,000 [5].

Cardiovascular Diseases in Central Sub-Saharan Africa

In Central Sub-Saharan Africa, CVD mortality rates across countries were relatively close, ranging from 323.5 to 464.6 per 100,000 in 2022 — a 1.4-fold difference. From 1990 to 2022, only a modest 12.3% re-

duction in CVD mortality was observed. Out of the 21 global regions, Central Sub-Saharan Africa ranked 6th in 1990 and 4th in 2022 for age-standardized CVD mortality. After CHD and all stroke subtypes, hypertensive heart disease had the highest DALY rate in 2022 — 1,110.7 per 100,000 population [5].

Cardiovascular Diseases in Central Latin America

In 2022, age-standardized cardiovascular disease CVD mortality rates in Central Latin American countries ranged from 109.5 to 329.4 per 100,000 population — a threefold difference. Over the 32-year observation period, CVD mortality declined by 25.1%. Among the 21 global regions, Central Latin America ranked 19th in 1990 and 14th in 2022 in terms of age-standardized CVD mortality. After CHD and all stroke subtypes, hypertensive heart disease had the highest age-standardized DALY rate in 2022 — 185.0 per 100,000 population [5].

Cardiovascular Diseases in Tropical Latin America

In the countries of Tropical Latin America, age-standardized CVD mortality rates ranged from 157.7 to 201.8 per 100,000 population in 2022, showing only a 1.3-fold difference between countries. Over the past 32 years, CVD mortality significantly decreased by 52.6%. Of the 21 global regions, Tropical Latin America ranked 12th in 1990 and 15th in 2022 in age-standardized CVD mortality. Following CHD and all stroke subtypes, hypertensive heart disease had the highest age-standardized DALY rate in 2022 — 245.4 per 100,000 population [5].

Analysis of CVD Mortality Trends Across Global Regions

In 2022, age-standardized CVD mortality rates varied widely — from 73.6 per 100,000 in the high-income Asia-Pacific region to 432.3 per 100,000 in Eastern Europe.

Overall, between 1990 and 2022, 12 global regions saw an average 38.5% decline in CVD mortality. Table 1 presents the dynamics of CVD mortality across these years, along with variations among countries within the 12 regions [5].

The greatest reductions in CVD mortality were seen in Australia, Asia-Pacific region, and Western Europe — with an average decline of around 63% over 32 years. As of 2022, CVD mortality in these regions ranged from 81.6 to 191.7 per 100,000 population. A similar trend is noted in North America and Tropical Latin America. It is worth noting that while Central Europe also showed a marked decrease in CVD mortality, some countries in this region still had high mortality rates in 2022. In contrast, Central Asia showed a 3-4 times smaller decline compared to the aforementioned regions. A similar situation is observed in Central Africa and Southeast Asia. Particularly in Central Asia, average CVD mortality remains among the highest across all analyzed regions globally.

Table 1. **Dynamics of mortality from CVD in different regions of the world (1990-2022)**

World regions	Dynamics of mortality from CVD, 1990-2022	Variation of mortality from CVD in countries of the regions, per 100 thousand population, in 2022
Eastern Europe	24.3 %	215.0–553.0
Central Europe	47.0 %	132.6–581.4
Central Asia	16.5 %	331.8-542.3
Western Europe	60.2 %	80.2-199.9
North America	45.9 %	99.4-191.6
Australia	65.5 %	92.0 — 122.5
Asia-Pacific Countries	64.2 %	72.7-252.6
Southeast Asia	16.9 %	123.2-406.2
North Africa and the Middle East	31.6 %	132.5-578.7
Central Africa	12.3 %	323.5-464.6
Central Latin American	25.1 %	109.5-329.4
Cardiovascular Diseases in Tropical Latin America	52.6 %	157.7-201.8

Impact of economic level and risk factors on CVD mortality

It is well established that numerous factors influence CVD mortality, including the efficiency of healthcare organization, chronic disease prevention, public health literacy, and access to medical services [8, 9]. All these issues are closely tied to the level of economic development. It is evident that countries with a high economic status have demonstrated more pronounced declines in mortality and currently exhibit lower CVD mortality rates compared to regions and countries with lower economic development [10]. A number of studies in the literature have explored the relationship between RF, economic development, and CVD mortality across various countries [11, 12].

One such project is the international, multicenter PURE study (Prospective Urban and Rural Epidemiological study). This study included 155,722 participants from 21 countries (aged 35–70 years), enrolled between 2005 and 2016 across five continents (excluding Australia).

The average follow-up period was 9.5 years [12]. The causes of death were analyzed based on economic development level (low, middle, and high), as well as the impact of modifiable RFs on the development of cardiovascular complications (CVC) — including cardiovascular diseases, myocardial infarction, stroke, and chronic heart failure — and related mortality in these categories of countries.

According to the obtained data, CVD was the cause of death in 43%, 42%, and 23% of cases, while cancer accounted for 15%, 30%, and 55% of deaths in countries with low, middle, and high economic levels, respectively. Age- and sex-standardized all-cause mortality rates decreased with increasing income levels — 13.3, 6.9, and 3.4 per 1,000 person-years in low-, middle-, and high-income countries, respectively.

An analysis by individual disease categories showed that low income was associated with higher mortality from cardiovascular and respiratory diseases, injuries, and infections, and lower mortality from cancer. The ratio of CVD mortality to cancer mortality was 3.0, 1.3, and 0.4 in low-, middle-, and high-income countries, respectively. The most significant cardiovascular risk factor was arterial hypertension, followed by elevated low-density lipoprotein (LDL) cholesterol, with air pollution ranking third. Smoking, poor diet, low educational attainment, and abdominal obesity had a comparable impact on cardiovascular risk. In high-income countries, behavioral and metabolic risk factors accounted for nearly the entire burden of CVD, whereas in middle- and low-income countries, lower educational levels and air pollution played a greater role [13].

The findings from the PURE study reaffirm that a country's economic status influences the incidence and mortality of CVD and other non-communicable diseases. Moreover, depending on the economic level, various additional RF alongside the major ones play a role in the development of CVD.

Conclusion

In most regions of the world, complications of CVD remain the leading cause of adult mortality, with CHD and stroke occupying central positions. Over the past decades, there has been a significant global decline in CVD mortality; however, this trend is more pronounced in regions with high economic development compared to low-income countries. At present, there is also substantial variability in CVD mortality rates across different regions worldwide.

Health policy efforts should focus on the specific RF that have the greatest impact in each group of countries. In high-income regions, a large proportion of cardiovascular complications can be prevented through optimal control of metabolic and behavioral risk factors. In low- and middle-income countries, the greatest benefit can be expected from tobacco control, blood pressure management, and increased investment in healthcare, including improved access to preventive medications and the use of advanced technologies for CVD treatment.

Conflict of interests: none declared.

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An innovative approach to assessing residual risk using advanced glycation end product autofluorescence in patients with coronary heart disease based on various lipid-lowering therapy regimens

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The aim of the study is to determine the relationship between the autofluorescence index and residual risk as part of a comprehensive assessment based on different cholesterol-lowering regimens in patients with CHD.

Methods. In this prospective study, 120 male patients with CHD underwent stepwise cholesterol-lowering therapy (monotherapy, dual, and triple therapy). Upon achieving the target level of low-density lipoprotein cholesterol (LDL-C), patients were divided into three cohorts. Each cohort underwent a comprehensive clinical and instrumental evaluation, including the determination of advanced glycation end products using the AGE Reader device (Diagnoptics Technologies B.V., Netherlands), which automatically calculated the autofluorescence index.

Results. LDL-C target levels were achieved by 27.5% of patients (n = 33) on monotherapy, 60% (n = 72) on dual therapy, and 12.5% (n = 15) on intensified triple therapy. AFI showed a decreasing trend at 6, 12, and 18 weeks, with final values as follows: cohort 1 (monotherapy) — 1.75 (95% CI: 1.70–1.95), cohort 2 (dual therapy) — 2.85 (95% CI: 2.30–3.80), cohort 3 (triple therapy) — 4.90 (95% CI: 4.15–4.90) To assess the relationship between achieved LDL-C levels and AFI after 18 weeks of treatment, a correlation analysis was performed. The resulting correlation coefficient (ρ = 0.388) indicated a moderate but statistically significant association ($p < 0.05$) according to the Chaddock scale. The relationship was strongest in cohort 3 (triple therapy) and weakest in cohort 1 (statin monotherapy), supporting the potential of AFI as a surrogate marker for residual cardiovascular risk.

Conclusion. The determination of AFI in routine clinical practice may serve as a convenient, non-invasive meth-

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od for the indirect assessment of residual cardiovascular risk in patients with CHD. This approach could enhance the implementation of secondary prevention strategies, including the intensification of lipid-lowering therapy for more stringent control of the lipid component of residual risk.

Keywords: coronary heart disease, residual risk, lipid-lowering therapy, PCSK9 inibitors, autofluorescence, AGE-reader, advanced glycation end products.

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Introduction

Increasing life expectancy, promoting health, and reducing mortality—particularly from cardiovascular diseases — are among the most critical objectives of healthcare systems in all countries [1]. Unfortunately, coronary heart disease (CHD) continues to rank among the leading causes of death worldwide, affecting predominantly males. Antianginal, lipid-lowering, and antiplatelet therapies are the cornerstones of CHD treatment, capable of improving quality of life and long-term outcomes. However, a residual risk remains — often unaccounted for in routine clinical practice. This residual risk refers to the ongoing possibility of adverse cardiovascular events in patients with CHD despite achieving target low-density lipoprotein cholesterol (LDL-C) levels. This type of risk has been recognized as an interdisciplinary issue and has been discussed globally since 2008, when the Residual Risk Reduction Initiative was launched [2–4]. A number of factors directly influence residual risk. These include atherogenic lipoprotein fractions that are rarely considered in routine practice — very-low and intermediate-density lipoproteins; hypertriglyceridemia; elevated lipoprotein(a) [Lp(a)] levels; and genetic polymorphisms related to familial hypercholesterolemia (both homozygous and heterozygous forms). There are also additional or "additive" factors, such as persistent hyperglycemia and glucotoxicity in diabetes mellitus, failure to achieve target glycated hemoglobin (HbA1C) levels, excessive variability in blood pressure with poor control within the target range, decompensated chronic heart failure (CHF) and other comorbid conditions, systemic inflammation, physical inactivity, etc. These conditions influence three critical pathophysiological components of residual risk: lipid, thrombotic, and inflammatory pathways. Their interplay forms the morphological substrate for cardiovascular events [5, 6].

Recently, the role of advanced glycation end-products (AGEs) as biomarkers reflecting a person's "biochemical passport" has been actively studied in the international scientific community. During non-enzymatic biochemical cascade reactions—where the substrate may be protein, lipid, or nucleic acid in nature — Schiff bases are formed. These are metabolically active intermediates that undergo irreversible reactions to form stable Amadori products. Through a series of oxidation processes, these ultimately generate fluorescent compounds, including pentosidine. There is a portable AGE analyzer that has proven convenient in clinical settings: the AGE Reader (Diagnoptics Technologies B.V., Netherlands). This device determines the autofluorescence index and automatically categorizes patients according to their total cardiovascular risk. It has found applications in diverse medical fields — from predicting the onset of diabetes mellitus (DM) to surgical practice [7–10].

However, in patients with CHD, the absolute cardiovascular risk is inherently very high. Therefore, it was hypothesized that this device could be used to assess residual risk in CHD patients, taking into account the influence of additive factors that can significantly modify residual risk. The AGE analysis procedure is non-invasive, quick, and easily applicable in a clinical setting.

The aim of the study is to determine the relationship between the autofluorescence index and residual risk as part of a comprehensive assessment based on different cholesterol-lowering regimens in patients with CHD.

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Methods

In the course of a prospective clinical study conducted in accordance with the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki, 120 male patients aged 55–75 years with CHD and comorbid conditions (arterial hypertension (AH), type 2 DM, metabolic syndrome) were observed. Each patient provided written informed consent to participate (REC protocol No. 3 dated 15.03.2023). Exclusion criteria included: female sex, age over 75 years, class III obesity, coexisting severe chronic kidney disease, CHF with a reduced ejection fraction below 40%, and DM with multiple complications.

At the start of the study, residual risk was comprehensively assessed in all participants based on medical and life history, physical examination, and results from laboratory and instrumental investigations. These included the following laboratory tests: complete blood count, urinalysis, blood biochemistry with lipid profile, Lp(a), glucose levels, HbA1c, creatinine, bilirubin, total protein, potassium, and sodium. The following instrumental tests were also performed: electrocardiography, echocardiography, duplex ultrasound of the brachiocephalic arteries, and autofluorescence analysis using the AGE Reader system (Diagnoptics Technologies B.V., Netherlands). This device measures AGEs in human skin; the autofluorescence index was determined three times on clean forearm skin, with the average value calculated. This method was applied for the first time to assess residual risk in CHD patients based on AGE analysis (invention application No. 2025101284 dated 22.01.2025).

Lipid-lowering therapy was adjusted stepwise:

- **Step 1:** All patients began with monotherapy using rosuvastatin 20 mg.
- **Step 2:** If the target low-density lipoprotein cholesterol (LDL-C) level <1.4 mmol/L was not achieved after 6 weeks, patients were prescribed a fixed combination of rosuvastatin 20 mg and ezetimibe 10 mg.
- **Step 3:** If target LDL-C was still not achieved after another 6 weeks, patients were switched to triple lipid-lowering therapy with the addition of a PCSK9 inhibitor — alirocumab 150 mg subcutaneously once every two weeks.

After 6 weeks, LDL-C target achievement was reassessed. Patients were divided into cohorts:

- **Cohort 1 (n=33):** reached the target LDL-C level on monotherapy
- **Cohort 2 (n=72):** on fixed combination therapy
- **Cohort 3 (n=15):** on triple therapy

All patients received adequate antihypertensive and antiplatelet therapy, as well as treatment for comorbid conditions. Patients who reached the target LDL-C level with any lipid-lowering regimen underwent a repeated comprehensive residual risk assessment, including using the AGE Reader device. The median follow-up period was 18 weeks.

Statistical analysis

Statistical analysis was performed using StatTech v. 4.7.3 (developed by Stattech LLC, Russia). Differences were considered statistically significant at $p < 0.05$. The distribution of quantitative variables was assessed for normality using the Shapiro–Wilk test. If the data did not follow a normal distribution, quantitative variables were described using the median (Me) and interquartile range (Q1–Q3). Categorical data were presented as absolute numbers and percentages. 95% confidence intervals (CIs) for percentages were calculated using the Clopper–Pearson method.

Results

The study design involving 120 patients is illustrated in Figure 1, which shows the selected multicomponent cholesterol inhibition regimen with sequential therapy intensification every 6 weeks.

