



International Heart and Vascular Disease Journal

Journal of the Cardioprogress Foundation



Priorities of primary prevention
of cardiovascular disease:
the results of multicenter
international cohort study AHS
I (Azerbaijan Heart Study,
part I)

Comparison of death risk
stratification criteria in
pulmonary embolism
based on the estimation
of pulmonary arterial bed
occlusion

Congress of the American
College of Cardiology:
results of clinical trials

Editor-in-Chief: **Rafael Oganov**

Deputy Editor: **Mehman Mamedov**

Senior Consulting Editors: **Nathan Wong**
Richard Williams

The *International Heart and Vascular Disease Journal* is a peer-reviewed open access publication printed quarterly. The journal features original research articles, case reports, clinical reviews, editorials, and letters to the Editor. All published articles are freely accessible from the journal's website.

The publication of articles within the journal is free of charge for authors. Guidelines for authors on submitting manuscripts are available at: www.cardioprogress.ru

EDITOR-IN-CHIEF

Rafael Oganov, Russia

DEPUTY EDITOR

Mehman Mamedov, Russia

ASSOCIATE EDITOR

Anna Artyeva, UK

SENIOR CONSULTING EDITORS

Nathan Wong, USA

Richard Williams, UK

STATISTICAL CONSULTANT

Alexander Deev, Russia

INTERNATIONAL EDITORIAL BOARD

Adnan Abaci, Turkey

Berndt Luderitz, Germany

Dayi Hu, China

Dusko Vulic, Bosnia and Herzegovina

Elena Mitchenko, Ukraine

Kazuaki Tanabe, Japan

Maciej Banach, Poland

Najeeb Jaha, Saudi Arabia

Ozlem Soran, USA

Pekka Puska, Finland

Pranas Serpytis, Lithuania

Rafael Bitzur, Israel

Sergey Kanorsky, Russia

Seth Baum, USA

Vladimir Khirmanov, Russia

Wilbert Aronow, USA

Yuri Vasyuk, Russia

Contact details:

Cardioprogress Foundation and Editorial
Office:

Room 213, Building 2, Prospect Gostinichny
6, Moscow 127106, Russia

Editorial Office tel.: (+7) 965 236 1600

Official website: www.cardioprogress.ru

Editorial correspondence should be sent to:
Mehman Mamedov, Deputy Editor,
editor.ihvdj@gmail.com

Articles for publication should be sent to:
Anna Artyeva, Associate Editor,
submissions.ihvdj@gmail.com

© International Heart and Vascular Disease
Journal is an official publication of the
Cardioprogress Foundation

Printed in Russia

Complete versions of all issues are published:
www.elibrary.ru, www.cyberleninka.ru

International Heart and Vascular Disease Journal

Journal of the Cardioprogress Foundation

Volume 6, Number 18, June 2018

Contents

Editor's Welcome	2
-------------------------------	---

LEADING ARTICLE

Priorities of primary prevention of cardiovascular disease: the results of multicenter international cohort study AHS I (Azerbaijan Heart Study, part I)	3
---	---

Mamedov M.N., Deev A.D., Mehdiyev S.Kh.

ORIGINAL ARTICLES

Efficacy of a Cardiovascular Behavioral Intervention Program and Full Body CT Scanning on Changes in Coronary Artery Calcium, Thoracic and Epicardial Fat	12
--	----

Nathan D. Wong, Alisa Eisenberg, Jolie Cecere, Damini Dey, Chris Patao, Wenjun Fan, Lewis Wexler, Harvey C. Eisenberg

Comparison of death risk stratification criteria in pulmonary embolism based on the estimation of pulmonary arterial bed occlusion	23
---	----

Tyurin V.P., Pronin A.G.

Relationship between the degree of epicardial fat volume and severity of coronary atherosclerosis	31
--	----

Chumakova G.A., Pokutnev A.P., Veselovskaya N.G., Bobrovskaya L.A.

REVIEW ARTICLES

Treatment of hypertension	37
--	----

Wilbert S. Aronow

CLINICAL TRIALS

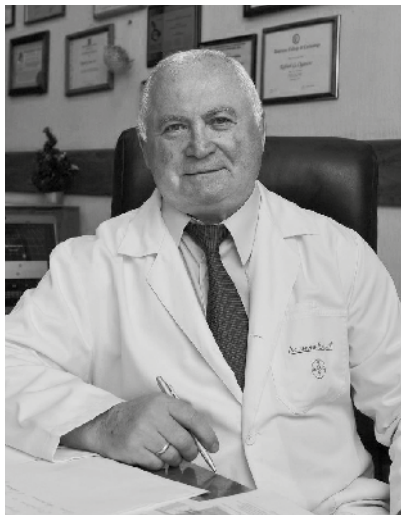
Congress of the American College of Cardiology: results of clinical trials	45
---	----

Kanorskii S.G.

CONGRESS REPORT

Results of the VII International Forum of cardiology and internal medicine	49
---	----

Guidelines for authors	50
-------------------------------------	----



Editor's Welcome

Dear colleagues!

In the 18th issue of the International Heart and Vascular Disease Journal, there are the leading article, original and review articles, results of major clinical trials and the report on the VII **Results of the VII International Forum of cardiology and internal medicine.**

The "Leading article" session includes a joint work of Azerbaijan and Russian specialists on the study of risk factors and cardiovascular risk in the cohort of patients with AH. A multicenter trial involved ethnic Azerbaijan citizens living in three states including 4 cities of Azerbaijan. The authors conclude that it is necessary to provide effective control of BP levels for needs of primary prevention, that will lead to regression of left ventricular hypertrophy and to conduct a serious educational work on bad habits in men, to correct metabolic abnormalities and plasma levels of cholesterol and glucose.

The "Original articles" section includes 3 articles. A group of authors from the USA studied the efficiency and positive results of a program of lifestyle intervention together with whole body CT-scan for control of coronary calcinosis progression and epicardial and chest fat accumulation. Another original article is dedicated to investigation of angiopulmonographic criteria of massive pulmonary arterial lesions for stratification of death risk in patients with pulmonary embolism according to the guidelines of the European Society of Cardiology. The third work deals with the interrelation between the degree of epicardial adipose tissue accumulation and the severity of coronary atherosclerosis. Authors indicate that correction of visceral obesity should be included into the programs of atherosclerosis prevention.

A review article from the USA represents the analysis of new diagnostic criteria and principles of AH treatment according to the new guidelines and the approaches for prevention of its complications.

Traditionally, our journal reviews the results of clinical studies presented at major scientific events. Another one of them discusses the annual session of the American College of Cardiology that demonstrated new opportunities of antiplatelet therapy and treatment of atherosclerosis, coronary heart disease, arrhythmias, heart failure, and arterial hypertension that, undoubtedly, will help the optimization of management of patients with common cardiovascular diseases.

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

Rafael G. Oganov

Editor-in-Chief

President of the "Cardioprogress" Foundation

Priorities of primary prevention of cardiovascular disease: the results of multicenter international cohort study AHS I (Azerbaijan Heart Study, part I)

Mamedov M.N.¹, Deev A.D.¹, Mehdiyev S.Kh.²

¹National Research Center for Preventive Medicine of the Ministry of Healthcare of the Russian Federation,
Moscow, Russia;

² Azerbaijan State Advanced Training Institute for Doctors named after A. Aliyev

Authors

Mekhman N. Mamedov, M.D., Ph.D., doctor of sciences, professor, head of the Laboratory of Interdisciplinary Approach for Prevention of Chronic Non-infectious Diseases, National Research Center for Preventive Medicine, Moscow, Russia.

Alexander D. Deev, Ph.D., head of the Laboratory of Biostatistics, National Research Center for Preventive Medicine, Moscow, Russia;

Samir Kh. Mehdiyev, M.D., Ph.D., associate professor of the Department of Internal Medicine, Azerbaijan State Advanced Training Institute for Doctors named after A. Aliyev, Baku, Azerbaijan

Summary

Objective

The objective of this study was to investigate the prevalence of main CVD risk factors and to assess cardiovascular risk in a cohort of men and women with arterial hypertension (AH) aiming to develop a strategy of primary CVD prevention.

Six centers from three countries took part in a cross-sectional, multicenter cohort study: 4 cities from Azerbaijan (Baku, Ganja, Sheki, Lenkoran), 1 from Georgia (Marneuli) and 1 from Russia (Derbent). The total number of patients was 760, including 503 women (66.2%) and 257 (33.8%) men, with the average age of 53 ± 1.15 years (from 30 to 59 years).

Material and methods

All patients were questioned using international ARIC questionnaire, underwent blood pressure, heart rate, and anthropometric parameters measurement and ECG registration at rest. Fasting blood levels of total cholesterol and glucose were determined. Total cardiovascular risk was estimated using the European SCORE scale.

Results

Mean blood pressure in the examined groups of men and women met the criteria of AH 2–3 stages, it was accompanied by hypertrophy of the left ventricle in 40–70 % of cases, which is known to increase the risk of cardiovascular complications. It has been shown that on average every second patient received combined antihypertensive therapy, while monotherapy was performed in 45 % of patients, and 15 % of patients did not adhere to therapy at all. Among the socio-demographic indicators, attention is drawn to the high incidence of non-working men with hypertension in all cities, the majority of women were housewives. The results of the study showed that the smoking rate in men with hypertension was between 19 % and 60 %, depending on the region. In the cities of Azerbaijan, the frequency of alcohol abuse was not higher than 10 %, whereas in contiguous states this indicator was 2–2.5 times higher in cohorts of men with AH. Abdominal obesity was one of the prominent risk factors for both men and women with AH. Diabetes mellitus in men was found in 9 % of cases, and among women this value was 15 %. The average total blood cholesterol levels of patients with AH met the criteria of mild hypercholesterolemia. Depending on the region and gender, high cardiovascular risk was detected in 20 % — 60 % of cases. Every fourth man and every third woman had very high cardiovascular risk.

Conclusion

For the purpose of primary prevention of cardiovascular complications in persons with hypertension, it is necessary to provide effective control of blood pressure, which will also lead to regression of left ventricular hypertrophy. Along with this, it is necessary to conduct serious work among men to combat bad habits, to correct metabolic disorders, as well as total blood cholesterol and glucose levels. Total cardiovascular risk assessment can serve as a good indicator for estimation of multifactorial prophylaxis efficacy in patients with AH.

Key words

Primary prevention, risk factors, arterial hypertension, cardiovascular risk

Introduction

Cardiovascular diseases (CVD) are the leader among chronic noninfectious diseases for the development of complications and disability of persons of working age, both in developed and developing countries [1]. During the last years there is a noticeable dynamics in the reduction of cardiovascular mortality in the EU and US countries, whereas, high rates of cardiovascular morbidity and mortality still persist in CIS countries, including Azerbaijan. This trend is found among men and women of working age [2]. At the same time, among women the frequency of cardiovascular complications in the structure of mortality was higher than in men [3, 4].

The causes of high cardiovascular mortality include several factors: socioeconomic problems, health system limitations after the collapse of the USSR, adult migration, urbanization, etc. The system of prevention, health check-up and rehabilitation in new conditions has not been restored at the required level [3].

On the other hand, during the last few years high-tech methods of medical assistance have been ac-

tively developed in the CIS countries, in particular in Azerbaijan. In this country there are several large vascular centers providing emergency and planned cardiac care. The need for cardiosurgical interventions is covered by the forces of local health structures and specialists.