LDL-C target achievement dynamics: at the beginning of the study (Visit 1), none of the patients had reached the target low-density lipoprotein cholesterol (LDL-C) level of <1.4 mmol/L. All patients were prescribed monotherapy with rosuvastatin 20 mg orally once daily. Additionally, they were educated on key principles of a healthy lifestyle, including a balanced diet with limited animal fats and simple carbohydrates, the importance of daily physical activity, and strict adherence to prescribed treatment. After 6 weeks of rosuvastatin monotherapy (Visit 2), 27% of patients (n=32) had achieved the target LDL-C level. For those who did not reach the target, a fixed-dose combination of rosuvastatin 20 mg + ezetimibe 10 mg was prescribed, with follow-up lipid profiling after another 6 weeks. By Visit 3, 60% of patients (n=72) had achieved LDL-C <1.4 mmol/L. The remaining 13% (n=15) were switched to triple therapy, with the addition of the PCSK9 inhibitor alirocumab 150 mg subcutaneously every two weeks to the statin-ezetimibe combination. By Visit 4, 12% (n=14) of patients had achieved the target LDL-C lev-

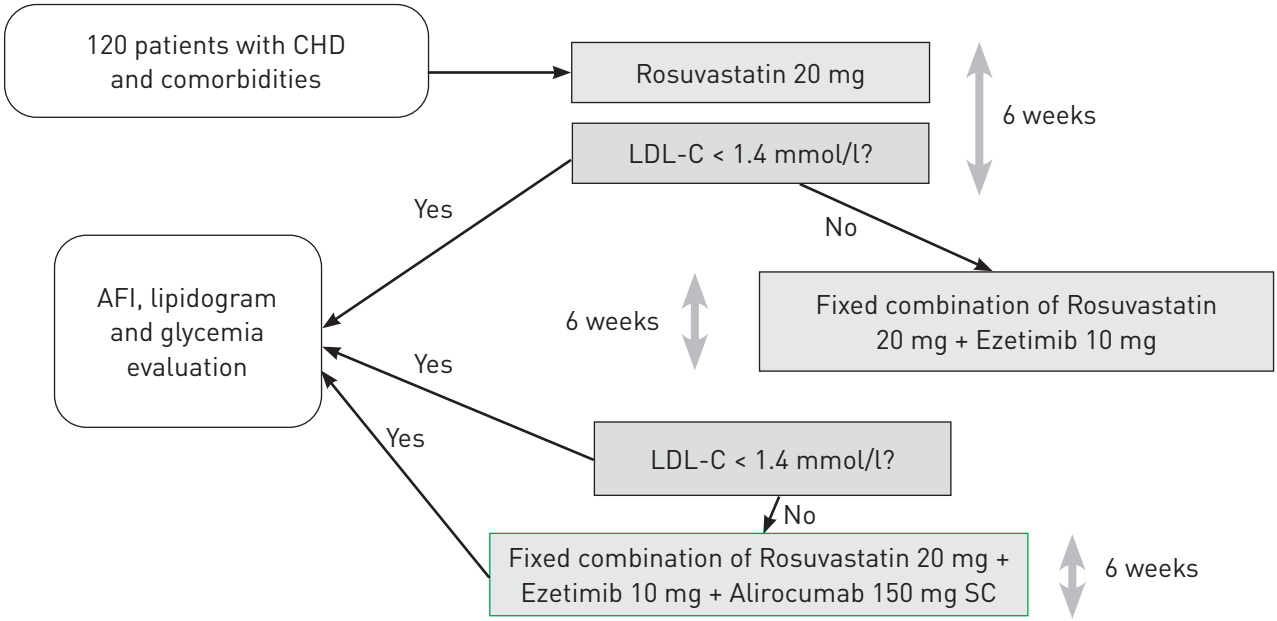

Fig. 1. Study design

el; 1 patient was referred to a regional lipid center for further differential diagnosis of suspected familial hypercholesterolemia. The dynamics of LDL-C target achievement are presented in Figure 2.

Table 1. **Characteristics of study participants by cohort**

Parameter	Cohort 1 n=33	Cohort 2 n=72	Cohort 3 n=15	p
Mean age (M±m)	64±3	63±4	69±2	0.04
History of CVD, n (%)	25 (75.7 %)	54 (75 %)	13 (87 %)	0.03
Smoking, n (%)	19 (58 %)	40 (56 %)	10 (67 %)	0.04
BMI 25-30 kg/m2, n (%)	15 (45 %)	29 (40 %)	6 (40 %)	0.03
BMI 30-39 kg/m2, n (%)	7 (21 %)	15 (20 %)	4 (27 %)	0.02
AH, targeted BP not achieved, n (%)	10 (30 %)	38 (53 %)	7 (47 %)	0.04
CHF, Stage 1, n (%)	14 (42 %)	47 (65 %)	7 (47 %)	0.04
Metabolic syndrome, n (%)	6 (18 %)	11 (15 %)	2 (13 %)	0.04
Type 2 DM, n (%)	8 (32 %)	27 (38 %)	4 (27 %)	0.03

Note. p<0.05.

Based on the achieved LDL-C level and the regimen required to reach it, patients were divided into three cohorts (Cohorts 1–3). Clinical and anamnestic characteristics of the cohorts are shown in Table 1.

An analysis of LDL-C target achievement dynamics in relation to additive factors was conducted using linear regression. Statistically significant associations were observed for parameters such as blood pressure control, body mass index, and Lp(a) level. These results are presented in Table 2.

During the analysis of AGEs using autofluorescence at baseline and at the 4th visit, median values of the autofluorescence index (AFI) were obtained for patients in all three cohorts (Table 3).

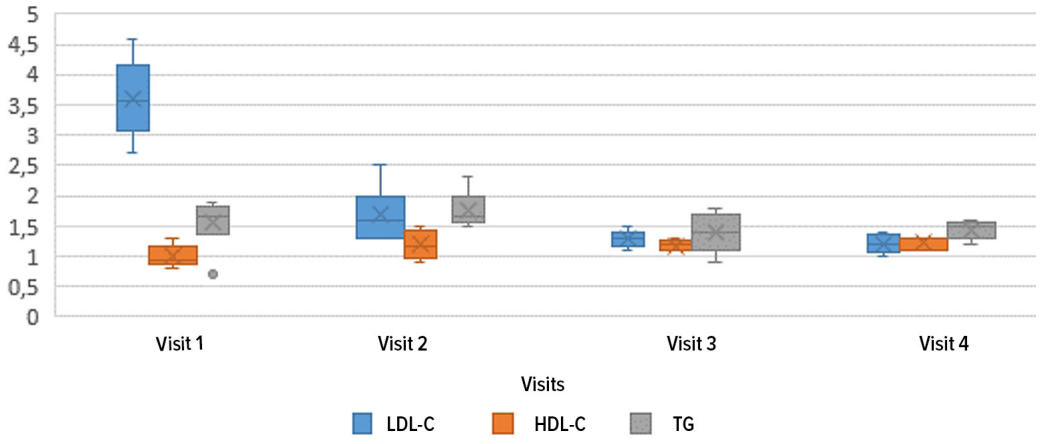

Fig. 2. Dynamics of achieving the target level of LDL-C by visits

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Table 2. **Analysis of the dynamics of LDL-C depending on the control of hypertension, Lp (a)**

	B	Std. error	t	p
Intercept	1.080	0.064	17.014	< 0.001*
Contolled AH	0.092	0.042	2.165	0.039*
Lp(a)	0.269	0.081	3.334	0.002*

Note. * the differences in the parameters are statistically significant (p < 0,05).

Table 3. **Summary of AFI characteristics by cohort**

Parameters	Cohort			p
	Cohort 1	Cohort 2	Cohort 3	
AFI before treatment, Me [IQR]	1.80 [1.80; 2.05]	3.05 [2.55; 4.03]	5.00 [4.90; 5.00]	p<0.05
AFI at 6 weeks, Me [IQR]	1.80 [1.80; 2.05]	3.00 [2.55; 4.00]	4.90 [4.70; 4.95]	p<0.05
AFI at 12 weeks, Me [IQR]	1.80 [1.80; 1.95]	2.90 [2.48; 3.98]	4.90 [4.30; 4.95]	p<0.05
AFI at 18 weeks, Me [IQR]	1.75 [1.70; 1.95]	2.85 [2.30; 3.80]	4.90 [4.15; 4.90]	p<0.05

Note. p<0.05.

The AFI demonstrated a decreasing trend at weeks 6, 12, and 18, respectively. At the final stage of the study, the median values were 1.75 in cohort 1 on monotherapy (CI: 1.70; 1.95), 2.85 in cohort 2 (CI: 2.30; 3.80), 4.9 in cohort 3 on triple therapy (CI: 4.15; 4.90).

To assess the relationship between the achieved LDL-C level and the AFI value after 18 weeks of treatment, a correlation analysis was performed, with the strength of association interpreted using Chaddock's scale (Figure 3). The resulting value of ρ = 0.388 indicates a statistically significant moderate correlation at p < 0.05.

Discussion

In the course of this prospective study, cascade-based multicomponent cholesterol inhibition in male patients with CHD was performed. The key parameter for cohort distribution was the method by which the target LDL-C level of less than 1.4 mmol/L was achieved — this being a strict requirement for patients at very high cardiovascular risk [11,12].

According to the lipid transport system dynamics illustrated in Figure 2, it is evident that at the first visit (baseline), all measured LDL-C values clearly exceeded the target threshold — not a single patient had reached an LDL-C level below 1.4 mmol/L.m. However, by the second visit, 27.5% of patients (n = 33) had achieved the target level. By the third visit on dual lipid-lowering therapy, 60% (n = 72) reached the goal, and on triple intensified therapy, 12.5% (n = 15) achieved it — a trend consistent with global study findings [13–15].

The patients were characterized by the following parameters: mean age — 65 ± 3 years, history of cardiovascular disease — 75%, smoking — 57.5%, uncontrolled arterial hypertension — 46%, type 2 DM — 32.5%. Detailed cohort characteristics are shown in Table 1. Among the factors directly influencing LDL-C target achievement, a statistically significant correlation was found with elevated Lp(a) levels and poor blood pressure control.

During the evaluation of AGEs using autofluorescence and calculation of the AFI, the following patterns were identified: although the baseline AFI level in each cohort was independent, the index tended to

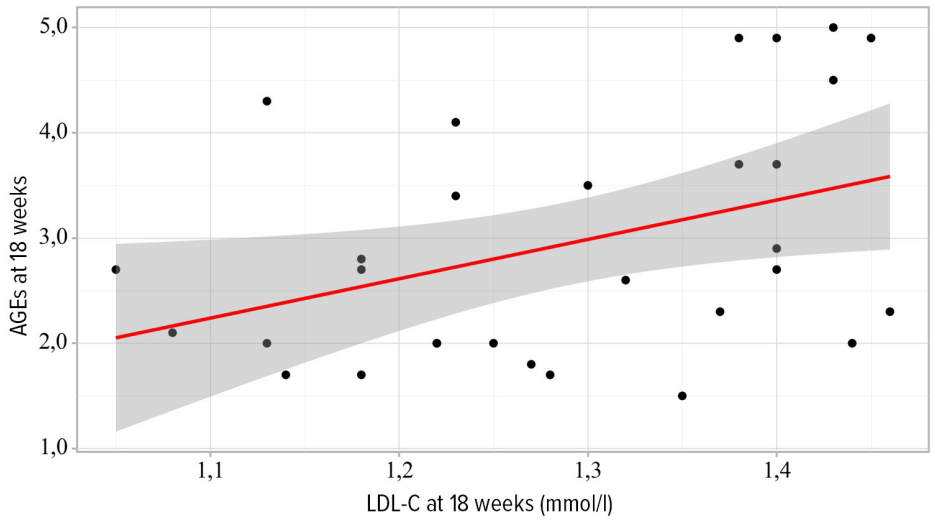

Fig. 3. Regression function graph characterizing the dependence of AGEs on LDL-C at 18 weeks from the start of the study

decline in parallel with achievement of LDL-C goals. The reduction of cholesterol remnants undoubtedly occurred alongside total cholesterol and LDL-C decreases, which ultimately may have led to weakened glycation end-product formation on lipid substrates, reduced AGE synthesis, and a corresponding AFI reduction by 3% in cohort 1, by 3.3% in cohort 2, and by 2% in cohort 3, respectively [16, 17].

To test the hypothesis of a relationship between achieving LDL-C targets and reducing the AFI, a correlation analysis was performed to assess the strength of association, if present (see Figure 3). Upon constructing the regression model, a moderate-strength relationship ($p < 0.05$) was identified, confirming a significant link between these parameters. This relationship was most pronounced in cohort 3 (triple-combination therapy) and least in cohort 1 (statin monotherapy). This suggests that determiningAGEs via the autofluorescence index could serve as a modeling parameter for residual cardiovascular risk. Provided there is adequate control of additive factors — such as glycemia, blood pressure regulation, smoking cessation, and increased physical activity — a further prospective reduction in newly formed AGEs may be possible. This, in turn, may attenuate the intensity of irreversible glycation reactions and lower AFI levels, although this requires further investigation [18–20].

Conclusion

Thus, AFI is influenced by multiple factors. In the process of achieving target LDL-C levels through various lipid-lowering regimens, a reduction in glycation end-product formation intensity occurs, reflecting a decrease in residual cardiovascular risk in patients with CHD — a finding supported by the moderate correlation strength according to the Chaddock scale ($p<0.05$). Multicomponent cholesterol inhibition more reliably reduces residual risk compared to statin monotherapy, and AFI measurement in daily practice may serve as a convenient, non-invasive method for assessing residual risk in patients with CHD.

Conflict of interests: none declared.

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Dynamics of cardiological parameters in athletes after COVID-19 infection

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Abstract

The aim of the study was to investigate the impact of coronavirus infection (COVID-19) on the cardiovascular system (CVS) of athletes and the dynamics of relevant parameters during physical activity after the recovery.

Methods. A total of 62 marathon runners (training duration: 3 to 7 years; mean age: 43.8 ± 3.5 years) were examined. The participants were divided into two groups: Group 1 (n=34) included athletes who had recovered from a mild form of COVID-19; Group 2 (n=28) included athletes without a history of COVID-19. All participants underwent electrocardiography (ECG), 24-hour Holter ECG monitoring, echocardiography (EchoCG), and Doppler echocardiography using the ALOKA ProSound 6-Premier system (Japan) at rest and after physical exertion. Cardiovascular response types and recovery dynamics were assessed.