According to authoritative prospective clinical studies in the development of CVD, an important role is played not only by socio-demographic indicators, but also by so-called risk factors. If we consider CVD as a long-term chronic process (atherosclerotic changes and their complications develop on average within 15 years), then the risk factors act as a triggering mechanism of functional and anatomical changes in the structure of the major arteries [5]. The combination of several risk factors increases the overall risk of developing cardiovascular diseases. There are various scales and tables (SCORE, PROCAM, Framingham) prepared on the basis of prospective studies and designed to calculate the predicted total risk of developing cardiovascular complications taking into account several risk factors [6–8]. The high-risk strategy is

one of the main platforms for the development of CVD prevention [9].

In recent years, the comorbidity of somatic diseases has also been seen as an important factor affecting the ability to work and the prognosis of patients with cardiac pathology [10]. It is not only about pathogenetically interrelated disorders, but also individual diseases of various organs and systems.

Primary prophylaxis of CVD involves the identification and systematic correction of a wide range of social, biological and behavioral risk factors until the moment of disease formation. According to major clinical studies, primary prevention programs can prevent CVD risk by up to 40%. It is proved that the primary prevention of CVD is economically more effective and expedient in comparison with the use of more complex procedures in patients with CVD complications [9].

The aim of the study

Study the prevalence of major CVD risk factors and assess cardiovascular risk in a cohort of men and women suffering from hypertension with the view to develop a strategy for primary prevention of CVD.

Materials and methods

Cohort formation

Six centers from three states took part in a one-stage multicenter cohort study: 4 cities from Azerbaijan (Baku, Ganja, Sheki, Lenkoran), 1 from Georgia (Marneuli) and 1 from Russia (Derbent). The study had been conducted from September 2015 to October 2016 as part of a cooperation agreement between National Research Center for Preventive medicine of the Ministry of Health of the Russian Federation and the Azerbaijan State Institute of Advanced Training of Physicians named after A. Aliyev.

The total number of patients was 760, including 503 women (66.2%) and 257 (33.8%) men. A detailed analysis of the number of cohorts surveyed in different cities is present in Table 1. The average age of the examined patients was 53 ± 1.15 years (varying from 30 to 59 years).

Inclusion criteria. The study included men and women aged from 30 to 59 years with arterial hypertension (AH) 1–3 stages. according to the classification of the European Society of Hypertension [11], with and without other cardiovascular risk factors and somatic diseases.

The criteria for exclusion were: Age < 30 and > 59 years; Presence of chronic heart failure (CHF);

Table 1. Summary of cohort population in 6 centers

Cities	Total number of patients in the cohort, n	Men, n	Women, n
Azerbaijan			
Baku	151	48 (32 %)	103 (68 %)
Ganja	200	56 (28 %)	144 (72 %)
Sheki	117	28 (24 %)	89 (76 %)
Lenkoran	115	60 (52 %)	55 (48 %)
Russia			
Derbent	52	12 (23 %)	40 (77 %)
Georgia			
Marneuli	125	53 (42 %)	72 (58 %)

Exertional angina pectoris; valvular and vascular defects; History of stroke of any genesis and myocardial infarction (MI); Atherosclerosis of peripheral vessels; Renal and hepatic impairment; Respiratory insufficiency; Oncological diseases (3–4 stages); Connective tissue disease; Endogenous mental disorders; Bilateral stenosis of renal arteries; Alcohol or drug addiction.

Clinical and instrumental methods

—Standard questionnaire using the Russian (Azerbaijan) version of the ARIC questionnaire: age, marital status, education, social status, hereditary burden, smoking, alcohol consumption, hypertension, therapy and concomitant somatic diseases [12].

The ones who smoked at least one cigarette / cigarette a day were considered as smokers. The status of smoking was defined as follows: never-smokers, smokers in the past, smokers at the moment.

The status of alcohol consumption was assessed by the following criteria: never consumed alcohol during the last year; for men: little and moderately — <168 g ethanol per week, much -> 168 g ethanol per week; for women: little and moderately — <84 g ethanol per week, much-> 84 g ethanol per week.

Measurement of blood pressure (BP) was performed using mechanical tonometer with the accuracy of 2 mm Hg. twice with 5-minute interval, in sitting position at rest. Systolic blood pressure (SBP) was recorded after appearance of the first Korotkov tone (phase I), the diastolic blood pressure (DBP) was recorded after disappearance of Korotkov’s tones (V phase). The average of the two measurements was used for the analysis. The information about heart rate (HR) per minute was included in the questionnaire.

Anthropometric parameters: measurement of body height accurate within 0.5 cm; measurement of body mass accurate within 0.1 kg; calculation of body mass index (BMI) (Quetelet index), as the ratio of body mass in kg to the square of the body height

in m; measurement of the waist circumference (WC) accurate within 0.5 cm.

Electrocardiogram registration (ECG) was performed in 12 standard leads in lying position with the use of standardized stationary devices.

ECG criteria (the Sokolov-Lyon criterion and the Cornell volcano index) have been used for the diagnosis of left ventricular hypertrophy (LVH).

Biochemical methods

Blood for sampling was taken from the ulnar vein in the morning after a 12-hour fasting with minimal venous occlusion (pressure under the bundle not > 90 mm Hg, <60 seconds). Serum was obtained after 10 minutes centrifugation at 3000–3500 rpm.

The levels of total cholesterol (Cholesterol) (mmol/l) in serum were determined using enzyme kits and automated colorimetric analyzers.

Plasma glucose levels (mmol/l) in venous blood taken during fasting period were measured by enzymatic hexokinase method with the use of standardized analyzers.

Assessment of cardiovascular risk

Each patient underwent the estimation of the risk levels for the development of complications of cardiovascular diseases (CVD) within 10 years according to the European scale SCORE. Total cardiovascular risk was the following: low risk — <1%, moderate risk — from 1% to 5%, high risk from — 6% to 9%, very high risk — 10–14% [6].

Statistical analysis

Data entry in regional research centers was carried out using the ACCESS MS OFFICE system. Editing and statistical analysis was carried out by the researchers of the National Research Center for Preventive Medicine (Moscow) using the SAS (Statistical Analysis System) software. Descriptive numerical characteristics of the investigated variables: mean, frequencies, standard deviations and standard errors were obtained using PROC SUMMARY, PROC UNIVARIATE, PROC FREQ procedures. Standard significance criteria have been used: χ^2 , and Student's t-test (two-sample).

Results

The results of the multicenter clinical study are present on the basis of the analysis of certain groups of violations and indicators taking into account gender aspects. Risk factors for CVD are divided into the following groups: socio-demographic, biological and behavioral.

Social status and demographic characteristics of the surveyed cohort of patients with AH

Marital status, education level and current occupation were analyzed as a part of social status of patients.

In all 6 cities, the absolute majority of men and women groups were married, which could be explained by established regional and national traditions (Table 2). In the examined cohort, divorces were present in less than 1% of cases. About 12% of examined women and 7% of examined men were widowed. Persons with secondary and special education prevailed in analyzed groups of patients with AH. 31% of men had higher education; the same characteristic in women was higher by a third and reached 44%. The highest number of men with AH having higher education lived in Lenkoran, and the majority of women with AH having higher education lived in Ganja. In other cities and neighboring countries the percentage of people with higher and secondary education turned out to be comparable.

The analysis of occupation status of the examined cohort demonstrated that 43% of men with AH were unemployed at the time of examination, and the majority of them belonged to the working-age population. This trend was detected in the capital Baku, regional centers, and the cities of neighboring states. One third part of women had a job, whereas 63% of females were housewives.

Hemodynamic characteristics of the cohorts of men and women with AH

To assess hemodynamic characteristics, we analyzed such parameters as SBP, DBP, HR and LVH determined by ECG criteria.

In all cities, the average SBP index exceeded 160 mm Hg with the exception of Baku. The highest values of SBP were registered in Ganja and Marneuli both among men and women (Table 3). Higher values of DBP were recorded in Ganja, Baku and Derbent.

In general, in all groups high BP values were accompanied by elevated HR with no gender differences (Table 4).

On the one hand, LVH is an indicator of CVD development, and on the other it is a compensatory mechanism of prolonged AH course [11]. The majority of examined patients had AH for at least 3–5 years. Every second patient of the cohort had ECG criteria of LVH (Table 5).

Adequately selected antihypertensive therapy affects not only hemodynamic parameters, but also

Table 2. **Gender characteristics of the social status of the examined cohort (absolute numbers, n)**

Cities	Marital Status		Education		Job Status	
	Men	Women	Men	Women	Men	Women
Baku	Married 46 Single 2	Married 92 Single 2 Widowed 9	Higher 17 Secondary 31	Higher 13 Secondary 90	Employed 24 Unemployed 24	Employed 18 Housewives 85
Ganja	Married 52 Widowed 4	Married 134 Widowed 10	Higher 14 Secondary 42	Higher 32 Secondary 24	Employed 36 Unemployed 18	Employed 83 Housewives 61
Sheki	Married 28	Married 88 Divorced 1	Higher 7 Secondary 21	Higher 18 Secondary 71	Employed 19 Unemployed 9	Employed 30 Housewives 59
Lenkoran	Married 53 Single 4 Widowed 3	Married 44 Widowed 11	Higher 26 Secondary 34	Higher 14 Secondary 41	Employed 30 Unemployed 30	Employed 17 Housewives 38
Derbent	Married 12	Married 39 Divorced 1	Higher 5 Secondary 35	Higher 10 Secondary 2	Employed 6 Unemployed 6	Employed 8 Housewives 32
Marneuli	Married 43 Divorced 1 Widowed 9	Married 47 Divorced 2 Widowed 23	Higher 21 Secondary 32	Higher 17 Secondary 55	Employed 29 Unemployed 24	Employed 30 Housewives 42

Table 3. **Mean values of SBP and DBP in men and women with AH**

	SBP, mm Hg.		DBP, mm Hg.	
Cities	Men	Women	Men	Women
Baku	155.6±3.1	160.6±2.1	97.5±1.5*	96.9±0.9
Ganja	181.7±3.1**	182.7±1.8*	104.3±1.7**	102.4±0.9**
Sheki	160.7±3.2	156.4±2.4	96.8±2.1	93.3±1.3
Lenkoran	164.2±2.3	161.0±1.6	91.7±0.9	92.4±0.7
Derbent	163.3±8.4	164.2±2.7	96.7±3.8	97.8±1.6*
Marneuli	170.1±2.3*	168.1±2.1*	91.2±1.3	90.3±0.8

* p < 0.05, ** p < 0.01 — significance of differences between groups (in comparison with the group with the minimum average value)

Table 4. **Mean HR (beats per minute) in the examined cohort of patients with AH**

Cities	Men	Women
Baku	74.1±1.9*	77.7±1.2*
Ganja	70.6±1.4	71.7±0.9
Sheki	72.5±3.3	72.2±1.5
Lenkoran	80.7±1.1**	80.0±1.4**
Derbent	69.8±2.2	79.9±2.0**
Marneuli	72.1±1.3	75.7±0.8*

* p < 0.05, ** p < 0.01 — significance of differences between groups (in comparison with the group with the minimum average value)

determines the long-term outcome of cardiovascular complications risk [2, 4]. In addition, we analyzed some aspects of prescribed antihypertensive drugs.