Results. EchoCG revealed no significant differences in chamber or wall sizes, except for the right atrium ($p<0.05$). In Group 1, 47.1% of participants had pericardial effusion >5.0 mm (mean 5.70±0.27 mm) ($p<0.05$), peaking at 7.0 mm by the 2nd–3rd month post-recovery and persisting up to six months. Physical exertion revealed increased grades of mitral regurgitation ($p<0.05$, Fisher's exact test), with no increase in aortic regurgitation

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(p=1.000). Holter monitoring showed supraventricular extrasystoles 46.8 times more frequently and ventricular extrasystoles 6.4 times more frequently (RYAN grade I) in Group 1. Episodes of paroxysmal supraventricular tachycardia were recorded in 23.5% of athletes and ventricular tachycardia in 5.8%. Asymptomatic ST-segment depression (downsloping and horizontal types) was observed in 17.5%. A hypertensive response to exertion (p<0.01) and delayed blood pressure recovery (up to 3 months) were also recorded.

Conclusion. Despite the mild clinical course of COVID-19, cardiovascular changes during physical activity peaked at 2–3 months post-recovery and persisted for at least six months. These findings should be considered when determining fitness to return to training and competition.

Keywords: COVID-19, athletes, cardiovascular system, dynamics, physical activity, electrocardiography.

Conflict of interest: none declared.

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Introduction

At the end of 2019, an outbreak of a novel infection occurred in the People's Republic of China. In 2020, the World Health Organization (WHO) officially designated the disease as COVID-19 ("Coronavirus disease 2019"). The International Committee on Taxonomy of Viruses named the pathogen SARS-CoV-2. Subsequently, the Delta and Omicron variants significantly increased viral transmissibility[1]. Among all SARS-CoV-2 variants, Omicron, characterized by multiple mutations in the spike (S) protein, demonstrated the highest level of contagiousness [1]. As of May 8, 2024, there have been 704,753,890 confirmed cases of COVID-19 in 231 countries, with over 7.0 million deaths worldwide; the case fatality rate stands at 0.99%[2].

Contemporary literature typically focuses on patients who experienced severe forms of the disease [2–4]. Among physically active individuals, COVID-19 often manifests with minimal clinical symptoms. Despite this, their training regimens are usually suspended or reduced for a short period. After recovery, many athletes, motivated by concerns about losing physical conditioning and competitive performance, return to full training too quickly, placing themselves at increased risk for complications [5, 6].

The aim of the study is to evaluate the impact of COVID-19 on the cardiovascular system (CVS) in athletes and assess the dynamics of cardiovascular indicators during the recovery period.

Methods

A total of 62 athletes (mean age 43.8 ± 3.5 years) were examined, of whom 34 (54.8%) had a history of mild COVID-19 and 28 (45.2%) had not been infected. All participants underwent assessments before and after physical exertion testing (ET).

Following a clinical examination, all athletes underwent electrocardiography (ECG), 24-hour Holter monitoring (HMECG), echocardiography (EchoCG), and Doppler echocardiography (Doppler EchoCG) using the ALOKA ProSound 6-Premier system (Japan), both at rest and after a combined stress test consisting of a 3-minute jog followed by a 15-second sprint at maximum intensity. The type of cardiovascular response and recovery parameters were recorded.

Statistical Analysis

Statistical analysis was performed using StatTech v 2.1.0. Differences were considered statistically significant at $p < 0.05$. If the data did not follow a normal distribution, results were presented as the median (Me) and interquartile range (Q1–Q3). The Mann–Whitney U test was used to assess differences in independent variables. Categorical data were described using absolute values and percentages. Comparison of proportions in 2×2 contingency tables was carried out using Fisher's exact test.

[1] Temporary guidelines: prevention, diagnosis and treatment of a coronavirus disease 2019 (COVID-19) of the Ministry of Health of the Russian Federation (version 16 of 18/08/2022)/ Russian

[2] World health organization /https://data.who.int/ dashboards|covid19|cases (date of access 08.05.2024). Russian

Results

According to EchoCG data, there were no significant differences in the sizes of the chambers and walls of the heart in the two groups, except for the the right atrium (p<0.05) (Table 1).

Table 1. **Echocardiographic parameters in the studied groups of athletes**

Parameters	Group 1 (M±m)	Group 2 (M±m)	p
Age, years	44.29±1.69	42.6±3.62	0.674 n/s
Aortic diameter (annulus), mm	27.68±0.54	26.00±1.06	0.165 n/s
Aortic diameter (sinus of Valsvalva), mm	36.69±0.84	35.27±1.23	0.345 n/s
Left atrium cavity, mm	40.78±0.62	39.37±1.05	0.254 n/s
Left ventricle cavity, mm	51.21±0.90	48.67±1.32	0.119 n/s
Interventricular septum thickness, mm	10.30±0.19	9.99±0.37	0.459 n/s
Left ventricle posterior wall thickness, mm	9.25±0.20	8.90±0.33	0.369 n/s
Right ventricle cavity, mm	38.79±0.50	37.47±1.12	0.287 n/s
Right atrium cavity, mm	43.40±0.76	40.23±1.19	⩽0.05
Ejection fraction, %	70.14±1.04	68.43±1.21	0.289 n/s

Note. Significant parameters are highlighted at p < 0.05.

Among individuals who had recovered from COVID-19, pericardial effusion greater than 4.0 mm was observed more frequently. Two subgroups were identified: athletes with pericardial fluid less than 5.0 mm and those with more than 5.0 mm. Individuals with effusion related to trauma, thyroid disease, rheumatologic or oncologic conditions, a history of myocardial infarction, or prior cardiac surgery were excluded from the analysis.

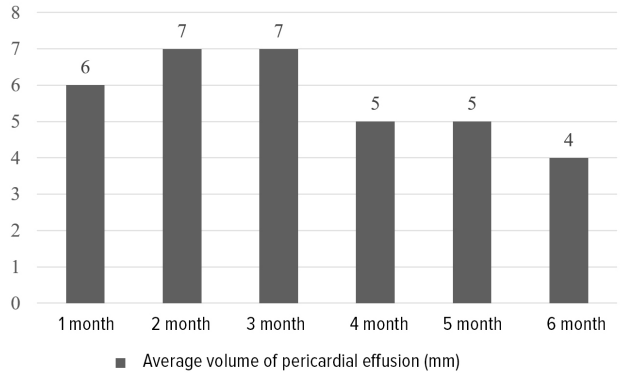

Fig. 1. Dynamics of pericardial effusion in the convalescent period (mm)

A pericardial effusion exceeding 5.0 mm was detected in 47.1% of the participants (mean: 5.70 ± 0.27 mm, p < 0.05) who had previously contracted COVID-19. During the first month, 6% of athletes in group 1 had an average effusion of 6.0 mm. In the second and third months, 31% of individuals presented with effusions reaching up to 7.0 mm. In the fourth and fifth months, 13% showed effusions up to 5.0 mm, and by the sixth month, the volume had decreased to 4.0 mm (Figure 1).

When assessing the degree of mitral and aortic regurgitation using Doppler EchoCG data (at rest and after ET), the following data were obtained (Tables 2-4).

Table 2. **Mitral and aortic regurgitation before and after exercise testing**

Studied groups	Paravalvular mitral regurgitation, %	Grade I mitral regurgitation, %	Paravalvular aortic regurgitation, %	Grade I aortic regurgitation, %
Group 1 before ET	5.9	-	5.9	-
Group 1 after ET	-	20.6	14.7	8.8
Group 2 before ET	7.1	-	-	-
Group 2 after ET	10.7	-	3.6	-

Table 3. **Analysis of the mitral regurgitation parameter after physical exercise**

Parameter	Categories	COVID-19		p
		no history of COVID-19	history of COVID-19	
Mitral regurgitation after ET	Paravalvular mitral regurgitation	3	0	0.008*
	Grade I mitral regurgitation, %	0	7	

Note. * – differences in parameters are statistically significant (p < 0.05).

Table 4. **Analysis of the aortic regurgitation parameter after physical exercise**

Parameter	Categories	Covid-19		p
		No history of COVID-19	History of COVID-19	
Aortic regurgitation* after ET	Paravalvular aortic regurgitation	1 (100.0)	5 (62.5)	1.000
	Grade I aortic regurgitation	0 (0,0)	(37,5)	

Note. * When comparing the aortic regurgitation parameter, we were unable to identify significant differences

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Table 5. **Holter ECG monitoring data in the study groups**

Groups	AV block, %	SA block, %	Supraventricular extrasystoles, count	Ventricular extrasystoles, count	Episodes of paroxysmal tachycardia, %	Early ventricular repolarization syndrome, %	ST-segment depression of downsloping and horizontal type, %	Bundle branch block, %	QT prolongation, %
Group 1	11.7	8.9	41514 (avg.1221) 50.9 /hour	10508 (avg 309.1) 12.9 /hour	supraventricular-23.5 ventricular-5.8	14.7	17.5	11.8	8.9
Group 2	10.7	3.6	732 (avg. 26.1)-1 / hour	1354 (avg 48.3) -2 / hour	supraventricular -3.6	14.3	-	3.6	-

According to the presented table, statistically significant differences were identified based on the variable "COVID-19" (p = 0.008) using Fisher's exact test.

The odds of mitral regurgitation grade I were higher in the group of individuals who had recovered from COVID-19 compared to those who had not contracted the infection; however, the difference in odds did not reach statistical significance.

ECG analysis revealed that after the functional load test (at 1–2 minutes of the recovery period), the right atrial overload was reliably observed in 59% of cases in group 1 and persisted in 26.5% of athletes during the five-month convalescent period. Sinus arrhythmia was more frequently detected during the first four months post-COVID-19 (20.6%), while ventricular extrasystoles were most commonly observed in the second month (8.8%).

No statistically significant differences were found in repolarization disorders (T-wave flattening or inversion) between the two groups (50% in group 1 vs. 55.5% in group 2), with the highest incidence observed in month 6 (11.8%).

HMECG demonstrated statistically significant differences in group 1: the frequency of supraventricular extrasystoles was 46.8 times higher, and ventricular extrasystoles were 6.4 times more common (Ryan Grade I). Paroxysmal supraventricular tachycardia during physical exertion was identified in 23.5% of subjects, while ventricular tachycardia occurred in 5.8%. Asymptomatic ST segment depression (descending and horizontal types) was observed in 17.5% of athletes in group 1; such changes were not recorded in the control group (Table 5)

When analyzing the types of response to physical exercise, an atypical (hypertensive) response was recorded significantly more often (p<0.01) (Table 6).

Table 6. **Types of cardiovascular system responses to physical exercise in the studied groups**

Categories	Type of response		Mann–Whitney U Test, p
	Normotonic response, %	Hypertensive response, %	
Group 1	64.7%	35.3	0.003*
Group 2	96.4%	3.6%	

Note. * The differences in the parameters were statistically significant (p < 0.01).

56% of athletes in the first group exhibited delayed blood pressure recovery (p < 0.01). No statistically significant differences were found in heart rate recovery between the groups (Figure 2).

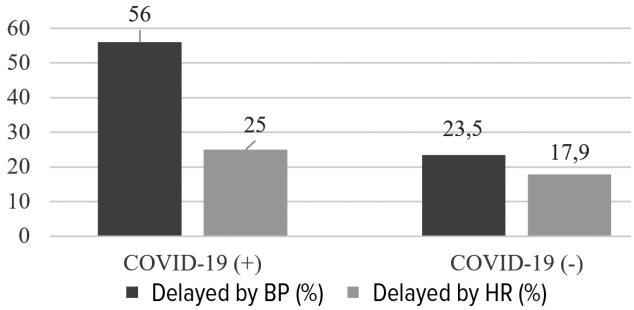

Fig. 2. Recovery time in the studied groups, (%)

The hypertensive type of response and delayed blood pressure recovery persisted during the 2nd and 3rd months of the convalescent period. Delayed heart rate recovery was observed up to 4 months (Fig. 3).

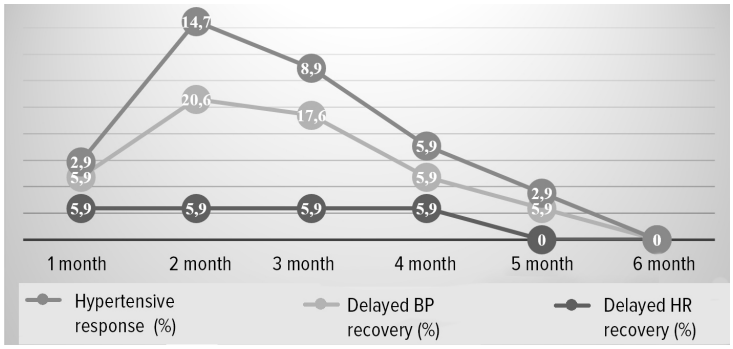

Fig. 3. Recovery dynamics after COVID-19

Discussion

In modern literature, most studies report findings among patients who experienced severe forms of COVID-19 [2] and focus on the role of comorbidities in disease severity [3]. Long-term alterations such as ECG and echocardiographic abnormalities and an increased incidence of pericardial effusion have been documented 6–12 months after hospital discharge [4,7,8]. Our study focused on cardiovascular changes in athletes who had recovered from mild COVID-19 and resumed marathon training. It was found that, post-clinical recovery, pericardial effusion exceeding 5.0 mm was observed in 47.1% of individuals ($p<0.05$), with the greatest effusion (up to 7.0 mm) seen within the first three months, persisting for up to six months.

Sinus arrhythmia was more frequently recorded within the first four months post-COVID-19, while ventricular extrasystoles were most prevalent during the second month of training. Following exercise stress testing, dynamic right atrial overload was identified and persisted for up to five months, affecting right atrial size, as confirmed by echocardiographic data.

No significant differences were found in repolarization disturbances, though such changes persisted and reached a peak by month six, likely due to ongoing training stress in both groups. HMECG monitoring revealed a significantly higher incidence of supraventricular and ventricular extrasystoles (Ryan Grade I) in post-COVID athletes. Exercise-induced paroxysmal supraventricular and ventricular tachycardia episodes were also recorded, along with asymptomatic ST-segment depression.

In the non-COVID group, these changes were not observed. Following exercise testing, a significant increase in mitral regurgitation grade was noted, persisting for up to five months of the convalescent period. Additionally, a hypertensive response to physical load ($p<0.01$) and delayed post-exercise blood pressure recovery were more frequently observed in the post-COVID group, lasting up to three months.

Conclusion

Among marathon athletes who had recovered from mild COVID-19, supraventricular and ventricular extrasystoles were recorded several times more frequently compared to those who had not contracted the virus. In this group, asymptomatic, exercise-induced episodes of paroxysmal tachycardia were also identified. Painless ST-segment depression of upsloping and horizontal type was observed in 17.5% of individuals with a history of mild COVID-19. Additionally, pericardial effusion exceeding 5.0 mm was detected more than three times as often in these individuals compared to non-infected athletes, with persistence for up to six months post-infection.