Patients with different stages of AH in different cities adhered to antihypertensive monotherapy with the frequency varying from 20 to 65 % of cases (Table 6). The most frequent intake of one antihypertensive

Table 5. **Identification of LVH by ECG criteria among men and women with hypertension in different cities, n**

Cities	Men, n	Women, n
Baku	30	67**
Ganja	32	70
Sheki	14	31
Lenkoran	28	30
Derbent	6	25*
Marneuli	36*	44*

* p < 0.05, ** p < 0.01 — significance of differences between groups (in comparison with the group with the minimum average value)
The greatest frequency of LVH was detected among AH patients in Baku, Ganja and Marneuli. Among women with AH, the same analogy was observed for the frequency of LVH (Figure 1).

* p < 0.05, ** p < 0.01 — significance of differences between groups (in comparison with the group with the minimum average value)

drug was registered in the cities of Baku and Ganja. In the group of persons receiving combined therapy, high frequency of taking two or more antihypertensive drugs was detected in 10–30 % of cases. On average,

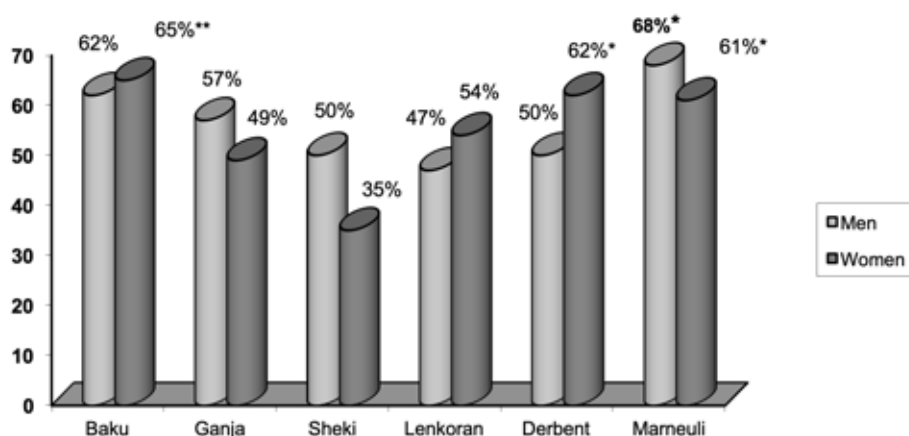


Figure 1. The incidence of LVH in the cohort of men and women with AH

Table 6. Antihypertensive therapy in the cohort of patients with AH

Cities	Monotherapy		Combined therapy		Without therapy	
	Men	Women	Men	Women	Men	Women
Baku	31 (64.6%)	79 (76.7%)	13 (27.1%)	12 (11.6%)	4 (8.3%)	12 (11.6%)
Ganja	35 (62%)	42 (29.2%)	19 (34%)	54 (37.5%)	2 (4%)	48 (33.3%)
Sheki	11 (39.3%)	27 (30.4%)	14 (50%)	52 (58.4%)	3 (10.7%)	10 (11.2%)
Lenkoran	8 (13.3%)	6 (10.9%)	35 (58.3%)	40 (72.7%)	17 (28.3%)	9 (16.4%)
Derbent	5 (42%)	16 (40%)	5 (42%)	18 (45%)	2 (16%)	6 (15%)
Marneuli	9 (17%)	25 (34.7%)	16 (30.2%)	41 (56.9%)	28 (52.8%)	6 (8.4%)

Table 7. Anthropometric parameters of men and women with AH

Cities	BMI, kg/m ²		WC, cm	
	Men	Women	Men	Women
Baku	30.9±0.6*	31.5±0.5*	103.5±1.3*	98.3±0.8
Ganja	28.2±1.3	27.2±0.9	97.2±1.9	93.3±1.3
Sheki	30.7±1.4*	31.4±0.6	104.2±2.3*	100.4±1.1*
Lenkoran	29.01±0.4	28.8±0.6	101.9±1.6	99.8±1.3
Derbent	27.9±0.6	31.8±0.9*	96.3±1.9	101.1±2.3*
Marneuli	30.3±0.5	30.7±0.9	96.3±1.9	92.8±1.6

* p < 0.05 — the significance of differences between groups (compared to the group with the minimum average value)

about 15% of patients with AH and different levels of cardiovascular risk did not receive long-term antihypertensive therapy. This fact was most evident among men with AH in Lenkoran and Marneuli (28.3% and 52.8% of cases, respectively) and women with AH in Ganja (33.3% of cases).

Analysis of behavioral and biological risk factors

In this study, patients were interviewed using an adapted international questionnaire, which allowed determination of the harmful habits presence including alcohol abuse and smoking [13].

About 40% of men with AH took small amount of alcohol regularly (or occasionally). In Baku and Ganja alcohol abuse was detected in 10% and 9% of men, respectively. The lowest frequency of alcohol abuse

was registered among men in Lenkoran and Sheki, while in Derbent and Marneuli this characteristic was present in 25% and 22% of cases, respectively. The smoking status picture was slightly different. Thus, the greatest number of smokers among men with AH was detected in Lenkoran (60%) and Ganja (39%), and the third position was taken by Baku (37%). In other cities, the status of smoking has the following characteristics: in Sheki — every third men with AH smoked (31%), in Derbent — every fourth (25%) and in Marneuli — every fifth (19%) men with AH was a smoker.

The use of alcohol and smoking by women was not recorded in any of 6 cities, which, apparently, could be explained by national and religious traditions.

In this study we estimated such anthropometric parameters like BMI and WC. According to the aver-

Table 8. Levels of total cholesterol and blood glucose in patients with AH

Cities	Total cholesterol, mmol/L	Glucose, mmol/L		
	Men	Women	Men	Women
Baku	5.8±0.4*	5.8±0.3	5.8±0.2	6.4±0.3*
Ganja	6.4±0.2*	6.0±0.09*	5.9±0.3	6.4±0.2*
Sheki	5.2±0.2	5.04±0.07	5.6±0.1	5.9±0.2
Lenkoran	5.2±0.1	5.4±0.1	5.4±0.4	5.2±0.2
Derbent	5.3±0.2	5.8±0.2	6.6±0.6*	5.6±0.2
Marneuli	5.5±0.4	5.4±0.4	6.5±0.2*	6.8±0.2**

* p < 0.05, ** p < 0.01 — the significance of differences between groups (in comparison with the group with the minimum average value)

age statistical values in the whole group, BMI values corresponded to excess body weight and obesity stage 1 (Table 7). The most evident BMI increase was registered in Baku, Marneuli and Sheki, both among men and women. It is known that WC is a marker of abdominal obesity [14]; according to this parameter, all groups regardless of gender are characterized by its high incidence (WC in men > 94 cm, in women > 80 cm). A more pronounced increase of WC values in men with AH was recorded in Baku, Lenkoran, Sheki and Ganja. Similar values were found among women, especially in women from Sheki, Derbent and Baku. Lower values of WC were found in AH patients in Marneuli and Ganja, but their average WC values exceeded the normal numbers by 15–20 %.

According to the protocol, the blood levels of total cholesterol and fasting blood glucose were analyzed in all patients. Mean values of total cholesterol in the blood of men and women with hypertension were higher than normal (Table 8). The highest rates were observed in patients, natives of the city of Ganja, the second position was taken by the patients with AH from Baku. It is interesting to mention that that men and women of both cities had similar trends. Smaller values of total cholesterol were detected in patients from Sheki and Lenkoran.

We observed that the average blood glucose levels were either above the norm or within the upper limit of normal values in all cities. Among the examined men with AH, the most pronounced hyperglycemia was observed in Derbent and Marneuli, while relatively low values of blood sugar were found in men with AH in Sheki and Lenkoran. In general, the frequency of hyperglycemia in women was higher in comparison with men. High fasting glucose in blood was detected in women with AH from Marneuli, Baku and Ganja. We assume that this could be due to the nature of food and lifestyle in urban settings.

Evaluation of cardiovascular risk in the cohort of men and women with different AH stages

One of the main objectives of this project was to assess the risk of cardiovascular complications. For this purpose, the SCORE scale recommended for wide application by the European Society of Cardiology has been used, both at the population level and in cohorts with the presence of various risk factors [6]. During the last 15 years, the SCORE scale has been actively used in the CIS and Russia.

The present study presents data on the incidence of high and very high cardiovascular risk among AH patients. The level of cardiovascular risk varied from city to city, which indicates a heterogeneity of risk factors that had been taken into account for assessing the total cardiovascular risk (Table 9).

Table 9. Assessment of cardiovascular risk according to the SCORE scale in the examined patients with AH, n (%)

Cities	Men, n	Women, n		
	High risk	Very high risk	High risk	Very high risk
Baku	21	8	41	29
Ganja	30*	16	56	37
Sheki	8	6	18	17
Lenkoran	16	12	14	12
Derbent	7**	3*	15*	12*
Marneuli	28*	13	31*	29*

* p < 0.05, ** p < 0.01 — the significance of differences between groups (in comparison with the group with the minimum average value)

Every second male with AH in three cities (Ganja, Marneuli and Derbent) had high cardiovascular risk according with the SCORE scale. In the same cities, it was found that every third man with AH had very high cardiovascular risk. The lowest frequency of high and very high cardiovascular risk was detected among men in Sheki and Lenkoran (Figure 2).

The picture of cardiovascular risk in women is slightly different from men. The highest frequency of very high cardiovascular complications risk was de-

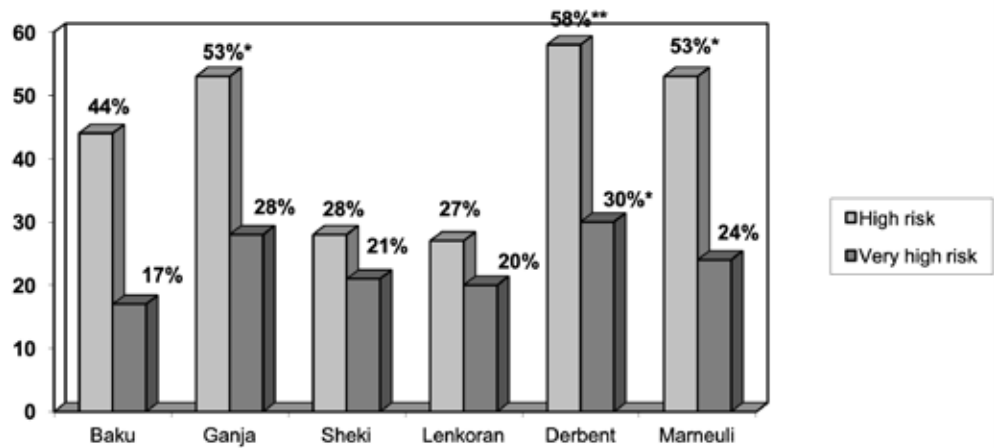


Figure 2. The incidence of high and very high cardiovascular risk in the cohort of men with AH

* $p < 0.05$, ** $p < 0.01$ — the significance of differences between groups (in comparison with the group with the minimum average value)

tected in Derbent and Marneuli with the frequency of 40 % and 44 %, respectively. Very high cardiovascular risk was registered in 26–28 % of women with AH in Baku and Ganja, every fifth woman of the other two cities had very high cardiovascular risk. In four cities more than 40 % of women with AH had a high cardiovascular risk (Figure 3).

Thus, high incidence of high and very high cardiovascular risk has been identified in the cohort of men and women with hypertension in two large cities of Azerbaijan and in the cities of neighboring countries with compact populations of Azerbaijanis.

Somatic comorbidity in patients with AH

Within the framework of the study we investigated gender features of somatic disease occurrence. According to the results, about 20 concomitant diseases of various organs and systems were detected. Among men, the frequency of individual comorbidities

varied from 0.4 % to 9 %. In women with AH somatic diseases were present in 0.4 % –15 % of cases.

In the surveyed cohort of patients with AH, the most frequent somatic disease was diabetes mellitus type 2, its occurrence in women with AH was — 15 % and in men — 9 % (Table 10). 9 % of men with AH had chronic cholecystitis, and 7 % of men had chronic gastritis. Other diseases were detected in less than 4 % of cases.

Osteochondrosis, chronic cholecystitis, chronic gastritis and neuroses were diagnosed in 5–6 % of female cases.

It should be emphasized that somatic diseases are registered on the basis of medical documentation. Examination methods provided in the project protocol did not allow the identification or verification of additional somatic diseases. We assume that the picture of the prevalence of somatic diseases could appear different after in-depth examination.

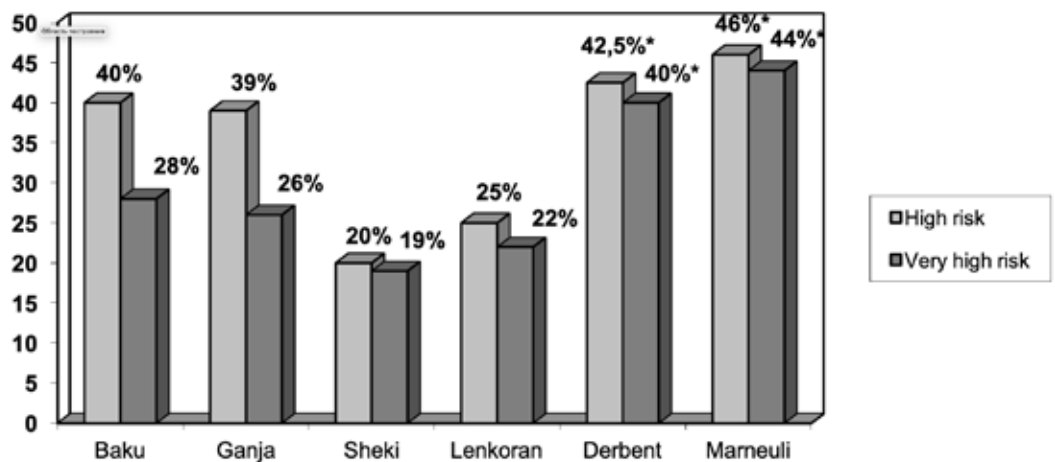


Figure 3. The incidence of high and very high cardiovascular risk in the cohort of women with AH

* $p < 0.05$ — the significance of differences between groups (compared to the group with the minimum average value)

Table 10. **Concomitant diseases in the cohort of patients with AH**

Diseases	Men, n = 257	Women, n = 503
Type 2 diabetes mellitus	24 (9%)	74 (15%) *
Chronic. cholecystitis	24 (9%)	25 (5%)
Chronic. gastritis	19 (7%)	29 (5.8%)
Osteochondrosis	8 (3%)	32 (6.4%)
Neurosis	7 (3%)	24 (4.8%)
COPD	10 (4%)	14 (2.8%)
Urolithiasis	5 (2%)	2 (0.4%)
Chronic pyelonephritis	-	6 (1%)
Cardiopsychoneurosis	-	7 (1.4%)
Prostatitis	5 (2%)	-
Fatty degeneration of the liver	6 (2%)	-
Arrhythmia	3 (1%)	9 (1.8%)
Hypothyroidism / goiter	1 (0.4%)	8 (1.6%)*
Pancreatitis	2 (0.8%)	-
Anemia	-	8 (1.6%)
Psoriasis	1 (0.4%)	-
Glaucoma	1 (0.4%)	-
Rheumatism	2 (0.8%)	-
Gout	-	2 (0.4%)
Thalassemia	-	1 (0.2%)

* p <0.05 — significance of differences between groups of men and women

Conclusion

The present study is the first multicenter national project with international participation, analyzing a wide range of risk factors, assessing the total cardiovascular risk and co-morbidity in cohorts of men and women with AH, and taking into account gender aspects.

For the purpose of primary prevention of cardiovascular complications in persons with hypertension, it is necessary to provide effective control of blood pressure, which will also lead to regression of left ventricular hypertrophy. Along with this, it is necessary to conduct serious work among men to combat bad habits, to correct metabolic disorders, as well as total blood cholesterol and glucose levels. Total cardiovascular risk assessment can serve as a good indicator for estimation of multifactorial prophylaxis efficacy in patients with AH.

References

1. Vlasoff T, Laatikainen T, Korpelainen V, Uhanov M, Pokusajeva S, Tossavainen K, Vartiainen E, Puska P. Trends and educational differences in non-communicable disease risk factors in Pitkäranta, Russia, from 1992 to 2007. *Scand J Public Health*. 2015 Feb; 43 (1): 91–8.
2. Shalnova SA, Oganov RG Five-year dynamics of the main clinical symptoms in patients with IHD with stable angina in Russia compared with other countries (CLARIFY Register). *Cardiology*. T. 57. № 1. P. 17–22. Russian.
3. Oganov RG, Maslennikova G.Ya. Demographic trends in the Russian Federation: the contribution of diseases of the cir-

culatory system. *International Journal of Heart and Vascular Diseases*. 2013; 1 (1): 3–10. Russian.

4. Mehdiev S.Kh., Mustafaev II, Mamedov MN, Deev A.D. Clinical and epidemiological features of arterial hypertension in patients with type 2 diabetes mellitus. *Cardiology*. 2016. P. 56. № 11. P. 43–49. Russian.
5. Evdokimova AA, Mamedov MN, Deev AD, Tokareva ZN, Eganyan RA, Oganov RG Estimation of the prevalence of risk factors and determination of the total cardiovascular risk in a random urban sample of men and women. *Preventive Medicine* 2010; 2: 3–8. Russian.
6. Conroy R. M., Pyorala K., Fitzgerald A.P. Et al. Estimation of ten-year risk of fatal cardiovascular disease in the Europa: the SCORE project. *Eur. Heart J*. 2003; 24: 987–1003.
7. Assman G., Cullen P., Schulte H. The Munster Heart Study (PROCAM). *European Heart Journal* 1998; 19 (Supp A): 2–11.
8. Castelli W., Anderson K. A population at risk. Prevalence of high cholesterol levels in hypertensive patients in the Framingham study. *Am. J. Med*. 1986; 80 (Supp 2A): 23–32.
9. Massimo F. Piepoli, Arno W. Hoes, Stefan Agewall, Christian Albus, Carlos Brotons, Alberico L. Catapano, Marie-Therese Cooney, Ugo Corrà, Bernard Cosyns, Christi Deaton. 2016 European guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). *Eur Heart J* (2016) 37 (29): 2315–2381.
10. Oganov RG, Drapkina OM Polymorbidity: the patterns of formation and the principles of combining several diseases in one patient. *Cardiovascular therapy and prevention*. 2016; 15. No. 4: 4–9. Russian.
11. 2013 ESH / ESC Guidelines for the management of arterial hypertension. *European Heart Journal*. 2013; 34: 2159–2219
12. Boitsov SA, Balanova Yu. A., Shalnova SA, Deev AD, Artamonova GV, Gatagonova TM, Duplyakov DV, Efanov A. Yu., Publisher: Zhernakova Yu. V., Konradi AO, Libis RA, Minakov AV, Nedogoda SV, Oschepkova EV, Romanchuk SA, Rotar O. P., Trubacheva I A., Chazova I. Ye., Shlyakhto E. V. on behalf of the participants in the study of ESSE-RF. Arterial hypertension among persons 25–64 years: prevalence, awareness, treatment and control. *Cardiovascular therapy and prevention*. 2014; 4 (13): 4–14. Russian.
13. Ivinskaya E.Yu., Rozanov VB, Aleksandrov AA, Pugoyeva Kh.S., Klimovich V.Yu. Association of risk factors for cardiovascular diseases and the likelihood of developing fatal cardiovascular events with the amount of alcohol consumed in a sample of 42–43 years old men. *International Journal of Heart and Vascular Diseases*. 2016; 4 (12): 3–16. Russian.
14. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases. *European Heart Journal*. 2013; 34: 3035–3087.

Efficacy of a Cardiovascular Behavioral Intervention Program and Full Body CT Scanning on Changes in Coronary Artery Calcium, Thoracic and Epicardial Fat

¹ *Nathan D. Wong, PhD, ²Alisa Eisenberg, MS, ²Jolie Cecere, RN, ³Damini Dey, PhD,
²Chris Patao, BS, ¹Wenjun Fan, MD, MS, ⁴Lewis Wexler, MD, and
²Harvey C. Eisenberg, MD

From the ¹Heart Disease Prevention Program, Division of Cardiology, University of California, Irvine, California, ²Re-Engineering Healthcare, Inc., Newport Beach, California, ³Dept. of Imaging, Cedars-Sinai Medical Center, Los Angeles, California, ⁴Dept. of Radiology, Stanford University School of Medicine, Stanford, California

Background

Limited data exist on the efficacy of multifactorial lifestyle programs on impacting the progression of atherosclerosis and body fat measures. We examined the efficacy of a lifestyle intervention program combined with a full body CT scan on progression of coronary artery calcium (CAC), thoracic and epicardial fat.

Methods

We studied 73 participants randomized to the RENEWTM lifestyle intervention program or standard of care. The RENEWTM Program included modules on responding to stress, enhancing the effects of relaxation, nourishing the immune system, physical activity, and social support. Participants received baseline and 2-year follow-up measures of risk factors and CAC (volume and Agatston score) from whole body computed tomography (CT); the intervention group also received a comprehensive physician consultation on the scan results. A subset also had epicardial and thoracic fat assessed by CT. We examined baseline-follow-up changes in CAC, epicardial and thoracic fat between treatment groups.

Results

Among 73 subjects (35 control and 38 intervention) who completed the program over 2 year follow-up, after adjustment for baseline CAC, age, gender, and risk factors, there were increases in (natural log units) both CAC vol-

ume (mean=0.17, 95% confidence interval= [0.07–0.25] cm³) and CAC score (0.24 [0.11–0.36]) in the control group relative to the intervention group [–0.29 [–0.63–0.02] cm³ for volume ($p=0.0071$ relative to controls) and –0.25 [–0.58–0.09] for score ($p=0.0031$ relative to controls). In a subset of 42 subjects with measures of epicardial and thoracic fat, intervention pre-post changes in epicardial fat volume were 10.6 [–4.5–25.2] cm³ in controls and –6.9 [–19.2–5.3] cm³ in intervention group participants ($p=0.081$ for difference) and thoracic fat volume changes were 4.6 [–20.2–28.6] cm³ and –29.9 [–49.5 to –9.3] ($p=0.044$ for difference) in fully adjusted analyses.