Thus, the findings indicate that even after a mild clinical course of COVID-19, and in the absence of overt symptoms or residual clinical signs, cardiovascular involvement may persist for at least six months in physically active individuals. These observations should be carefully considered when making decisions about resuming training or participation in competitive sports.

Conflict of interests: none declared.

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Possibilities of immunological diagnostics of chronic heart failure in patients with rheumatoid arthritis

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Abstract

Cardiorheumatology is one of the most pressing fields in current medical research, with numerous unresolved issues. Systemic inflammation contributes to the progression of atherosclerosis, alterations in the morphofunctional characteristics of the myocardium, an increase in recurrent hospitalizations, and a worsened prognosis.

Methods. This review presents modern categories of immunological biomarkers, including those indicating direct myocardial injury, secondary angiogenesis, myocardial fibrosis, and general vascular risk markers, which hold significant potential for assessing the progression of chronic heart failure in the context of rheumatoid arthritis.

Results. The presented groups of markers are not currently included in clinical guidelines for the management of chronic heart failure. However, they demonstrate meaningful associations with established parameters such as natriuretic peptides, left ventricular ejection fraction, and indicators of diastolic dysfunction, thereby offering practical value in daily clinical decision-making.

Conclusion. Immunological diagnostics in evaluating cardiovascular diseases associated with comorbid conditions is an emerging and actively evolving field. This approach is particularly relevant for patients with chronic heart failure and rheumatoid arthritis, given the strong pathophysiological link between autoimmune inflammation and heart failure development. Markers such as galectin-3, pentraxin-3, transforming growth factor-beta, γ-carboxyglutamate-containing matrix protein), neopterin, and vascular endothelial growth factor may help predict early signs of CHF decompensation.

Keywords: chronic heart failure, rheumatoid arthritis, galectin-3, pentraxin-3, transforming growth factor-beta, vascular endothelial growth factor.

Conflict of interests: none declared.

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Introduction

Chronic heart failure (CHF) and rheumatic diseases are among the most common chronic non-communicable conditions that lead to persistent disability, deteriorate patients' quality of life, and negatively affect prognosis. The global prevalence of CHF is estimated to be between 1–2% [1]. Among individuals aged over 65, the prevalence increases sharply, exceeding 10%. Precise estimation of CHF prevalence remains difficult due to varying inclusion criteria in different registries, significant heterogeneity in clinical presentations depending on disease stage and left ventricular ejection fraction (LVEF), and differences in patient adherence to regular follow-up for disease monitoring. According to pooled data from various registries, the global number of patients with CHF is estimated to range between 23 and 37.7 million [2]. In the Russian Federation, the average number of patients with CHF has increased from 8 to 12.3 million over the past decade [3]. This growing burden poses a significant challenge to national healthcare systems.

The increase in CHF cases is primarily driven by a high prevalence of arterial hypertension (AH), coronary heart disease (CHD), obesity, and type 2 diabetes mellitus. AH is the leading cause of CHF in 95.5% of cases, followed by CHD in 69.7% [4]. Valvular heart diseases have become less common as a cause of CHF (only 4.3%) due to the advancement of surgical treatment methods.

Rheumatic diseases — comprising over 80 nosological entities — have a well-established role in contributing to long-term disability, declining health status, and increased risk of cardiovascular complications. Numerous studies and meta-analyses confirm that rheumatic conditions significantly contribute to the development of myocardial infarction, stroke, thrombosis, and the progression of AH, CHF, and atherosclerosis [5]. Among the most frequently encountered rheumatic disorders with an autoimmune inflammatory basis is rheumatoid arthritis (RA), which is also commonly associated with cardiovascular disease. In the Russian Federation, the prevalence of RA is approximately 610 cases per 100,000 population [6]. However, the exact prevalence of CHF among RA patients is difficult to determine, as most registries and studies focus on clinically overt CHF, particularly in hospitalized patients with decompensation.

Estimates suggest that the coexistence of CHF and RA ranges from 2.6% to 11.6% in the general population. Notably, early-onset RA has been associated with an increased risk of both ischemic and non-ischemic CHF compared to individuals without RA [7]. Prospective studies indicate that patients with both CHF and RA have higher all-cause mortality than those without RA [8]. Interestingly, preserved LVEF in CHF is more frequently observed in patients with RA than in those without, possibly due to the beneficial impact of anti-inflammatory therapy on myocardial structure and function, although this remains a subject of ongoing debate [9]. According to registry data, mortality rates among CHF patients with RA are twice as high compared to CHF patients without RA [10].

Thus, the influence of RA on the course of CHF is a topic of increasing clinical and scientific relevance. Key areas of interest include early detection of CHF progression, the effects of anti-inflammatory therapy for RA in CHF patients, and the ability to predict the risk of heart failure decompensation.

Methods

A non-systematic review of domestic and international literature on the research topic was conducted using comprehensive sampling in the databases PubMed, RSCI (Russian Science Citation Index), and eLibrary. The search was performed using the following keywords and their combinations: arterial hypertension, coronary heart disease, chronic heart failure, rheumatoid arthritis, nonsteroidal anti-inflammatory drugs (NSAIDs), as well as combined queries such as chronic heart failure and rheumatoid arthritis, coronary heart disease and rheumatoid arthritis, arterial hypertension and rheumatoid arthritis, chronic heart failure and NSAIDs. The review included analysis of data from literature reviews, original research articles, and meta-analyses. In total, 65 sources were analyzed. The search depth covered an 8-year period from 2014 to 2023.

Results and discussion

The role of systemic autoimmune processes in the progression of chronic heart failure

Chronic autoimmune inflammation is a well-established factor contributing to the destabilization of cardiovascular diseases, significantly worsening both disease prognosis and overall survival. Persistently elevated levels of C-reactive protein, interleukin-1, and interleukin-6 promote endothelial dysfunction

and accelerate the progression of atherosclerosis. It has been demonstrated that patients with rheumatoid arthritis (RA) have a higher incidence of atherosclerotic processes compared to the general population [11]. The inflammation exerts direct cytotoxic effects on myocardial cells and microcirculation, thereby accelerating myocardial remodeling. As is known, the synovial membrane is the primary target of the immune process in RA. The immunological cascade characteristic of RA leads to sustained high concentrations of pro-inflammatory cytokines and mononuclear cells in the bloodstream. Cellular and interstitial changes in the myocardium associated with RA are believed to be contributors to the development of CHF.

Key pathophysiological changes identified by researchers include: myocardial cellular and interstitial remodeling, hypertrophy, enlargement of the left atrium, ventricular dilation, alterations in collagen structure, and interstitial fibrosis [12]. One of the central mechanisms in the development of CHF in RA is the overproduction of matrix metalloproteinases (MMPs), a process activated by tumor necrosis factor-alpha (TNF-α). Dysregulation of MMP activity promotes collagen synthesis and left ventricular dilatation [13].

Prolonged systemic inflammation also exerts a detrimental impact on endothelial function, arterial intima structure, and the balance of vasodilatory and vasoconstrictive mediators, significantly increasing the risk of systemic atherosclerosis progression. These changes substantially elevate the likelihood of acute cardiovascular events in this patient group [14].

Several small-scale prospective studies have shown that even in patients with RA and arterial hypertension (AH) who receive maximally tolerated doses of antihypertensive therapy, there is progressive worsening of arterial stiffness, increased intima-media thickness, and elevated peripheral vascular resistance [15]. Taken together, these pathophysiological mechanisms are expected to negatively impact disease prognosis in patients with CHF, particularly when heart failure arises due to coronary heart disease (CHD) and AH in the context of RA.

Systemic autoimmune inflammation has been shown to contribute to the development of cardiac arrhythmias in patients with CHF and RA, representing yet another destabilizing factor in the progression of CHF within this comorbid context. According to the Danish National Registry data published in 2017, the incidence of atrial fibrillation (AF) in patients with RA was 40% higher compared to the control group [16, 17]. Several studies have supported the existence of a strong link between systemic inflammation and the development of AF [18, 19]. Researchers suggest that the primary mechanisms responsible for arrhythmogenesis in these patients include the influence of circulating autoimmune complexes, which interfere with potassium and L-type calcium currents, as well as M2-muscarinic cholinergic and beta-adrenergic receptor function [20, 21].

Another critical factor exacerbating CHF in the context of systemic autoimmune disease is the presence of chronic pain syndrome. Persistent pain stimulates the production of numerous pro-inflammatory mediators, such as prostaglandins, interleukins, and tumor necrosis factor-alpha (TNF-α), which have detrimental effects on cardiovascular function. Meta-analyses have shown that chronic pain associated with rheumatic diseases significantly increases the risk of CVD in the general population. Moreover, a statistically significant association between chronic pain syndrome and increased mortality has been demonstrated [22].

Although specific studies examining the direct impact of chronic pain on CHF in patients with RA remain limited, several investigations have highlighted a significant deterioration in quality of life among patients with CHF who experience persistent pain [23].

Taken together, these comorbid pathophysiological mechanisms considerably worsen the course of CHF in patients with RA (Figure 1). This underscores the need for the identification and clinical implementation of early diagnostic markers of CHF decompensation in the setting of RA, with the aim of preventing disease progression and improving patient outcomes.

Immunological markers for the diagnosis of chronic heart failure in the presence of rheumatoid arthritis

To date, a significant number of immunomodulatory cytokines have been identified that may serve as diagnostic tools in CHF. These biomarkers reflect various stages of the inflammatory process and, depending on their properties, can provide insight not only into the presence and severity of CHF, but also into specific pathological changes occurring in the myocardium. Such markers, according to experts, may

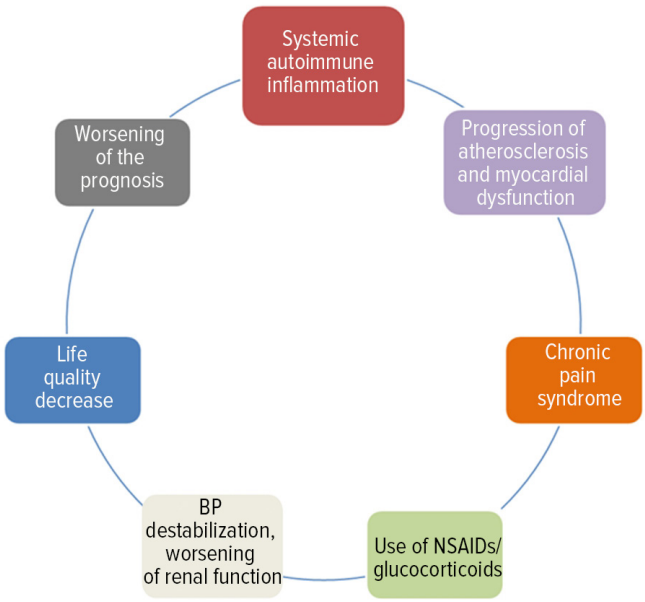

Fig. 1. Cascade of pathogenetic processes in patients with chronic heart failure and rheumatoid arthritis

pave the way for novel therapeutic strategies targeting disease progression.

Figure 2 presents several groups of biomarkers that are not currently included in major clinical guidelines but are considered promising indicators of myocardial dysfunction in CHF.

Cytoplasmic fatty acid-binding proteins (FABPs) are an emerging class of biomarkers indicative of myocardial injury. These proteins play a key role in fatty acid metabolism and regulation. Six isoforms of heart-type FABPs (Heart-FABPs) are known to be sensitive to myocardial damage. Upon myocardial injury, Heart-FABPs are rapidly released into the bloodstream, reaching peak concentrations approximately three hours after an acute myocardial infarction. This makes them useful for the early detection of myocardial injury [24]. Beyond acute coronary syndromes, preliminary data suggest that H-FABPs may also serve as predictive markers for worsening CHF, myocardial ischemia, impaired renal function, and overall prognosis in heart failure patients [25]. There are no data yet on the use of this marker in patients with RA, but given the mechanisms of this association, studying its properties in RA may be promising.

Excessive lipid peroxidation, particularly of the atherogenic low-density lipoprotein (LDL) fraction, is a critical factor in atherosclerotic plaque formation. Given the well-documented impact of systemic inflammation on atherogenesis, investigating oxidative stress markers may offer valuable insight into the studied comorbidity. Oxidized LDL are taken up by macrophages and smooth muscle cells in the vascular wall, leading to the formation of foam cells—key components of early atherosclerotic lesions. These modified lipoproteins elicit an immune response, resulting in the production of autoantibodies to oxidized LDL (oLAB) [26].

In a study by F. Besli et al., patients with CHF exhibited significantly elevated levels of oLABs compared to controls, with a strong correlation between oLAB concentrations and NT-proBNP levels [27]. Similarly, B. Nowak et al. reported increased oLAB levels in a cohort of 37 patients with RA relative to healthy individuals. Furthermore, oLAB levels were positively correlated with RA disease activity, carotid intima-media thickness, SCORE index, erythrocyte sedimentation rate (ESR), and disease duration [28].

These findings suggest not only the prognostic utility of oLABs but also reinforce the mechanistic links underlying the comorbid relationship between CHF and RA. The integration of such immunological markers into clinical practice may offer new opportunities for early risk stratification, diagnosis, and targeted intervention.

Chronic myocardial and vascular damage in the context of systemic autoimmune disease triggers secondary (pathological) angiogenesis, a phenomenon observed in various pathological conditions.

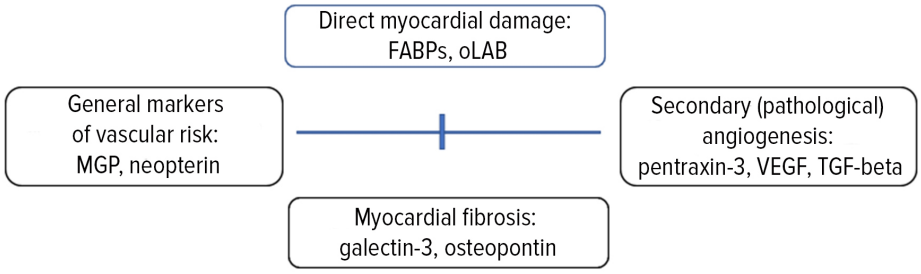

Fig. 2. Markers of systemic autoimmune inflammatory processes

Currently, secondary angiogenesis is known to develop in CHF, cancer and metastasis, RA, bronchial asthma, obesity, psoriasis, and age-related macular degeneration, among others [29]. Investigating this process in patients with CHF has become one of the most relevant areas of modern cardiology. More than 30 immunological biomarkers of pathological angiogenesis have been described. One of the most significant among them is Pentraxin-3, a protein synthesized locally at the site of inflammation. Pentraxin-3 has been identified as a potential prognostic marker of adverse outcomes in patients with CHF [30]. Its elevated levels, particularly values above 3.64 ng/mL, have been associated with a higher risk of disease progression and mortality in CHF patients [31–33].