Conclusions

Our findings suggest a potentially beneficial impact of a multifactorial behavioral intervention program combined with a full body CT scan consultation on retarding progression of CAC and on reducing epicardial and thoracic fat volume. Larger scale trials are needed to confirm findings and implications on cardiovascular outcomes.

Key words

Behavior, coronary calcium, cardiovascular disease, computed tomography, fat

Introduction

There is a wealth of data demonstrating that increased levels of coronary calcium (CAC) assessed by computed tomography (CT), a marker of atherosclerosis burden, predict future coronary heart disease (CHD), cardiovascular disease (CVD) events (1, 2), and mortality (3, 4) and improves risk prediction more than other biomarkers and measures of sub-clinical CVD (5). In addition, pericardial and visceral fat measured by CT has been shown to be related to prevalent CVD in the Framingham Heart Study (6) and both pericardial fat and thoracic fat are associated with a greater likelihood of major adverse cardiac events, with the former improving risk prediction (7). Epicardial fat has also been shown to relate to high risk plaque features and stenosis on CT angiography (8) and thoracic fat to the extent and severity of CAC (9).

We have previously shown progression of CAC to also relate to a greater risk of CHD events overall and independent of baseline CAC score (10). While several key CHD risk factors predict the progression of CAC (11), interventions shown to retard the progression of CAC are limited (12), and studies involving statin interventions have been negative (13, 14). A key question remains as to whether CAC progression more closely relates to progression of vulnerable plaque as opposed to plaque stabilization as others have suggested (15). CAC findings have also been noted to motivate individuals' adherence to lifestyle and medical therapy recommendations (16, 17) and a low-risk lifestyle to predict less progression of CAC (18). Also, among adolescents, epicardial fat was greater in those with unhealthy lifestyle habits (19), and in a small trial of adults with impaired glucose tolerance, a combined low-fat diet and endurance

exercise program related to greater improvements in abdominal, thigh, and thoracic fat (20). While there are data documenting the association of behavioral and psychosocial factors with cardiovascular disease events (21), there are few investigations (22–24) that have examined whether a comprehensive lifestyle/behavioral intervention program may impact the progression of CAC or changes in epicardial or thoracic fat as measured by CT.

Our hypothesis was that the combination of a multifactorial behavioral intervention program with an intensive physician consultation of whole body CT results would beneficially impact on the progression of CAC and changes in epicardial and thoracic fat.

Materials and Methods

Eligible individuals included healthy volunteers, men or women aged 35 and over who provided informed consent to participate including the baseline, interim, and follow-up clinic visits, as well as willingness to participate in the on-line intervention (if selected to be in that group). Exclusions consisted of those with known cardiovascular disease, cancer, or any life-threatening or debilitating illness, including psychiatric illnesses, or significant difficulty with the English language that would preclude successful participation in the program. We initially enrolled 267 volunteer asymptomatic adults consisting of firefighters/police workers ($n=173$), active military personnel ($n=57$) and community college staff ($n=37$). The first two cohorts were among those included as target populations proposed based on the Department of Defense contract that funded the study, with the third cohort added to complete recruitment efforts. Participants were recruited by union leaders and/or direct advertisements to participants.

Subjects were randomized (using a blocked randomization list created by a computerized random assignment generator) either to an intervention group or to usual care. A whole body CT scan was performed using a multidetector CT scan on all participants at baseline with the results discussed by a physician only in the intervention group (since the physician feedback was part of the intervention), and after 2 years of follow-up a repeat scan was performed with a detailed evaluation of the results discussed by a physician with all participants (in part as a motivation to complete the study). The intervention group additionally received The RENEW™ Program (www.therenewprogram.net) of lifestyle intervention (as described below). Participants' physicians, regardless of study group were notified as to potentially significant findings needing further follow-up. The whole body CT was part of the approved protocol and was utilized to screen for possible pathology throughout the chest and abdomen and surrounding organs. This study was carried out in accordance with the recommendations of the Western Institutional Review Board with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Western Institutional Review Board and is registered in clinicaltrials.gov with Unique Protocol ID:20111268. The current analysis of CT findings reports on the primary outcome of changes in coronary calcium as well as on secondary outcomes of pericardial and thoracic fat.

The RENEW™ Program's comprehensive intervention was provided by a licensed behavioral therapist or trained lifestyle coach and included direct contact for all sessions via webcam. This consisted of 7 bi-monthly hour-long sessions over 16–18 weeks followed by an average of 15 monthly 30 minute check-in sessions (maintenance) over 80 weeks. This included modules on responding to stress, enhancing effects of relaxation, nourishing the immune system, physical activity, and social support. Specific interventions were included in all modules, for example: responding to stress more effectively (using solution focused, cognitive behavioral tools), enhancing the effects of relaxation (practicing mindfulness and understanding how this affects biochemistry), nourishing the immune system (nutrition, addressing previous eating habits and ways to improve, including medical needs and underlying emotional issues), energizing your body (physical activity addressing markers for wellness, healthy aging and sports per-

formance), and welcoming others as support (social support and communication skills). A prescribed set of questions determined participants' level of coping skills associated with characteristics of resilience and health habits. Interventions in module one (stress) used these results to customize tools aimed at Type A Personality traits or dominance of Negative Appraisal, for example. Module one offered concrete solutions for participants to improve the way they address challenges based on these measurements. Interventions in module two (relaxation) were geared towards training participants to use the relaxation response in real life situations to gain mastery over their biochemistry, for improved sleep, and to become more aware of their personal stress signals. These improved life skills influenced the foods they habitually craved or ate regularly. Participants were guided in module three (nutrition) to make needed changes according to their medical needs and health habit surveys. Dietary suggestions were based on a Mediterranean style of eating combined with the Food Pyramid and participants medical needs, preferences and physical location. Additional topics included: organic foods, toxins in food and plastics, emotional vs. physical hunger, for example. Physical activity was addressed in module four and included issues of wellness, healthy aging or sports performance, depending on participants needs and according to American Heart Association guidelines. Care of the spine and how to strengthen core muscles was addressed by specific exercises, for example, in response to body scan report on those issues. Participants tracked their progress, reported obstacles and were guided to build a routine that included their medical needs and personal preferences. Module five (social support) included communication skills, how to build a social network and was customized to participants answers to prescribed questions regarding emotional and physical support. Module six (maintenance) addressed issues related to sustaining changes made over the course of the study. Topics explored included expectations, anticipating obstacles, staying inspired, how to get back on track and keeping your emphasis on feeling good, according to participants individual value system and medical needs based on their blood work, blood pressure, BMI and body scan report.

Coronary artery calcium (CAC) was assessed by a trained technologist with the Agatston score measured and volume score calculated, summed among the four major coronary arteries according to conventional methods (25). The QFAT™ software was uti-

lized to provide measures of epicardial and thoracic fat volume (in cm³) as described previously (26) in a subset of participants who had the required DICOM-archived CT scan data both pre and post-intervention. Data for these analyses in earlier participants (who are included in the CAC analyses) were not available due to unavailability of the required DICOM-archived CT data.

We utilized the Student's t-test for continuous measures or Chi-square test of proportions for categorical measures to compare baseline demographic and clinical factors initially between subjects included versus not included in the current analysis as well as between included intervention and control group participants. Coronary calcium score was log-transformed with baseline and 2-year changes (mean and 95% confidence intervals) in CAC score and volume compared by the Student's t-test between groups, with analysis of covariance utilized for comparison of means (with 95% confidence intervals) adjusted for age, gender, baseline CAC score or volume, and standard risk factors between groups. Similar methodology was used to compare changes in epicardial and thoracic fat from baseline to follow-up between intervention groups, unadjusted and adjusted for covariates as well as baseline fat volume. These fully adjusted changes are also plotted for calcium score and volume changes and for thoracic and pericardial fat

volume changes. An exploratory analysis was done to evaluate for changes in CAC density (Agatston score divided by area score) between groups among the subset of participants with CAC>0 at baseline. Finally, Pearson correlation analyses were done to examine within the overall sample the association between changes in key psychosocial indices of interest and changes in thoracic and pericardial fat volume as well as natural log of coronary calcium score and volume.

Results

Two hundred and sixty-seven subjects (mean age 45.8 years, 23.8% female) were enrolled, including 135 randomized to RENEW and 132 to standard care. 73 subjects had baseline and follow-up CT scan data available for analysis (35 control and 38 intervention) for the current analysis and report. Table 1 shows baseline demographic and clinical characteristics according to the 73 subjects included vs. 194 subjects not included in the current report. There were no significant differences in age, gender, or baseline cardiovascular risk factors between groups except for HDL-C cholesterol levels being significantly lower and baseline CAC scores, volumes, and the presence of CAC being significantly greater among those included subjects. Table 2, however, shows no differences in baseline risk factors or CAC scores or volume among those subjects who were randomized

Table 1. **Baseline Characteristics Between Included and Not Included Participants**

	Included (n=73)	Not Included (n=194)	p-value
Age (yr)	46.6±6.5	45.3±6.6	0.1654
Female Gender (%)	17 (23.3)	48 (24.9)	0.7558
Prior CHD ¹ (%)	0 (0.0)	1 (0.5)	0.5245
Prior Diabetes ¹ (%)	3 (4.1)	10 (5.2)	0.6427
Cholesterol Lowering Therapy (%)	13 (17.8)	19 (9.8)	0.1115
Total Cholesterol (mg/dL)	178.8±30.7	188.5±36.8	0.0524
HDL Cholesterol (mg/dL)	44.2±12.8	50.7±16.7	0.0015
Glucose (mg/dL)	88.5±16.6	90.9±21.1	0.3442
Waist (inches)	39.0±5.7	37.9±4.9	0.1090
Weight (lbs)	201.7±38.1	194.3±36.4	0.1530
Pulse (Beats/Sec)	61.3±11.5	63.9±10.3	0.0852
Diastolic Blood Pressure (mmHg)	78.2±9.0	80.0±12.5	0.2087
Systolic Blood Pressure (mmHg)	117.7±12.3	118.6±11.2	0.6031
CAC Present (score>0) (n,%)	31 (42.5)	52 (26.8)	0.0115
CAC Volume	41.6±91.5	27.1±104.1	0.2963
Natural Log Transformed CAC Volume ²	1.7±2.1	1.0±1.8	0.0048
CAC Score	39.9±99.8	25.7±109.7	0.3362
Natural Log Transformed CAC Score ²	1.5±2.0	0.8±1.7	0.0145

¹ Two Sided Fisher's Exact Test. ² Natural Log (Variable+1). Values indicate mean + standard deviation or n (%).