Another important angiogenic factor is vascular endothelial growth factor (VEGF). VEGF proteins are key regulators of capillary formation and oxygen delivery in hypoxic tissues. Several studies have demonstrated that measuring VEGF levels alongside NT-proBNP enhances diagnostic accuracy in identifying CHF decompensation in patients presenting with dyspnea [34]. Meta-analyses have shown that VEGF levels are significantly elevated in patients with RA compared to healthy controls and correlate with disease activity indices [35]. According to S. Dai, VEGF may serve as a therapeutic target for evaluating the effectiveness of anti-inflammatory treatment in RA [36].

The transforming growth factor beta (TGF-ß) is another immunomodulatory cytokine of interest, known to indirectly influence multiple biological processes such as myocardial hypertrophy, fibrosis, apoptosis, cellular differentiation, and angiogenesis. TGF-ß production is induced in response to inflammatory stimuli. Small-scale cross-sectional studies have demonstrated significantly elevated TGF-β levels in CHF patients compared to healthy individuals [37]. TGF-ß is being explored as a potential target in RA therapy,

The culmination of the cascade of immune responses, chronic metabolic disturbances, and microcirculatory dysfunction is the development of myocardial fibrosis. The most extensively studied immunological biomarker associated with this process is Galectin-3, a beta-galactoside-binding lectin involved in vascular fibrosis, atherosclerosis, and myocardial remodeling. A circulating level above 17.8 ng/mL is associated with an increased risk of adverse outcomes in patients with CHF. According to experts, Galectin-3 has the highest diagnostic utility among cardiovascular biomarkers not yet included in current clinical guidelines for CHF management [38].

In patients with cardiovascular diseases and RA, multifactorial analyses have demonstrated a significant association between Galectin-3 levels and parameters such as pulse wave velocity, stroke volume, and LVEF [39–41]. In our own study of patients with concomitant CHF and RA, elevated Galectin-3 levels were found to correlate with worsening dyslipidemia, declining renal function, and increased blood pressure [42].

Another biomarker currently under discussion for its prognostic potential in CHF is osteopontin. Physiologically, osteopontin plays a regulatory role in the expression of a number of key cytokines, including interleukins-3, -10, -12, interferon-gamma, integrin avB3, and macrophage activity. It contributes to the remodeling and repair of damaged tissues. Literature sources increasingly highlight its value as a predictor of CHF progression. Studies have shown significantly elevated osteopontin levels in CHF patients compared to healthy individuals [43], with a proportional increase in both osteopontin and circulating T-lymphocytes as CHF severity increases and LVEF decreases [44]. A similar pattern has been observed in RA patients, making osteopontin a promising biomarker in individuals with coexisting CHF and RA.

In the context of examining individual pathogenetic pathways involved in the comorbid association of CHF and RA, as well as the immunological markers that characterize these processes, the search for novel biomarkers that reflect overall cardiovascular risk remains highly relevant. Among such markers, particular attention has been given to matrix Gla protein (MGP), a vitamin K–dependent protein synthesized by vascular smooth muscle cells. MGP plays a critical role in the regulation of vascular calcification, including within atherosclerotic plaques, as well as in various other tissues and organs. According to current research, elevated levels of MGP are associated with both the onset and progression of CHF, as well as cardiac arrhythmias [45]. Furthermore, experimental studies have demonstrated a relationship between MGP expression and inflammatory and degenerative processes within bone and cartilage structures in patients with osteoarthritis [46].

Irreversible myocardial changes resulting from ischemia, prolonged metabolic disturbances, or

apoptosis, which contribute to an increased risk of acute cardiovascular events, may also be predicted through the measurement of neopterin. Neopterin is a pteridine derivative produced by monocytes and macrophages in response to interferon-gamma stimulation. While currently utilized primarily in the diagnosis of viral, bacterial (notably tuberculosis), and parasitic infections [47], growing evidence supports its use as a prognostic marker in cardiovascular diseases.

Elevated neopterin concentrations have been shown to correlate with the severity and extent of atherosclerotic disease, including degree of stenosis and calcification. Increased neopterin levels have also been observed in patients with CHF of both ischemic and non-ischemic origin, with a moderate inverse correlation with LVEF ($r = –0.33$; $p = 0.017$), and a positive correlation with end-systolic left ventricular volume ($r = 0.32$; $p = 0.024$) [48]. Given its connection to both infectious and autoimmune inflammation, neopterin may serve as a promising biomarker in assessing cardiovascular risk in patients with CHF and concomitant RA.

The number of patients with CHF and RA is likely to increase, primarily due to rising life expectancy among individuals with CHD and AH. A current clinical reality is the growing population of patients with CHF with preserved or mildly reduced LVEF — a population whose true size remains uncertain. Another driver of the increased prevalence of this comorbid association is systemic autoimmune inflammation, which contributes to CHF development through a cascade of mechanisms, including cytokine-mediated myocardial and coronary artery damage, vascular stiffness, and cardiac and vascular remodeling.

Based on the analyzed data, it becomes evident that the pathogenesis of this comorbidity is not a simple linear cause-and-effect relationship but rather a complex interplay of interconnected processes. This complexity likely accounts for the wide variety of immunological markers proposed for the diagnosis and monitoring of CHF in the context of RA. The primary challenge in managing this condition lies in predicting episodes of CHF decompensation in patients with RA and developing evidence-based strategies to prevent such outcomes. We believe that priority should be given to the investigation of broad cardiovascular risk biomarkers in large-scale, long-term prospective studies, with the aim of integrating these markers into routine clinical practice.

Conclusion

Patients with CHF and RA require particular attention from both internists and cardiologists due to their markedly elevated risk of CHF decompensation. A critical feature of this association is the development of irreversible myocardial changes at pre-symptomatic stages under the influence of ongoing autoimmune inflammation. From this perspective, an urgent clinical objective is the implementation of immunological screening protocols aimed at identifying high-risk patients early and adjusting therapeutic strategies to mitigate adverse cardiovascular outcomes.

Conflict of interests: none declared.

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Electrocardiography for early diagnosis and prevention of cardiovascular disease in asymptomatic patients

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Abstract

Echocardiography (EchoCG) is a key non-invasive method in the early detection of cardiovascular diseases (CVD) in patients without overt symptoms. In this review, echocardiographic markers that might predict CVD are discussed and EchoCG screening's effectiveness is thoroughly investigated. These markers include systolic and diastolic function analysis and also hypertrophy and dilation of structures of the heart. In this article, different screening strategies, their clinical significance and possible consequences for asymptomatic patients are compared, accentuating the necessity of personalized screening approach, with respect to individual risk of CVD. Studies show that EchoCG may significantly facilitate heart anomalies early diagnosis and potentially lead to well-timed intervention, improving patient outcomes, thus stating the importance of integration of EchoCG into standard screening guidelines for early CVD diagnosis and prevention optimization.

Keywords: echocardiography, cardiovascular disease, left ventricular function, risk factors, screening.

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Introduction

Cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke are the most common cause of death and disability worldwide with their distribution continuously and significantly growing, from 271 million cases and 12.1 million deaths per year in 1990 to 523 million cases and 18.6 million deaths per year in 2019 [1]. While smoking, unhealthy diet, lack of physical activity, arterial hypertension (AH), and diabetes mellitus (DM) still remain being the most influential CVD risk factors, combating them must be prioritized by the public health strategies [2]. Judging from an economic perspective, CVD is considered a significant burden, due to high treatment costs, productivity losses, and social protection expenditure [3]. Ominous growth of the age-standardized rate (ASR) of CVD in high-income countries and among the young indicates the necessity of novel approaches to prophylaxis and disease prevention and management [4]. Echocardiography (EchoCG) is a vital non-invasive diagnostic method, providing highly detailed heart images via ultrasound waves reflection for real-time medical analysis of its structure and function [5, 6]. EchoCG, due to its safety and effectiveness, has become the basic method of cardiac pathology diagnosis, including valvular heart disease, heart failure (HF) and myocardial disorders [7].

Accurate ejection fraction, ventricular function and volume evaluation with no need for exposing patients to invasive procedures are the key advantages that make EchoCG an irreplaceable instrument for diagnosis, disease progression monitoring, and treatment evaluation [8].

Moreover, through providing a rapid way of cardiac function evaluation, EchoCG is of great use in cases of emergency, like myocardial infarction (MI) and heart anomalies, requiring an immediate intervention [5].

Development of echocardiography began in the 1950s, when ultrasound was for the first time used for heart visualization by Swedish researchers Ingvar and Edler, providing momentum for the use of EchoCG as a non-invasive method of cardiac pathology diagnosis [8]. In the 1960s ultrasound technologies became more accessible for medical application, which allowed ultrasound cardiac assessment clinical use [9].

By the 1970s, technology was in the state of rapid development, and the first ultrasound scanners for heart assessment became available in the market. Scanning and data processing technique advancement have resulted in more clear and detailed images. During this decade, a number of technological breakthroughs have facilitated the quality of imaging and expanded the capabilities of various heart diseases diagnostics [9].

Since the 1980s, with the emergence of computer technology and digital data processing methods, EchoCG has made a significant advancement [10]. Nowadays, transthoracic, transesophageal, three-dimensional, and stress echocardiography are used for precise heart disease diagnosis and evaluation, depending on clinical conditions [11].

Based on the increasing role of echocardiography in the diagnosis and evaluation of heart disease, its potential application in predictive medicine should also be considered. By accurately visualizing and analyzing the state of the heart muscle and valves, as well as detecting EchoCG abnormalities such as left ventricular hypertrophy (LVH) and left ventricular dysfunction (LVD). EchoCG offers new opportunities for early detection of CVD risk in patients with no prior history of CVD. This is particularly relevant in light of the increasing incidence of CVD among young people and the population of high-income countries, which demands novel approaches to prevention and monitoring.

The aim of the study is to systematically analyze the literature on using echocardiography to diagnose CVD early in asymptomatic patients. The focus is on evaluating the effectiveness of echocardiographic screening in detecting early signs of CVD that are not yet clinically apparent but have the potential to progress to serious disease. The study aims to identify the most important markers and parameters to evaluate during screening and to compare different screening approaches among asymptomatic patients, in order to provide optimal clinical practice strategies.

The goal is to improve strategies for preventing CVD through early identification and intervention, which can significantly reduce the individual and socioeconomic burden of these diseases.

Methods

Literature review

The study was performed in accordance with Good Clinical Practice standards and the principles of the Declaration of Helsinki. This review article used a systematic approach to analyze the scientific literature,

focusing on the identification, evaluation, and synthesis of evidence on early diagnosis of CVD among asymptomatic patients using EchoCG. Studies were selected from PubMed, Scopus, and Web of Science databases from 2015 to 2023. The search included combinations of the following keywords: "asymptomatic cardiovascular diagnostics", "early diagnosis of CVD", 'echocardiography' and "screening".

Inclusion and Exclusion Criteria

Articles describing clinical trials, observational studies, and meta-analyses evaluating the efficacy and accuracy of EchoCG in the early detection of CVD in asymptomatic patients were included. Studies involving only symptomatic patients, as well as those lacking clear information on study methodology, were excluded.

Data Analysis

Data from the selected sources were systematized to identify major themes and findings. Particular attention was paid to evaluating screening methods, the sensitivity and specificity of echocardiography, and risk predictors of CVD. The findings were then compared and analyzed to determine the most effective approaches to early diagnosis.

Ethical Considerations

For the purposes of this article, only studies that met the ethical standards for conducting clinical trials were considered. These standards include obtaining informed consent from participants, ensuring the anonymity of data, and receiving approval from the appropriate ethics committees.

Limitations

The review article is limited to English-language publications, which may have excluded relevant studies published in other languages. Additionally, the time period of the studies may not reflect the latest technological and methodological advances in echocardiography.

Echocardiographic abnormalities and their clinical significance

There are several EchoCG abnormalities: LVH, LVD, LAD, and aortic root dilation (Table 1).

Left ventricular hypertrophy

LVH refers to an increase in the thickness of the left ventricular wall, which is frequently considered an adaptive response to an elevated workload. The development of LVH is influenced by a number of significant mechanisms, including genetic factors, prolonged AH, and increased cardiac exercise. Genetic predisposition to LVH includes mutations in genes encoding sarcomeric proteins, such as myosin heavy chain (MYH7), cardiac troponin T (TNNT2), and cardiac myosin-binding protein C (MYBPC3) [12]. Genetic variations in these loci can modify sarcomere function, resulting in a reduction in myocyte contractility and an increase in myocyte size, leading to hypertrophy [13].

Hypertension has been demonstrated to induce LVH as an adaptive response intended to minimize

Table 1

Abnormality	Description and pathogenetic mechanism	Diagnosis and risk stratification
LVH	An increased left ventricular (LV) wall thickness is often an adaptive response to an increased workload. Genetic factors include mutations in the MYH7, TNNT2, and MYBPC3 genes, which alter sarcomere function. Physical exertion and hypertension might also play a role.	An increased left ventricular wall thickness is associated with an increased risk of cardiac events (CVEs). Echocardiography is used for the early diagnosis and risk stratification of these events.
LAD	Factors such as hypertension, valve malformations, inflammation, and cardiomyopathies increase the risk of CH by enlarging the left atrial (LA) cavity.	There is an increased risk of CVEs. It is important to use echocardiography to measure left atrial size and function in order to predict atrial fibrillation.
Aortic root dilation	The pathological dilation of the aortic root can result in an aneurysm, aortic dissection, or aortic rupture. Genetic mutations and hypertension have been demonstrated to exacerbate this condition.	Early detection and surgical intervention are of paramount importance due to the potential for severe cardiovascular complications. EchoCG is utilized for the purposes of evaluation and monitoring.
Left ventricular dysfunction	Diastolic dysfunction can lead to dyspnea and an increased risk of hospitalization. Pathogenesis includes genetic and hemodynamic factors that affect myocyte metabolism and structure.	Left ventricular diastolic dysfunction has been identified as a significant marker of CVD risk. Early diagnosis is imperative for the prevention of heart failure (HF), particularly in patients with diabetes or hypertension.

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ventricular wall stress. The study revealed that hypertrophied LV exhibited structural and molecular alterations, including the accumulation of lipid droplets in cardiomyocytes, the upregulation of fatty acid transporter CD36, protein kinase C, and matrix metalloproteinase-2, and the enhanced activation of the phosphatidylinositol 3-kinase/activated protein kinase pathway [14].

Prolonged and strenuous physical activity has been demonstrated to induce physiological alterations in the cardiovascular system, manifesting in the augmentation of left ventricular wall thickness and cavity diameter. These adaptations often meet diagnostic criteria for LVH, though are considered physiological [15], align with the diagnostic criteria for left ventricular hypertrophy, yet are typically regarded as physiological responses rather than pathological manifestations [15]. Intense aerobic exercise has been demonstrated to result in a substantial decrease in blood pressure (BP), thereby reducing the hemodynamic load on the heart and potentially diminishing the stimulus for pathologic LVH [16]. These alterations are deemed safe and reversible, representing a physiological response to an elevated cardiovascular workload. However, the degree to which physical activity contributes to cardiac health varies significantly. A study by Holtermann A. et al. found that individuals engaged in high-intensity occupational activities, characterized by static loads and repetitive movements, exhibited a 35% increased risk of CVD and a 27% increased risk of mortality compared to those with low levels of activity (odds ratio (OR)=1.35 for CVD and OR=1.27 for mortality). Conversely, active leisure time has been shown to reduce these risks: high leisure time physical activity has been demonstrated to reduce the risk of cardiovascular disease by 23% and the risk of mortality by 41% [17]. Such activity has been shown to enhance cardiovascular and metabolic function, in contrast to occupational activity, which is often not dynamic enough and does not involve recovery periods.

Epidemiology studies confirm LVH is a significant independent cardiovascular disease risk factor [16, 18]. LVH can result in CVD through various mechanisms, including the development of arrhythmias and alterations in the structure and function of the heart muscle [18]. A study by Fernandes L. P. et al. demonstrated that increased LV wall thickness is associated with non-fatal CVD (relative risk (RR) 2.16), CVD death (RR 2.58), and total mortality (RR 2.02) [19].

The assessment of LVH geometry serves as a critical risk stratification tool, facilitating the identification of patients at high risk of developing CVD prior to the manifestation of any clinical signs.

The management of patients with LVH requires a comprehensive approach, including pharmacological treatment to control BP, lifestyle modifications, and potentially a cardioverter-defibrillator implantation (ICD) to prevent sudden cardiac death. In summary, a comprehensive understanding of the underlying pathophysiology of LVH, including its epidemiological associations with CVD, is imperative for the development of effective diagnostic strategies and management plans for this condition.

Left ventricular dysfunction

Left ventricular dysfunction is a diastolic dysfunction that has been associated with an elevated risk of fatal and nonfatal CVEs. The study reported an odds ratio (OR) of 2.01, with a 95% confidence interval (CI) of 1.32-3.07 [19]. The primary mechanisms underlying LVD development are impaired ventricular relaxation and increased viscoelastic stiffness, resulting in dyspnea and an elevated risk of hospitalization [20].

Physical exercise exerts a substantial influence on diastolic function, particularly in patients diagnosed with systolic left ventricular dysfunction with normal ejection fraction (sLVD-nEF), leading to a deterioration in systolic function during periods of exercise [12]. This contributes to increased left ventricular pressure and the development of sLVD-nEF.

Genetic factors have been demonstrated to play a pivotal role in the development of LVD. It has been established that certain genetic variations exert an influence on the metabolism and structural characteristics of cardiomyocytes, thereby contributing to alterations and impaired relaxation with an increased myocardial stiffness [12, 14]. In particular, TTN, PLN, and GJA1 genes have been associated with diastolic function [20].

Risk stratification is a central component of the assessment of LVD. Diastolic dysfunction can serve as an important marker for determining CVD risk in patients without a prior history of HF, thereby allowing the detection of an occult cardiac disease and timely therapeutic interventions to prevent HF. For instance, a study by Chee et al. has demonstrated that diastol-

ic LV dysfunction affects the majority of patients with type 2 diabetes mellitus with no prior history of CVD, indicating the high prevalence of this condition and the importance of its early detection [21].

Furthermore, a study by Kiel P. et al. revealed a considerably higher median coronary artery calcium (CAC) score in patients with LVD, emphasizing the importance of CAC assessment in the diagnosis of LVD in patients with AH [22]. Also, a study by Han B. G. et al. indicated that patients with diabetic kidney disease of stages 3 and 5 exhibited an elevated risk of cardiovascular disease. This finding highlights the necessity for the early detection and prevention of CVD risk factors in these patients [23]. A study by Lindstedt M. et al. found that diastolic dysfunction affected 50% of patients with idiopathic inflammatory myopathy, suggesting a high risk of developing sLVD-nEF in this group [24]. These data reinforce the significance of risk stratification and early diagnosis of diastolic dysfunction to avoid the development of severe cardiovascular disease.

Left atrial dilation

LAD is defined as a dilation of the left atrial cavity that may be caused by various pathological conditions, including hypertension, valve defects, cardiomyopathy, inflammation, or fibrosis. This condition can potentially impact cardiovascular function and elevate the risk of developing heart failure.

Risk stratification is a critical component of evaluating patients with LAD, as this condition is associated with an elevated risk of CVEs (RR 1.78; 95% CI 1.16-2.73) [19]. Alterations in the PITX2 gene, associated with LA development and function, serve as a significant risk marker. Epigenetic modifications, including hypermethylation of the Pitx2 gene, have been associated with an elevated risk of developing atrial fibrillation [24].

The mechanisms affecting LAD include pressure and volume overload, as well as increased levels of matrix metalloproteinases that promote fibrosis and tissue remodeling. This emphasizes the potential role of therapeutic targets in preventing and reversing changes in LA structure.

The assessment of left atrial dimensions and functionality through echocardiography, including the indexed maximum left atrial volume, facilitates accurate risk stratification [24]. This measurement is closely related to cardiac outcomes and is particularly important for predicting atrial fibrillation in patients with severely dilated LA.

For instance, a study by Jagadeesan V. et al. demonstrates the necessity of incorporating LA dilation into risk assessments for re-hospitalization following embolic strokes [25]. This suggests that LA dilation may have a role in predicting outcomes for patients with embolic stroke of unknown etiology and other cardiovascular diseases.

Aortic Root Dilation

The anomaly is characterized by the presence of an abnormal dilation of the aortic root. This condition can lead to serious complications, including aneurysm, dissection, or rupture of the aorta. These complications are often associated with abnormalities in the structure and function of the aortic valve and vascular wall.

The following mechanisms have been identified as contributing to the development of dilation:

Genetic factors. Genetic factors play a significant role in the development of aortic dilation. Mutations in genes such as FBN1, TGFBR1, and TGFBR2 can result in abnormalities in the structure of connective tissue, which can contribute to the dilation of the aortic wall [26].

Molecular Mechanisms. Abnormalities in the transforming growth factor beta (TGF-ß) signaling pathway may contribute to the breakdown of elastic fibers and collagen matrix, weakening the aortic wall [27].

Hemodynamic factors. The hemodynamic factors involved in this condition include high blood pressure, which exerts a mechanical load on the aortic wall, contributing to its dilation [28].

Aortic root dilation has been identified as a significant risk factor for the development of CVD. This condition can lead to aortic regurgitation, aneurysms, and dissections, significantly increasing the risk of mortality and the need for surgical intervention [26]. Thus, aortic root dilation is associated with an elevated risk of CVEs (RR 1.25; 95% CI 1.09-1.43) [19]. The early identification of patients at high risk of complications is of paramount importance for the timely initiation of treatment and prophylaxis. This can be achieved through the use of risk stratification tools, such as echocardiography and other imaging techniques, that can accurately assess the risk of complications.

EchoCG, being a non-invasive method, plays a crucial role in the diagnosis of aortic root dilation due to its accessibility and high degree of diagnostic accuracy.

Current challenges in the early diagnosis of cardiovascular disease review

Early diagnosis of cardiovascular disease poses a significant challenge in contemporary cardiology, particularly in cases involving asymptomatic patients. The complexity of this task is further compounded by the fact that the majority of cardiovascular disorders develop subtly and often do not manifest until serious events, such as myocardial infarction or stroke, occur [30].

Difficulties in early diagnosis

The absence of symptoms. The absence of symptoms is a hallmark of most cardiovascular diseases in their early stages, rendering them challenging to detect early. A multitude of symptoms, including fatigue and stress, may be erroneously attributed to less severe conditions, thereby delaying the diagnosis [31].

Patient Unawareness. Low level of awareness regarding the signs of CVD and its risk factors among the population can result in a delay in medical care seeking [31].

Lack of informativeness of traditional methods. Traditional diagnostic methods, such as BP and cholesterol levels measurements, are not always effective in identifying diseases before they progress [30].

Statistical significance

According to a study by Tsai et al., nearly half of the adult population in the United States has some form of CVD, with many remaining asymptomatic in the initial stages [30]. A study by Zwartkruis et al., involving 100,311 participants, revealed that 1325 participants had undiagnosed cardiovascular disease, which underscores the significance of early screening and diagnosis [31].

A proactive screening, incorporating both symptom-based assessment and a comprehensive questionnaire, has been demonstrated to enhance the efficacy of early detection of CVD in primary care settings. This approach has the potential to prevent CVEs and disease progression. The study accentuates the necessity to develop and implement simple yet effective screening methods that can be seamlessly integrated into routine clinical practice [30].

The efficacy of timely diagnosis and prevention of CVD has been demonstrated to markedly enhance patient prognoses and quality of life, while concurrently reducing the economic burden associated with advanced-stage disease management. The implementation of enhanced methods for early diagnosis and screening, aimed at identifying patients in the early stages of the disease, has emerged as a priority task in contemporary medical practice.

Early Signs of Echocardiographic Abnormalities Review

Echocardiography is a non-invasive technique that plays a critical role in detecting early signs of CVD, even in patients presenting with no symptoms. This method can detect changes such as LAD, abnormalities in aortic root structure and function, LVH, and LVD. This capability is essential for initiating timely treatment and preventing serious CVEs.

Early signs of aortic root changes

A slight increase in aortic root diameter: this change has been observed, which may be indicative of the initial stages of aortic aneurysm or other pathologic conditions that may not be symptomatic in the early stages. Early detection of such changes is critical to assess the risk of developing serious complications [26].

Aortic valve cusps thickening. Aortic valve cusps thickening may indicate the initial processes of fibrosis or calcification. EchoCG has been demonstrated to detect these changes in patients who are not yet symptomatic, which is important for early diagnosis and prevention of aortic stenosis [26].

Subvalvular fibrous ridges. Subvalvular fibrous ridges are a common finding in patients with ankylosing spondylitis, potentially indicative of inflammatory processes or the initial stages of structural changes of the aorta. Early detection of these signs may prevent the development of serious aortic disease [26].

The two-dimensional EchoCG is utilized to evaluate these changes, enabling their detection prior to the manifestation of clinical symptoms of aortic regurgitation [26].

Early signs of left atrial changes

Changes in LA volume and function can be detected echocardiographically in asymptomatic patients, indicating early cardiac involvement in the pathologic process [24].

A study by Christensen et al. demonstrated that in patients with asymptomatic severe aortic stenosis, LA dilation may serve as an indicator of advanced disease stage. It has been associated with an increase in LA mass and end-diastolic volume, which are the risk factors for cardiac events [32].

An additional study by Cameli et al. emphasizes that LA deformation is a useful index for early detection of cardiac damage in chronic mitral regurgitation. Speckle-tracking echocardiography allows analyzing LA function and can indirectly identify structural tissue changes in the early stages of the disease before complete deterioration of atrial function [33].

Early signs of left ventricular hypertrophy

LVH is prevalent among patients with long-term AH and can be detected early through echocardiographic imaging. Increased LV myocardial mass and structural changes can be detected before the onset of clinical symptoms, thereby providing an opportunity for an early intervention [33]. The CHELLO study has demonstrated that 44% of elderly patients with asymptomatic hypertension had LVH, emphasizing the importance of early detection for improving outcomes [33].

Early signs of Left Ventricular Dysfunction

LV diastolic and systolic dysfunction can be detected at an early asymptomatic stage, thus preventing the development of HF. Diastolic dysfunction, defined as impaired ventricular relaxation and filling, can be detected through analysis of isovolumic relaxation and changes in filling velocities [33]. Systolic dysfunction, evaluated by decreased EF and global longitudinal strain, can be identified in a presymptomatic stage, which is crucial for timely diagnosis [33].

Early diagnosis of CVD remains a critical component of contemporary cardiology. The recognition and detection of asymptomatic changes with echocardiography has been demonstrated to result in a substantial improvement in patient outcomes, thereby enabling the initiation of treatment before the onset of serious complications. This approach not only reduces the economic burden associated with advanced stages of CVD but also presents an opportunity to improve patients' quality of life.

EchoCG is an invaluable tool in the early diagnosis of asymptomatic CVD. It provides essential data on heart muscle condition and function, enabling the well-timed administration of required treatment. Early detection and diagnosis of CVD play a key role in preventing disease progression and improving patient prognosis. For this reason, EchoCG is considered an indispensable method in modern cardiology practice.

Selection of patients without signs of cardiovascular disease for echocardiographic examination

EchoCG is a valuable tool in the preventive screening of CVD, especially among patients who do not exhibit explicit symptoms. However, studies have demonstrated that its efficacy and cost-effectiveness depend on the selection of suitable candidates for screening.

Population Screening Using EchoCG

Paton et al. demonstrated in their study that widespread screening using EchoCG in the general population did not result in a substantial decrease in mortality or the risk of CVEs, including MI and stroke. These data emphasize that without careful selection of patients by risk, this approach may not be effective [34].

Risk Assessment and Feasibility of Echocardiography

Winchester et al. discuss the use of echocardiography for risk assessment in asymptomatic patients, especially those with AH. They emphasize that the direct benefit of EchoCG in the prevention of heart disease has not been proven and that its use should be carefully justified, taking into account the individual risks of the patient [35].

Preventive Use of Echocardiography

Post-hoc data from the Irish STOP-HF randomized controlled trial, published by Cannone et al., demonstrated that in patients with cardiovascular risk factors, applying a threshold level of endogenous BNP to refer individuals for transthoracic EchoCG and subsequent interdisciplinary management enabled the timely detection of asymptomatic systolic LVD and shown statistically significant reduction in the risk of progression to clinical HF [36].

Patient selection criteria for echocardiographic examination

Studies emphasize the importance of selecting patients for echocardiographic screening based on the presence of relevant risk factors:

Age and comorbid conditions. A new prospective analysis from the Australian SCREEN-HF study (Coller et al.) showed that in individuals aged ⩾60 years with at least one classical cardiovascular risk factor — including CHD, arterial hypertension, diabetes mellitus, or chronic kidney disease — targeted echocardiography effectively detects asymptomatic systolic LVD and helps to prevent progression to symptomatic HF. The novel formulation below is based on these findings and aligns with current ESC 2021 and ACC/AHA/HFSA 2022 guidelines, which also emphasize the importance of early detection of stage B/pre-HF in such populations [37].