Sample sizes across variables vary slightly due to available data. CAC=coronary artery calcium; HDL=high density lipoprotein

Table 2. **Baseline Characteristics by Groups**

	Intervention n=38		Control n=35		P-value
	N	%	N	%	
Gender (Female %)	12	31.6	5	14.3	0.0807
Prior Diabetes ¹	1	2.6	2	5.7	0.6038
	Mean	SD	Mean	SD	
Age (yr)	47.4	6.7	45.8	6.2	0.2975
Total Cholesterol (mg/dL)	179.2	25.8	178.3	35.9	0.9101
HDL Cholesterol (mg/dL)	45.1	11.4	43.2	14.4	0.5573
Triglycerides (mg/dL)	140.9	79.7	131.4	108.2	0.6798
LDL Cholesterol (mg/dL)	108.5	28.9	111.0	32.4	0.7476
Non-HDL Cholesterol (mg/dL)	131.0	34.6	129.4	29.1	0.8362
Total Cholesterol/HDL	4.2	1.2	4.4	1.4	0.5896
Glucose (mg/dL)	88.5	17.5	88.5	15.8	0.9949
Waist (inches)	38.3	5.8	39.8	5.4	0.2841
Weight (lbs)	195.3	36.0	208.7	39.6	0.1400
Pulse (Beats/Sec)	62.3	10.7	60.3	12.4	0.4669
Diastolic Blood Pressure (mmHg)	77.3	7.8	79.2	10.2	0.3748
Systolic Blood Pressure (mmHg)	117.2	13.6	118.3	10.9	0.7123
CAC Volume	28.7	61.2	55.6	115.3	0.2249
Natural Log Transformed CAC Volume ²	1.4	2.0	2.0	2.2	0.2393
Coronary Calcium Score	25.2	65.1	55.9	126.4	0.2035
Natural Log Transformed CAC Score ²	1.2	1.9	1.8	2.2	0.2151

1. Two Sided Fisher’s Exact Test.
2. Natural Log [Variable+1]. CAC=coronary artery calcium; HDL=high density lipoprotein, LDL=low density lipoprotein

to the intervention vs. control groups among the 73 included subjects. Absolute baseline and log-transformed CAC scores and volumes are also presented.

The Figure 1 shows the distribution of the unadjusted changes in log-transformed CAC score for intervention and control groups noting increases in CAC score were more frequent among control compared to intervention group participants. Table 3

shows results of unadjusted and adjusted changes in CAC volume and score. From analyses fully adjusted for baseline volume or score, age, sex, LDL-cholesterol, systolic blood pressure, smoking status and diabetes, the control group showed progression of CAC volume (0.17) and score (0.24) relative to the intervention group [−0.29 for volume, $p=0.007$ relative to control and −0.25 for score, $p=0.003$ relative

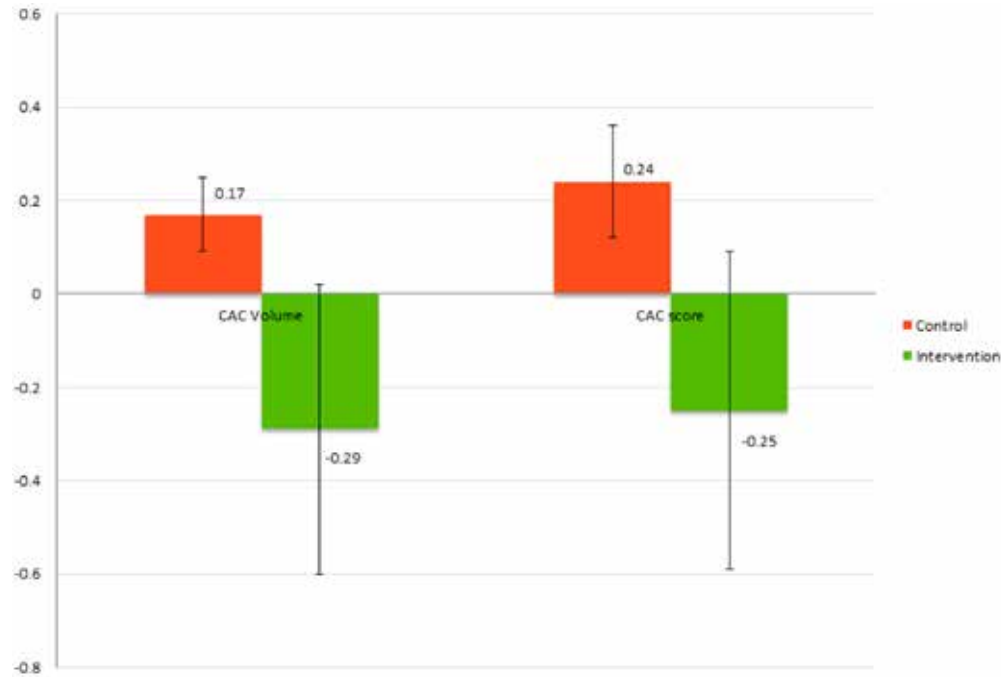


Figure 1. Adjusted Changes of CAC Volume and CAC Score between Control and Intervention Group. $p<0.01$ comparing the change between control and intervention group for both CAC volume and CAC score

Table 3. **Changes in Coronary Volume and Coronary Calcium Scores (log-transformed) Within and Between Intervention Groups**

	Control (n=35)	Intervention (n=38)	p-value
Unadjusted			
CAC Volume	0.45 [-1.10-2.00]	0.18 [-0.86-1.22]	0.0837
CAC Score	0.55 [-0.96-2.06]	0.20 [-0.88-1.28]	0.0264
Adjusted ¹			
CAC Volume	0.44 [0.21-0.66]	0.19 [-0.02-0.41]	0.1246
CAC Score	0.53 [0.31-0.76]	0.21 [-0.01-0.43]	0.0428
Adjusted ²			
CAC Volume	0.17 [0.07-0.25]	-0.29 [-0.63-0.02]	0.0071
CAC Score	0.24 [0.11-0.36]	-0.25 [-0.58-0.09]	0.0031

1. Numbers were displayed as means with 95 %Confidence Interval
2. Adjusted for Baseline Volume or Score Value;
3. Adjusted for baseline volume or score value, age, sex, LDL -Cholesterol, systolic blood pressure, smoking status and diabetes.
CTL = control group (n=35), INT = intervention group (n=38)

to control). In an exploratory analysis of changes in CAC density in the subset of participants with CAC volume >0 at baseline and follow-up (14 intervention and 17 control group participants), there were no significant differences in CAC density change either in unadjusted analyses (0.25 vs. 0.52 for intervention vs. control group, participants, respectively, p=0.34) or fully adjusted analyses (-0.47 vs.-0.07, p=0.42).

In a subset of 42 subjects with measures of epicardial and thoracic fat, adjusted baseline measures in epicardial fat volume and thoracic fat volume were not significantly different between intervention and control groups (107.8 cm³ vs. 122.5 cm³ for epicardial fat and 183.3 cm³ vs. 214.9 cm³ for thoracic fat);

however, in fully adjusted analyses (including baseline fat volume and all other covariates), intervention group pre-post changes in epicardial fat volume were 17.5 cm³ lower (p=0.0807) and thoracic fat volume 34.5 cm³ lower (p=0.0437) when compared to the control group (Figure 2,Table 4).

We also examined components of the RENEW Program and whether increases in score components were associated with reductions in epicardial or thoracic fat, or reduced progression of CAC. From fully adjusted analyses, subjects with increases (improvements) in the following psychosocial measures had significant (p<0.05 to p<0.01) decreases in thoracic fat: social support network (p=0.037), cognitive

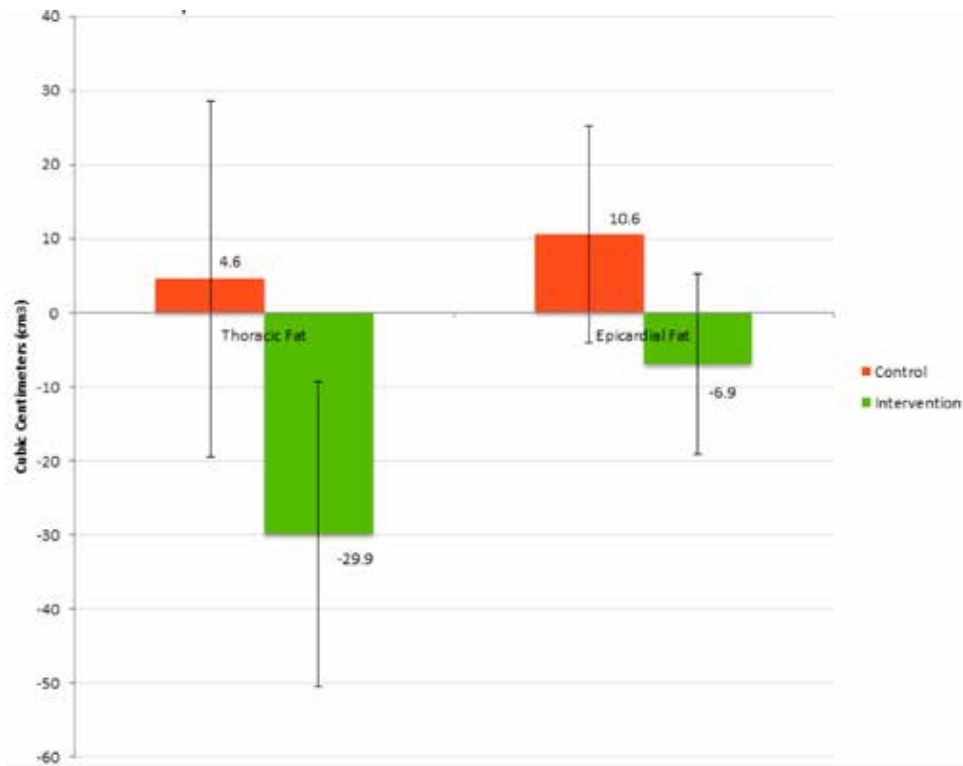


Figure 2. Adjusted Changes of Thoracic Fat and Epicardial Fat between Control and Intervention Group. p<0.05 comparing thoracic fat change and p=0.0807 comparing epicardial fat change between control and intervention group.

Table 4. **Difference of Epicardial and Thoracic Fat Change Between Control and Intervention Groups**

Dependent Variable		Control (n=19)	Intervention (n=23)	Parameter (Slope)	p-value
Baseline					
Epicardial Volume	Unadjusted	122.5 (53.1–191.9)	107.8 (–1.2–214.4)	–14.7	0.32
Epicardial Volume	Adjusted	111.7 (92.2–131.2)	111.4 (95.3–127.4)	–0.4	0.98
Thoracic Fat Volume	Unadjusted	214.9 (–74.2–355.6)	183.3 (–20.0–386.6)	–31.6	0.27
Thoracic Fat Volume	Adjusted	190.8 (151.2–230.4)	196.6 (164.0–229.3)	5.8	0.83
Changes from baseline to follow-up					
Epicardial Volume	Unadjusted	12.1 (–43.0–67.2)	–5.6 (–53.6–42.4)	–17.7	0.035
Epicardial Volume	Adjusted	10.6 (–4.5–25.2)	–6.9 (–19.2–5.3)	–17.5	0.081
Thoracic Fat Volume	Unadjusted	–4.5 (–109.6–100.6)	–23.0 (–123.0–77.0)	–18.5	0.26
Thoracic Fat Volume	Adjusted	4.6 (–20.2–28.6)	–29.9 (–49.5– –9.3)	–34.5	0.044

Numbers were displayed as means with 95 %Confidence Interval

Method=0 (Control) (n=19); Method=1 (Intervention)(n=23)

Covariates: age, gender, race, BMI, hypertension, HDL –C, LDL –C, current smoker, diabetes, and additionally when comparing adjusted differences in changes between intervention and control groups, the baseline epicardial or thoracic fat volume.

hardiness ($p=0.044$), negative appraisal coping style ($p=0.035$), alcohol recreational drugs and cigarettes (ARC) score ($p=0.012$), and psychological well-being ($p=0.026$); epicardial fat: social support network ($p=0.018$), type A behavior ($p=0.0094$), cognitive hardiness ($p=0.0025$), negative appraisal coping style ($p=0.025$), coping style threat minimization ($p=0.014$), exercise ($p=0.0079$), and rest and sleep ($p=0.0055$); progression of CAC volume: stress ($p=0.025$).