Cardiooncology. In the field of cardio-oncology, echocardiography plays a central role in the early detection and monitoring of cancer therapy–related cardiotoxicity. This is particularly evident in patients receiving cardiotoxic treatments with echocardiographically revealed early signs of cardiac dysfunction [29].

Clinical Guidelines. Based on Framingham risk score or other validated risk assessment models, echocardiography may be recommended for individuals at intermediate or high cardiovascular risk. This allows for the detection of conditions such as left ventricular hypertrophy and LVD even in asymptomatic patients [29, 35].

The preventive use of echocardiography is a vital component of early diagnosis and risk management in asymptomatic individuals. Careful patient selection, grounded in thorough risk assessment, can contribute to more effective prevention of CVD and improved treatment outcomes.

Conclusion

Echocardiography remains a cornerstone of preventive cardiology, with the ability to identify subclinical structural and functional cardiac abnormalities long before symptoms arise. Systematic analysis has shown that targeted screening of individuals aged ⩾60 years with major cardiovascular risk factors or elevated BNP levels provides the best balance between clinical effectiveness and cost-efficiency, helping to prevent the progression to heart failure and reducing the incidence of major cardiovascular events. The integration of modern technologies, such as global longitudinal and left atrial strain assessment, three-dimensional EchoCG, and AI-powered post-processing algorithms, further enhances the diagnostic value of echocardiography. Developing standardized protocols for patient selection and management could transform echocardiography from a diagnostic tool into an effective mechanism for primary prevention.

Conflict of interests: none declared.

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Early Predictors and Diagnostic Consideration of Childhood Hypertension in South Africa

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Abstract

Childhood hypertension is not just a rising, but an urgent public health concern in South Africa, a trend that is similarly reflected in other parts of the country. This review examines childhood hypertension's prevalence, risk factors, early predictors and diagnostic considerations of Childhood Hypertension in South Africa.

The available literature on Childhood hypertension in South Africa is evolving, with estimated prevalence from literature ranging from 1.3-32.6%, with a particular increase in adolescents. The increase in the prevalence can be attributed to rapid nutritional transition, socioeconomic inequalities, urbanization, and lifestyle changes. Early identification of children at risk for hypertension is crucial. Unchecked hypertension in childhood tremendously increases the risk of developing adult cardiovascular diseases, such as Organ Damage in the heart, kidneys, and blood vessels, along with problems related to the vision of the child. Family history of Hypertension, Low Birth Weight, and Rapid Weight Gain in Infancy and Early Childhood are early predictors of prime importance. Diagnosis requires accurately measuring blood pressure (Multiple Measurements) using the Appropriate Cuff Size. Tackling childhood hypertension in South Africa requires a serious public health response through prioritizing prevention, early detection, and effective management strategies.

Keywords: childhood hypertension, prevalence, early predictors, South Africa.

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Introduction

Blood pressure (BP) readings in children are expressed as percentiles for age, sex and height. Blood pressure percentiles ⩾95% on three different occasions is described as hypertension [1]. Prehypertension is when the readings fall between the 90th and 95th percentiles among preadolescents [2]. Although less common in children than adults, evidence suggests that adult essential hypertension has its roots in childhood [1, 2]. Childhood hypertension is an emerging significant global public health burden in the face of increasing obesity, especially in Africa. Community-based studies conducted within the last five years estimated the prevalence of hypertension among South African children to range between as low as 1.3% and up to 32.6% across different regions [2-4].

In South Africa, obesity, physical inactivity, poor diets heavy in processed foods and salt, family history of hypertension, and socioeconomic factors are major risk factors for Childhood hypertension [5-7]. Compared to their rural counterparts, children in urban areas are frequently more impacted by food and lifestyle changes [7].

In severe circumstances, childhood hypertension can result in kidney damage or heart failure in addition to other acute health problems like headaches and eye problems [8]. Untreated childhood hypertension raises the risk of adulthood chronic kidney and cardiovascular diseases [8–11].

Children with hypertension are usually diagnosed by taking multiple blood pressure readings while accounting for percentiles of height, gender, and age [8,10]. It is advised that children with a family history of hypertension, obesity, or other co-occurring diseases like diabetes should have routine blood pressure screening [1].

Management of hypertension in South Africa has been reported to be focused on encouraging healthy lifestyles through school-based initiatives, community-based health interventions, and legislation targeting reducing childhood obesity and enhancing nutritional practices [12]. South Africa, being a country with a very heterogeneous population and wide gap in the socioeconomic strata, faces serious public health challenges; one such challenge is the rise in juvenile hypertension. Thus, a better understanding of the epidemiology and socioeconomic determinants that may all contribute to its growing concern should be recorded appropriately. These can be understood in the prevalence, risk factors, and socioeconomic determinants that further this increasing concern. It is necessary to look at the prevalence, risk factors, and socioeconomic determinants that contribute to this increasing concern to comprehend the epidemiology of this ailment in South Africa.

Earl Predictors and Epidemiology of Childhood Hypertension in South Africa

While influenced by local conditions, the epidemiology of childhood hypertension in South Africa follows the larger global trends with the prevalence of similar modifiable/nonmodifiable risk factors (Figure 1) [8]. In South Africa, the prevalence of childhood hypertension has been increasing in tandem with rises in childhood obesity and other illnesses linked to lifestyle choices [2, 8, 13]. Research has shown that rates of hypertension in children in South Africa vary greatly, from 1.3% to 32.6%, depending on the community, diagnostic instrument and criteria standards applied [2, 4, 14]. These rising rates result from urbanisation, dietary modifications, and sedentary lifestyles, especially in cities where processed food availability and decreased physical activity are more prevalent [6, 15-17]. Generally, some of the key early predictors of childhood hypertension can be traced to factors such as birth weight, maternal health, and infant feeding practices [8,13]. Low birth weight, maternal hypertension or preeclampsia and smoking during pregnancy have been linked as significant predictors.

Obesity, poor dietary habits, socioeconomic, family history, and physical inactivity influence hypertension in South African children [13, 17, 18]. Poor dietary habits, including shorter duration of breastfeeding, early introduction of solid food, high sodium intake and low consumption of fruits and vegetables, are prevalent among South African children and contribute to the risk of hypertension [6, 7, 13, 16]. Due to the high levels of income disparity in the nation, children

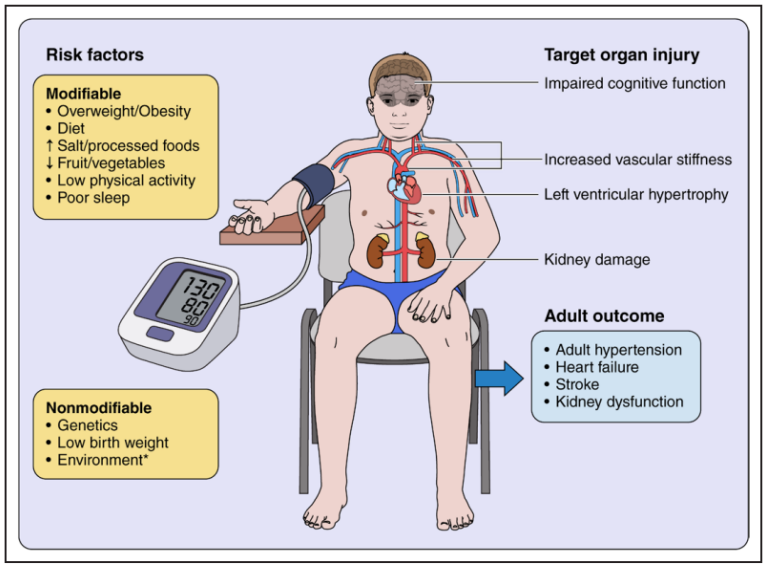

Fig. 1. Modifiable risk factors for high BP in children and adolescents, including improving dietary intake and physical activity and reducing excess adiposity [8]

from lower-income families are more susceptible to hypertension and the risk factors that go along with it [7]. Insufficient availability of healthcare services in certain regions may lead to delays in diagnosing and treating hypertension, culminating in more severe health consequences [2, 7].

Besides, the nutritional transition in South Africa, characterised by the switch from traditional to Westernised diets typically high in processed foods, sweets, and fats, has significantly affected children's health [16]. The scenario is clearer in urban and peri-urban areas where economic development influences changes in lifestyle and food availability [15, 19]. Though not directly linked to the cause, the high prevalence of some diseases, such as HIV, can impact childhood health and potentially increase the risk of hypertension [3].

Clinical and Diagnostic Considerations of Childhood Hypertension

Growing awareness of childhood hypertension as a health issue calls for rigorous clinical and diagnostic assessment. Hypertension is asymptomatic in many children, and many do not exhibit symptoms, so routine screening is crucial [9, 10]. Without overt signs, hypertension may go undiagnosed in children and discovered secondary to another health issue. When symptoms arise, they could include headaches, light-headedness, blurred vision, bleeding from the nose, exhaustion, and agitation [9,10]. The general nature of these symptoms makes them easily mistaken for other illnesses, which makes early diagnosis more difficult. During standard physical examinations, children's blood pressure and additional indicators of secondary hypertension, such as Cushing's syndrome symptoms and skin abnormalities suggesting neurofibromatosis or abdominal tumours, are usually recommended to be checked [10].

To accurately diagnose childhood hypertension, children should be in a calm environment, sitting quietly for at least three to five minutes with their backs supported and feet flat on the floor. Blood pressure is taken on both arms and legs to check for aortic coarctation. A minimum of three different readings is recommended for confirmation [9, 10]. Since most childhood hypertension is asymptomatic, some doctors recommend 24-hour ambulatory blood pressure monitoring (ABPM) [8, 20]. The ABPM monitoring offers a thorough evaluation, catches fluctuations, and aids in the diagnosis of asymptomatic, underdiagnosed, masked hypertension (normal readings in a clinical setting but elevated outside) or white coat hypertension (elevated readings in a clinical setting but not in everyday life). The percentiles of ABPM are compared to normative data for children's age, sex, and height [8, 20].

Secondary causes of childhood hypertension can be assessed through urinalysis, blood tests, renal ultrasonography, hormonal assays, doppler examinations, or echocardiography, depending on the preliminary results. Normal blood pressure is below the 90th percentile; elevated blood pressure is between the

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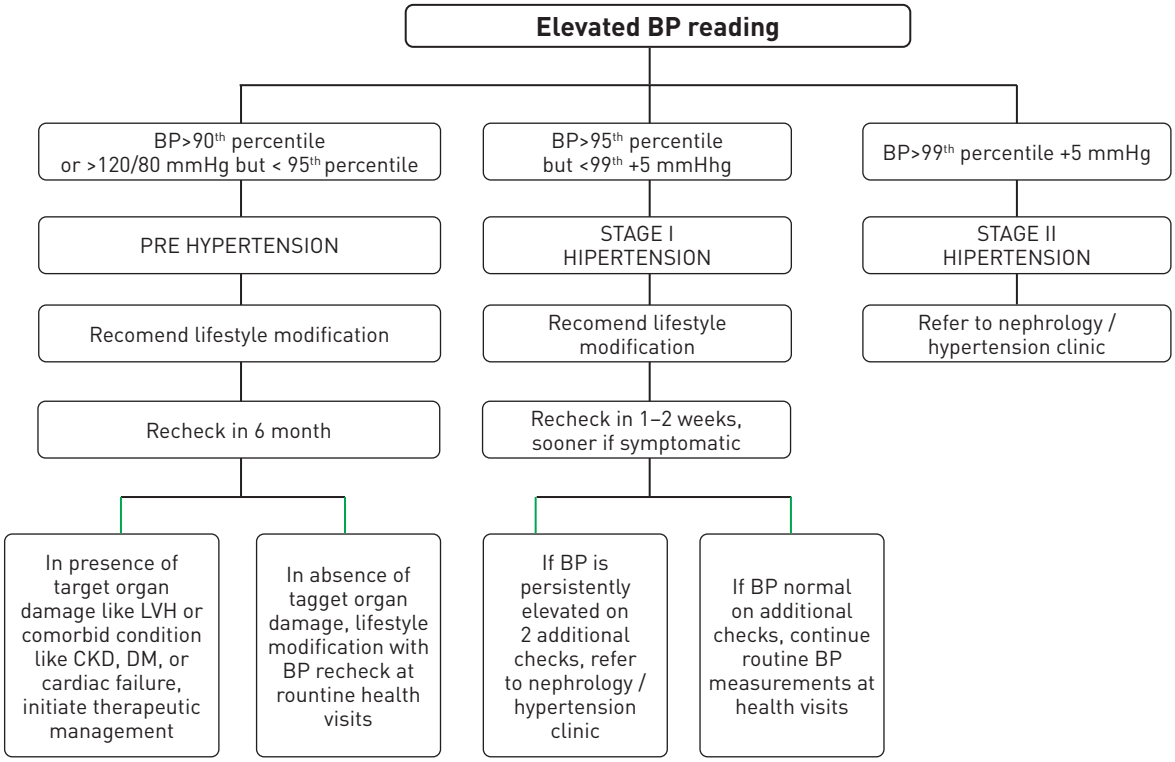

Fig. 2. Diagnosis of Hypertension in the Teenager-Pediatric Clinics [1]

90th and 95th percentile or above 120/80 mmHg. Stage 1 hypertension is blood pressure between the 95th percentile and 5 mmHg above the 99th percentile, and Stage 2 hypertension is blood pressure greater than 5 mmHg above the 99th percentile (Figure 2) [1, 8].

Knowledge gaps in childhood hypertension in South Africa

In South Africa, like the rest of the African continent, childhood hypertension is a growing underdiagnosed public health issue that requires urgent attention. Furthermore, the paucity of information on diagnosis, management, and prevention are a significant challenge. Understanding these challenges is important for properly managing the condition and minimising its chronic health effects. One of the major knowledge or information voids is the absence of thorough epidemiological data regarding the prevalence/distribution of childhood hypertension and the utilisation or effectiveness of antihypertensive agents in children and adolescents from different communities and regions in South Africa.

Childhood hypertension in South Africa is understood mainly due to a lack of knowledge about factors like genetic predispositions, socioeconomic situations, and environmental effects. The lack of standard procedures for screening and diagnosis can lead to incorrect or underdiagnosed diagnoses [21]. The best ways to manage and treat childhood hypertension, including pharmaceutical therapies and lifestyle modifications, are also unclear [3].

Recommendations for diagnosis and treatment of childhood hypertension

Regular screening, such as routine checks during hospital visits, school/community-based screening and awareness, will help to identify children at risk of developing high blood pressure early [2, 12]. Early diagnosis and prevention of childhood hypertension remains a critical focus, especially for high-risk populations such as South Africa, and is crucial in the management. A proper blood pressure measuring technique is necessary for accurately identifying childhood-onset hypertension, and the currently suggested blood pressure monitoring should be done on at least three different days/occasions because of variability in BP measurements [8]. Systolic blood pressure beyond the 95th percentile is considered hypertension. Hypertension is also defined by diastolic blood pressure ⩾95th percentile and systolic blood pressure ⩾95th percentile (Table 1).

Table 1. **Definitions of Normal and Abnormal Childhood Blood Pressure Levels [8]**

BP Category	Age <13 years	Age ⩾13 years
Normal BP	<90th percentile for age, sex, and height	<120/<80 mmHg
Elevated BP	90th to <95th Percentile for age, sex and Height	⩾120/<80 to 129/<80 mmHg
Stage 1 Hypertension	⩾95th percentile to 95th percentile plus 11mmHg	130-139/ 80-89 mmHg
Stage 2 Hypertension	⩾95th percentile plus 12mmHg	⩾140/⩾90 mHg

Obtaining an accurate blood pressure measurement in children and adolescents can be challenging since blood pressure varies with cuff size, anxiety level, caffeine intake, time of day and patient positioning [8, 10, 22]. Before and during the measurement, the patient should be rested in a quiet position for three to five minutes with their back supported and their feet flat on the floor (not crossed). Unless it is contraindicated (arteriovenous fistula present), the blood pressure should be taken from the right arm. The arm should be supported when applying the cuff so its midpoint is at heart level [8, 10]. The upper arm should be exposed beneath the cuff to prevent a tightly wrapped sleeve above the cuff. During measurement, it is expected that the patient and medical staff should refrain from conversing, reading, using electronics, and engaging in any other type of distraction [8, 10, 22].

The middle upper arm circumference is usually measured halfway between the olecranon and acromion to find the appropriate cuff size [8, 10, 22]. It is usually expected that bladder length should be at least 80% of the middle upper arm circumference, and the bladder width should be between 37% and 50% when measuring blood pressure manually by auscultation [10]. The recommended arm-circumference range on the cuff should be considered when choosing an automated instrument for blood pressure monitoring. To guarantee equal compression of the brachial artery during measurement, the cuff is positioned at the midpoint of the inflated portion (usually the delineated artery) 2 cm above the palpated brachial artery in the antecubital fossa [8, 10, 22]. Applying the cuff snugly means that there should not be room for more than two fingers to pass between the skin and the cuff [8, 10, 22].

Manual auscultation is begun by palpating the pulse in the radial artery and inflating the cuff 20–30 mmHg above the point at which the pulse stops [8, 10, 22]. The stethoscope diaphragm is placed over the location of the brachial artery, being careful not to tuck it under the cuff. Inflating the cuff to maximum capacity, it is deflated at 2–3 mmHg per second [8, 10, 22]. The first Korotkoff sound is the systolic blood pressure (K1), while the last audible sound represents the diastolic pressure (K5) [8, 10, 22].

Once a high blood pressure reading is confirmed in the office, the further management of the patient is mostly determined by the stage and severity of elevation (figure 3) [10]. Before starting medication, it is advised that lifestyle modifications be made to treat and manage hypertension. These adjustments entail eating a balanced diet low in processed sugar, salt, and saturated fat and high in fruits, vegetables, whole grains, and lean proteins. Also, weight loss and daily physical activity ranging from mild to intense are encouraged [9]. Antihypertensive medication is recommended to be introduced when lifestyle changes seem insufficient, and medication will depend on the child's underlying condition and need. Some common antihypertensive drugs used include Diuretics, angiotensin II receptor blockers, ACE inhibitors, beta-blockers, and calcium channel blockers [23].

Conclusion

Early identification of hypertension in children in South Africa is paramount to avert long-term cardiovascular implications. Such major predictors as obesity, family history, socioeconomic status, and lifestyle habits need to be incorporated into the regular screening. Simplifying early diagnosis by boosting awareness, access to medical care, and uniform diagnostic thresholds will improve early treatment and decrease the escalating childhood hypertension burden.

Gratitude

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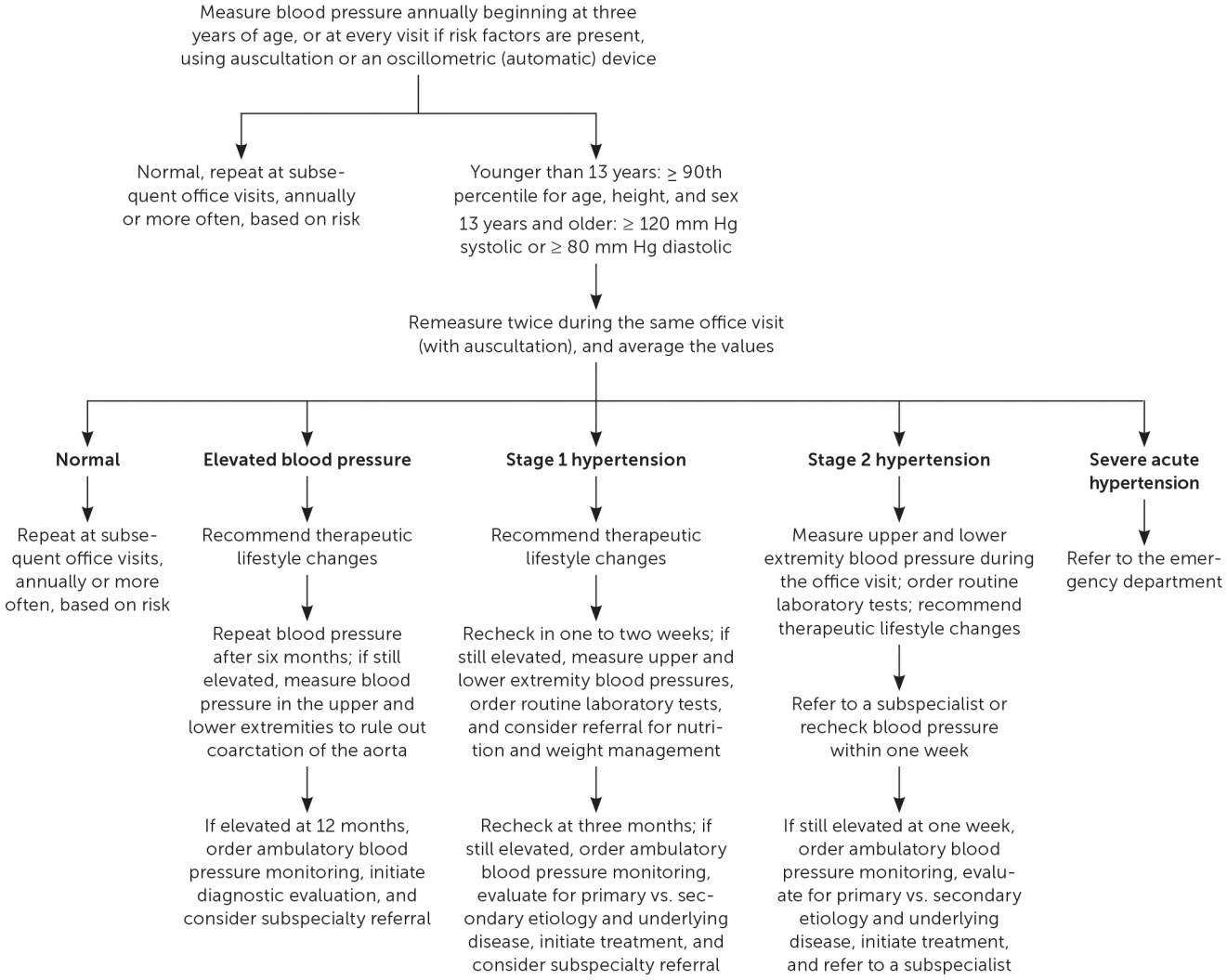

Fig. 3. Management/treatment guidelines for hypertension in children and adolescents [10]

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Author Guidelines

Manuscript publication rules
in the International heart and vascular disease journal

Edit from December, 2021

Disclaimer: The rules came into effect from December 2021. The rules describe the conditions of publication of manuscripts (articles) through the site http://www.heart-vdj.com. The editorial Board is ready to answer questions and help authors by e-mail: submissions.ihvdj@gmail.com.

The *International heart and vascular disease journal* has been published since 2013. It is official journal of the Cardioprogress Foundation. The target audience of this peer-reviewed journal is cardiologists and internal disease specialists. The journal is primarily focused on questions of epidemiology, prevention, and cardiac pharmacotherapy. It also publishes lectures and literature reviews on various problems of modern cardiology, reports on new diagnostic methods, and other information which is important for the practitioners.

The General criteria for the publication of articles in the International heart and vascular disease journal are the relevance, novelty of the material and its value in theoretical and/or applied aspects.

The languages of publications are Russian and English. Journal is peer-reviewed, with multistage editing. Editorial board is presented by the leading cardiologists from different countries and Russia.

International heart and vascular disease journal aims to ensure that its publications fulfill the requirements of international publishing standards, such as the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, by the International Committee of Medical Journal Editors, ICMJE (http://www.icmje.org), and the recommendations by the Committee on Publication Ethics, COPE (http://www.publicationethics.org.uk).

All clinical trials should be performed and described in full accordance with the CONSORT standards (http://www.consort-statement.org), observational research — STROBE (http://www.strobe-statement.org), systematic reviews and meta-analyses — PRISMA (http://www.prisma-statement.org), diagnostic accuracy — STAR (http://www.stard-statement.org).

I. The International heart and vascular disease journal accepts the following manuscripts:

1) *Original papers* present the results of clinical studies. The word limit is 3.000 (including references, tables, and figure legends). The maximal number of references is 15. The structured abstract should contain 5 sections (**Aim, Material and Methods, Results, Conclusion**, and **Key words**), and be no longer than 300 words.

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"Directional (cover) letter" is scanned. File format. jpeg attached as an additional file of the manuscript.

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Example of design:

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Muromtseva G.A.[1], Kontsevaya A.V.[1], Konstantinov V.V. [1], Artamonova G.V. [2], Galaganova T.M. [3],...

[1] FGBU State research center of preventive medicine of the Ministry of health of Russia, Moscow;

[2] FGBU Research Institute of complex problems of cardiovascular diseases SB RAMS, Kemerovo;

[3] RD VPO North Ossetian state medical Academy, Vladikavkaz;..., Russia.

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Text
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The first reference to an abbreviation is always accompanied by the full spelling of the abbreviated concept, and the abbreviation is indicated in brackets. For example, blood pressure (BP); heart rate (HR). Capital letters are more often used to denote abbreviations. If abbreviations are used only in tables and figures, and are not used in the text, they should not be included in the list of abbreviations, but should be given a transcript in the note to the table or figure. The summary of the article, as a separate document, is subject to the same rules as the article (abbreviations are made when they are used 3 or more times).

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The editorial Board informs the Author of the results of the review by e-mail.

If the reviewer makes a conclusion about the possibility of publication of the article and does not make significant corrections, the article is given to the expert on statistics and after a positive report is accepted for further work.

If the reviewer makes a conclusion about the possibility of publication of the article and gives instructions on the need for its correction, the Editorial Board sends the review to the Author with a proposal to take into account the recommendations of the reviewer in the preparation of a new version of the ar-

ticle or to refute them. In this case, the Author needs to make changes to the last version of the article file, which is located on the site (download file from the site, make changes and place the corrected article again, after removing the primary (uncorrected) version). The revised article is re-sent for review, and the conclusion is given that all the recommendations of the reviewer were taken into account. After receiving a positive response of the reviewer, the article is given to the expert on statistics and after a positive report is accepted for further work.

If the reviewer makes a conclusion about the impossibility of publication of the article. The author of the reviewed work is given the opportunity to read the text of the review, if he does not agree with the conclusions of the reviewer. In case of disagreement with the opinion of the reviewer, the Author has the right to provide a reasoned response to the Editor. The article can be sent for re-review or for approval to the editorial Board. The editorial Board or its authorized editor shall send its response to the Author.

All manuscripts that have been reviewed and evaluated by an expert in statistics are submitted to the editorial Board, which decides on the publication. After the decision on the admission of article for publication, the Editorial office inserts the publication of the article in terms of publications. Information about the annual (thematic) plan of publications is placed on the website of the journal.

The decision to publish a manuscript is made solely on the basis of its significance, originality, clarity of presentation and compliance of the research topic with the direction of the journal. Reports on studies in which negative results are obtained or the provisions of previously published articles are challenged are considered on General grounds.

Original reviews are kept in the Editorial office for 5 years from the date of publication.

In case of a decision to refuse to publish an article, its archive copy remains in the electronic system of the editorial Board, but access to it by editors or reviewers is closed.

IX. The manner of publication of manuscripts

According to the requirements of the Higher attestation Commission, the journal provides priority for post-graduate and doctoral works, the period of their publication depends on the expected date of protection, which the authors must specify in the primary documents attached to the manuscript.

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All selected articles are submitted to the scientific editor and proofreader. After creating the layout of the article and editing it, the article will be available to the Author through the site. At this stage, it will be possible to send comments on the text of the article. The author is obliged to send his / her consent to the publication or his / her comments within the established time specified in the cover letter.

The editorial office does not send the author's copy by mail or PDF of the article by e-mail, access to the published numbers is open.

Subscription to the printed version is carried out by half a year (through subscription agencies).

X. After the publication in the journal

Information on publication is distributed in the following scientific citation databases: Russian science citation index, CYBERLENINKA and others. The article is assigned a DOI index and the full text is publicly available on the journal's website.

Information about the publication of the issue is distributed by mailing of The Cardioprogress Foundation and in social networks.

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a small part of the rest of the high-quality publication is unreliable (especially because of conscientious errors); the list of authors / sponsors contains errors (i.e., it does not contain someone who is worthy to be an author, or a person who does not meet the authorship criteria).

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XII. Position E-log backup (if journal is no longer published)

The purpose of backup is to prevent loss of information in case of hardware, software, critical and crisis situations, etc.

Information of the following main categories is subject to backup: — personal information of authors (personal directories on file servers); — pdf of published articles; — information about literary links to the article in the DOI system.

All this information is publicly available in The system of the Russian citation index on the website of the Electronic library www.elibrary.ru

XIII. Journal subscription

Information on subscriptions is available on the journal website in the section "Subscription":

XIV. Journal subscription

The name of the journal in English is International heart and vascular disease journal.

Official sites where information about the journal is placed:

http://www.heart-vdj.com

On the reception of the articles, making decisions about publication, reviews — mmamedov@mail.ru

On organizational issues (working with the site, subscription) — editor.ihvdj@gmail.com

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Files with a letter of transmittal and General information have been prepared for upload to the site.

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