Discussion

Our clinical trial suggests a web based (direct contact), comprehensive behavioral intervention program (The RENEW Program™) combined with a detailed physician review of whole body CT results may have a beneficial impact on atherosclerosis progression by reducing the progression of CAC (as a marker of atherosclerotic burden) as well as reducing both epicardial and thoracic fat measured by repeat CT scans over a two-year period. Previous studies have shown the extent of progression of CAC relates to increased risks of CHD events, even independent of baseline CAC score (10) and measures of both pericardial and thoracic fat to relate to cardiovascular events (6–7), epicardial fat to high risk plaque features (8) and thoracic fat to subclinical atherosclerosis (9).

There are limited data on the efficacy of behavioral interventions on reducing CHD event risk. The Recurrent Coronary Primary Prevention Study showed modification of Type A Behavior in CHD patients to reduce recurrent CHD events (27); however, the

ENRICH Clinical Trial also in CHD patients showed modification of depression not to reduce recurrent events or mortality (28). Moreover, observational data from the Multiethnic Study of Atherosclerosis (18) have shown subjects following a healthy lifestyle (based on a score consisting of diet, exercise, body mass index, and smoking status) to have both less progression of CAC over 3.1 years as well as lower all-cause mortality over 7.6 years.

Clinical trials involving statin therapy have not been shown to have an impact on changes in CAC (14, 15); however, a single dietary supplement trial involving aged garlic extract has shown positive effects in retarding progression of CAC (29) as well as increase in epicardial, pericardial, and periaortic adipose tissue (30). More recent data suggests statins may have an impact on stabilizing atherosclerotic plaque (31, 32). While we have previously shown progression of CAC to relate to greater risks of future CHD events (10), there is controversy as to whether CAC progression is a sign of atherosclerotic progression or stabilization, and some have argued further study should be done to understand this before investigations are proposed to utilize CAC progression as an efficacy endpoint (15).

The potential role of CAC screening in modifying preventive behaviors has been previously documented by our group and others. We previously showed in an observational study of 703 men and women aged 28–84 who received CAC scanning, that the CAC score was independently associated with participants' new

Table 5. **Adjusted Regression Coefficients (with 95 % confidence limits) for the Change in Clinical Measures (Thoracic Fat, Epicardial Fat, CAC score and CAC volume) with the Change in Psychosocial Measures.**

	Thoracic Fat	Epicardial Fat	CAC Volume	CAC Score
Prevention Score	-110.93 (-259.94-38.08) (p=0.12)	-54.48 (-127.17-18.20) (p=0.12)	-0.69 (-1.96-0.58) (p=0.26)	-0.15 (-1.76-1.46) (p=0.84)
Stress	-1.32 (-11.42-8.79) (0.77)	-2.00 (-6.69-2.70) (p=0.35)	-0.08 (-0.14- -0.01) (p=0.025)	-0.08 (-0.17-0.01) (p=0.062)
Health Habits	-4.55 (-12.92-3.82) (p=0.25)	-2.92 (-6.71-0.86) (p=0.11)	0.01 (-0.04-0.06) (p=0.77)	0.03 (-0.03-0.09) (p=0.30)
Social Support Network	-3.31 (-6.37- -0.25) (p=0.037)	-1.77 (-3.15- -0.39) (p=0.018)	-0.01 (-0.05-0.03) (p=0.56)	0.01 (-0.04-0.06) (p=0.68)
Type A Behavior	-4.80 (-14.20-4.59) (p=0.27)	-4.69 (-7.87- -1.50) (0.0094)	-0.01 (-0.09-0.07) (0.87)	0.03 (-0.07-0.13) (p=0.51)
Cognitive Hardiness	-2.70 (-5.31- -0.09) (p=0.044)	-1.71 (-2.63- -0.80) (p=0.0025)	<0.01 (-0.03-0.03) (p=0.98)	0.01 (-0.02-0.04) (p=0.49)
Coping Style Positive Appraisal	-6.76 (-15.88-2.37) (p=0.13)	-2.16 (-7.06-2.75) (p=0.34)	-0.06 (-0.19-0.08) (p=0.39)	-0.03 (-0.20-0.14) (p=0.73)
Coping Style Negative Appraisal	-14.25 (-27.20- -1.30) (p=0.035)	-7.27 (-13.36- -1.17) (p=0.025)	-0.05 (-0.19-0.10) (p=0.51)	-0.01 (-0.19-0.16) (p=0.88)
Coping Style Threat minimization	-11.20 (-22.75-0.35) (0.056)	-6.57 (-11.37- -1.76) (p=0.014)	-0.05 (-0.23-0.13) (p=0.59)	0.06 (-0.16-0.28) (p=0.59)
Coping Style Problem Focus	-8.85 (-18.36-0.67) (0.064)	-3.93 (-8.81-0.95) (p=0.10)	-0.06 (-0.20-0.07) (p=0.33)	-0.03 (-0.19-0.14) (p=0.74)
ARC score	-17.97 (-30.68- -5.25) (p=0.012)	-7.06 (-14.59-0.47) (p=0.063)	-0.12 (-0.30-0.07) (p=0.21)	-0.07 (-0.31-0.17) (p=0.53)
Psychological Well Being	-3.35 (-6.18- -0.52) (p=0.026)	-1.40 (-2.95-0.14) (p=0.070)	-0.04 (-0.09-0.01) (p=0.083)	-0.03 (-0.09-0.04) (p=0.39)
Health Habits-Exercise	-14.02 (-28.13-0.09) (0.051)	-8.48 (-14.04- -2.91) (p=0.0079)	<-0.01 (-0.16-0.16) (p=0.99)	0.09 (-0.10-0.27) (p=0.34)
Health Habits-Rest Sleep	-9.54 (-20.89-1.80) (p=0.088)	-6.60 (-10.63- -2.56) (p=0.0055)	-0.09 (-0.20-0.02) (p=0.095)	-0.06 (-0.20-0.08) (0.36)
Health Habits- Eating	-14.59 (-38.28-9.11) (p=0.19)	-9.05 (-19.70-1.60) (p=0.086)	-0.08 (-0.24-0.08) (p=0.29)	-0.07 (-0.27-0.13) (0.47)
Beck Score	3.73 (-5.63-13.09) (p=0.12)	-1.67 (-29.99-26.64) (0.59)	<-0.01 (-0.05-0.05) (p=0.97)	0.02 (-0.04-0.08) (p=0.57)

ARC Score: alcohol recreational drugs and cigarettes.

Adjusted for age, gender, race, BMI, hypertension, diabetes, HDL -C, LDL -C, smoking status.

Sample size=42 for thoracic fat and epicardial fat; sample size=73 for CAC volume and CAC score.

aspirin usage, cholesterol medication, consulting with a physician, losing weight, decreasing dietary fat, but also increased worry, noting that potentially important risk-reducing behaviors may be reinforced by the knowledge of a positive coronary artery scan, independent of preexisting coronary risk factor status (16). More recently, Rozanski et al. showed in the EISNER clinical trial, which randomized over 2,000 intermediate risk persons to CAC scanning vs. no scanning, an increase in the Framingham Risk Score (FRS) in the no-scan group compared to change in

Framingham risk in the scan group (0.7 ± 5.1 vs. 0.002 ± 4.9 , $p = 0.003$). Within the scan group, the baseline CAC score was additionally associated with an improvement in risk factors and FRS ($p < 0.01$) (17).

Some studies have also examined relationships of lifestyle modification efforts with CAC progression or changes in body or epicardial fat. In the SAFE-LIFE randomized trial of patients with established CHD, while lifestyle modification with stress reduction showed reductions in blood pressure, heart rate, and need for anti-ischemic medications, there was

no impact on change in CAC score [22]. A study of 64 Japanese Americans showed the combination of an American Heart Association step 2 diet combined with endurance and stretching exercise to reduce subcutaneous, thoracic, and thigh fat measured by CT [20]. A recently published systematic review and meta-analyses of the effects of lifestyle interventions on ectopic fat deposition described overall decreases on fat in the liver, heart, and pancreas [23], but not general thoracic fat, and others have described diet-induced weight loss to impact of diet and/or exercise only focused interventions on changes in epicardial fat only [24]. Our study showed that certain components of our prescribed intervention program, including increased social support, cognitive hardiness, negative appraisal coping style, exercise, and good sleep habits appeared to be inversely related to changes in thoracic and/or epicardial fat, but not coronary calcium.

Our study has strengths and weaknesses. An important strength is the systematic collection of risk factors and standardized assessment of coronary calcium and measures of epicardial and thoracic fat by CT. An important limitation of the study is that follow-up CT scan data were not available in over 50% of randomized subjects, due largely to logistical reasons preventing a repeat scan from being performed; in addition, availability of epicardial and thoracic fat measures was limited to subjects with DICOM-archived data available. However, when comparing baseline characteristics, intervention vs. control group participants who did complete were roughly comparable to those who did not complete the study, with the exception of having greater amounts of coronary calcium and lower HDL-C levels, suggesting our results in the participants who did complete the study are moderately generalizable to the larger group of randomized participants. Also, while the study was randomized, the nature of the intervention (lifestyle management and scan consultation) precluded blinding of participants and staff. While our findings regarding CAC score and volume as well as thoracic fat volume did reach statistical significance, even in fully adjusted analyses (adjusting for baseline CAC score and volume or baseline thoracic fat volume, as well as other risk factors), our sample sizes are small and the results need to be treated with caution and need validation in larger samples. In addition, the clinical significance of the degree of CAC progression differences and changes in epicardial or thoracic fat between the groups in terms of future event risk is uncertain although clearly these measures have

been shown to relate to cardiovascular event risk and atherosclerosis in other studies [6–8]. Further, this analysis does not identify the relative effect of specific behavioral factors (e.g., dietary, exercise, or stress management components) or the relative contribution of the physician consultation versus the lifestyle intervention program on changes in CAC progression, epicardial or thoracic fat. Larger-scale studies with multiple treatment arms would be needed to better document this.

Our data suggests a multifactorial, web based, direct contact behavioral intervention combined with a physician-provided consultation of whole body CT results may have had a beneficial effect on retarding progression of CAC as well as epicardial and thoracic fat measures by CT. Further study in a larger sample of subjects and identification of which specific measures (e.g., certain behavioral modification or face-to-face physician-provided consultation) is needed to confirm these findings. Moreover, the clinical significance of changes in these measures over baseline measures of CAC or epicardial or thoracic fat, as well as other clinical risk factors in the prediction of long-term clinical outcomes needs to be further established.

Acknowledgements and Conflicts of Interest

This project was previously presented and published in abstract form in the journal *Cardiology* by the International Academy of Cardiology Annual Scientific Sessions 2016 21st World Congress on Heart Disease, Boston, Mass., USA, July 30-August 1, 2016. This study was funded by a contract from the Department of Defense provided to Reengineering Healthcare, Inc. contract # W81XWH-09-2-0121. Dr. Eisenberg was the Principal Investigator. Dr. Wong served as a consultant to Reengineering Healthcare, Inc. for the duration of the contract. Dr. Eisenberg, Ms. Eisenberg, Ms. Cecere, and Mr. Patao are employees of Reengineering Healthcare, Inc.

Author Contributions

NW and WF contributed to the writing of the manuscript, WF, DD, and CP did the analysis and managed the data, and AE, JC, HE, and CP conducted the clinic visits. LW, HE, AE, and DD provided critical review and revision of the content of the manuscript.

References

1. Wong ND, Hsu JC, Detrano RC, Diamond G, Eisenberg H, Gardin JM. Coronary artery calcium evaluation by electron beam com-

- puted tomography: relation to new cardiovascular events. *Am J Cardiol* (2000) 86: 495–98.
2. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* (2008) 358: 1336–45.
 3. Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH, et al. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. *J Am Coll Cardiol* (2007) 49: 1860–70.
 4. Shaw LJ, Raggi P, Schisterman E, Berman DS, Callister TQ. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. *Radiology* (2003) 228: 826–33.
 5. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA* (2012) 308: 788–95.
 6. Mahabadi AA, Massaro JM, Rosito GA, Levy D, Murabito JM, Wolf PA, et al. Association of pericardial fat, intrathoracic fat, and visceral abdominal fat with cardiovascular disease burden: the Framingham Heart Study. *Eur Heart J* (2009) 30: 850–6.
 7. Cheng VY, Dey D, Tamarappoo B, Nakazato R, Gransar H, Miranda-Peats R, et al. Pericardial fat burden on ECG-gated noncontrast CT in asymptomatic patients who subsequently experience adverse cardiovascular events. *JACC Cardiovasc Imaging* (2010) 3: 352–60.
 8. Rajani R, Shmilovich H, Nakazato R, Nakanishi R, Otaki Y, Cheng VY, et al. Relationship of epicardial fat volume to coronary plaque, severe coronary stenosis, and high-risk coronary plaque features assessed by coronary CT angiography. *J Cardiovasc Comput Tomogr* (2013) 7: 125–32.
 9. Wassel CL, Laughlin GA, Araneta MR, Kang E, Morgan CM, Barrett-Connor E, et al. Associations of pericardial and intrathoracic fat with coronary calcium presence and progression in a multiethnic study. *Obesity (Silver Spring)* (2013) 21: 1704–12.
 10. Budoff MJ, Young R, Lopez VA, Kronmal RA, Nasir K, Blumenthal RS, et al. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* (2013) 61: 1231–9.
 11. Gassett AJ, Sheppard L, McClelland RL, Olives C, Kronmal R, Blaha MJ, et al. Risk Factors for Long-Term Coronary Artery Calcium Progression in the Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc* (2015) 4: e001726.
 12. Budoff MJ, Ahmadi N, Gul KM, Liu ST, Flores FR, Tian J, et al. Aged garlic extract supplemented with B vitamins, folic acid and L-arginine retards the progression of subclinical atherosclerosis: a randomized clinical trial. *Prev Med* (2009) 49: 101–7.
 13. Arad Y, Spadaro LA, Roth M, Newstein D, Guerci AD. Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: the St. Francis Heart Study randomized clinical trial. *J Am Coll Cardiol* (2005) 46: 166–72.
 14. Raggi P, Davidson M, Callister TQ, Welty FK, Bachmann GA, Hecht H, et al. Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic postmenopausal women: Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES). *Circulation* (2005) 112: 563–71.
 15. Rodriguez-Granillo GA, Carrascosa P, Bruining N. Progression of coronary artery calcification at the crossroads: sign of progression or stabilization of coronary atherosclerosis? *Cardiovasc Diagn Ther* 2016;6 (3): 250–258.
 16. Wong ND, Detrano RC, Diamond G, Rezayat C, Mahmoudi R, Chong C, et al. Does coronary artery screening by electron beam computed tomography motivate healthy lifestyle behaviors? *Am J Cardiol* (1996) 78: 1220–3.
 17. Rozanaski A, Gransar H, Shaw LJ, Kim J, Miranda-Peats L, Wong ND, et al. Impact of coronary calcium scanning on coronary risk factors and downstream testing: the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) prospective randomized trial. *J Am Coll Cardiol* (2011) 57: 1622–32.
 18. Ahmed HM, Blaha MJ, Nasir K, et al. Low-risk lifestyle, coronary calcium, cardiovascular events, and mortality: results from MESA. *Am J Epidemiol* (2013) 178: 12–21.
 19. Cena H, Fonte ML, Casali PM, Maffoni S, Roggi C, Biino G. Epicardial fat thickness: threshold values and lifestyle association in male adolescents. *Pediatr Obes* (2015) 10: 105–11.
 20. Liao D, Ashberry PJ, Shofer JB, et al. Improvement in BMI, body composition, and body fat distribution with lifestyle modification in Japanese Americans with impaired glucose tolerance. *Diabetes Care* (2002) 25: 1504–10.
 21. Wong ND. Evidence for Psychosocial Risk Factors and Behavioral Interventions in Cardiovascular Disease (Review). *Curr Cardiovasc Risk Rep* (2012) 6: 528–33.
 22. Lehmann N, Paul A, Moebus S, Budde T, Dobos GL, Michalsen A. Effects of lifestyle modification on coronary artery calcium progression and prognostic factors in coronary patients—3 year results of the randomized SAFE-LIFE trial. *Atherosclerosis* (2011) 219: 630–6.
 23. Hens W, Taeymans J, Carnelis J, et al. The effects of lifestyle intervention on excess ectopic fat deposition measured by non-invasive techniques in overweight and obese adults: a systematic review and meta-analysis. *J Phys Act Health* (2016) 13 (6).
 24. Snel M, Jonker JT, Schoones J, et al. Ectopic fat and insulin resistance: pathophysiology and effect of diet and lifestyle interventions. *Int J Endocrinol* (2012) 983814.
 25. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* (1990) 15: 827–32.

26. Dey D, Nakazato R, Li D, Berman DS. Epicardial and thoracic fat—Noninvasive measurement and clinical implications. *Cardiovasc Diagn Ther* (2012) 2: 85–93.
27. Friedman M, Thoresen CE, Gill JJ, Ulmer D, Powell LH, Price VA, et al. Alteration of type A behavior and its effect on cardiac recurrences in post myocardial infarction patients: summary results of the recurrent coronary prevention project. *Am Heart J* (1986) 112: 653–65.
28. Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, et al. Enhancing Recovery in Coronary Heart Disease Patients Investigators (ENRICHD). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *JAMA* (2003) 289: 3106–16.
29. Ahmadi N, Nabavi V, Hajsadeghi F, Zeb I, Flores F, Ebrahimi R, et al. Aged garlic extract with supplement is associated with increase in brown adipose, decrease in white adipose tissue and predict lack of progression in coronary atherosclerosis. *Int J Cardiol* (2013) 168: 2310–4.
30. Zeb I, Ahmadi N, Flores F, Budoff MJ. Randomized trial evaluating the effect of aged garlic extract with supplements versus placebo on adipose tissue surrogates for coronary atherosclerosis progression. *Coron Artery Dis* (2017) (epub ahead of print).
31. Puri R, Nicholls SJ, Shao M, et al. Impact of statins on serial coronary calcification during atheroma progression and regression. *J Am Coll Cardiol* (2015) 65: 1273–82.
32. Henein MY, Owen A. Statins moderate coronary stenosis but not coronary calcification: results from meta-analyses. *Int J Cardiol* (2011) 153: 31–5.

Comparison of death risk stratification criteria in pulmonary embolism based on the estimation of pulmonary arterial bed occlusion

Tyurin V.P., Pronin A.G.*

National Pirogov Medical Surgical Center of Ministry of Healthcare
of the Russian Federation, Moscow, Russia

Authors:

Vladimir P. Tyurin, M.D., Ph.D., doctor of sciences, National Pirogov Medical Surgical Center, Moscow, Russia

Andrei G. Pronin, M.D., Ph.D., National Pirogov Medical Surgical Center, Moscow, Russia

Summary

Objective

To clarify angiographic criteria of massive pulmonary thrombotic masses for stratification of the risk of death in patients with pulmonary embolism according to the recommendations of the European society of cardiology (2014).

Material and methods

We analyzed the volume of pulmonary lesions in 371 patients with pulmonary embolism with different risk of early death according to the criteria of the European society of cardiology (2014)

Results

It was found that patients with high, moderately high, and moderately low risk of death from pulmonary embolism did not differ significantly in the volume and degree of obstruction of the arteries of the small circle of blood circulation. Early death risk stratification is most accurate when patients were hospitalized on the first day of the development of symptoms of the disease. At this time, the most informative indicators were plasma concentration of troponin and brain natriuretic peptide that came back to normal levels after 3 and 5 days, respectively. When patients were admitted to hospital at a later date, these laboratory indicators were not specific for the stratification of the risk of death. This leads to undervalued assessment of the risk of death in this category of patients, and

* Corresponding author. Tel.: +7-977-344-79-44, E-mail: lek32@yandex.ru

therefore it may cause not enough adequate choice of tactics of management of these patients. Estimation of the volume of pulmonary bed thrombotic occlusion could be useful to neutralize this difference between the groups can estimate the volume of thrombotic occlusion of the pulmonary bed. Total absence of blood flow in 10 or more segmental arteries was critical for manifestation of clinical, ECG and EchoCG symptoms of volumetric overload of the right heart.

Conclusion

The total absence of blood flow in 10 or more segmental arteries is comparable with occlusion of one main pulmonary artery and can be treated as a massive lesion of the small circle of blood circulation. The application of this assessment of pulmonary lesions severity in pulmonary embolism is not inferior to the classification proposed by the European society of cardiology in 2014 due to high prevalence of all criteria used in this classification.

Keyword

Pulmonary embolism, massive lesions, segmental arteries.

Introduction

Pulmonary embolism (PE) is the occlusion of pulmonary artery branches with thrombotic masses that often leads to patient's death [1, 2, 3]. According to epidemiological data, this disease is diagnosed in 0.15-0.20% of the world population [4]. Around 2 000 000 and 700 000 cases of PE are registered in the USA and Europe every year. PE frequency in Russia is 35-40 cases for 100 000 persons per year [1, 3, 5]. Total mortality rate in PE reaches 30% [5, 6]. But well-timed diagnostics and adequate therapy allow to keep this number as low as 3% [7, 8].

Nowadays the stratification of the European society of cardiology (ESC) (2014) including groups of high, moderate and low risk of death is used for optimization of PE treatment [3]. Distribution of patients into these groups is based on clinical manifestations and results of laboratory and instrumental tests. In addition, Pulmonary Embolism Severity Index (PESI) and its modification sPESI are taken into consideration [9, 10].

This classification does not consider the volume of pulmonary vessels occluded by thrombi and excluded from circulation. It is particularly important for patients with moderately-high risk of death since these patients can receive both systemic thrombolytic therapy and anticoagulant treatment [11, 12]. In these cases, the severity of thrombotic lesion of the arteries of the pulmonary circulation can play a crucial role.

It is common to evaluate the level of lesion of the pulmonary arteries by the proximal level of occlusion. However, often CT angiopulmonography detects an incomplete obturation of the lumen of the pulmonary artery branches of any order. This type of lesion, even in the presence of thrombotic masses in the main pulmonary arteries, often does not lead to

evident hemodynamic disturbances. [13, 14]. In these patients, a large number of thrombotic masses occluding smaller arteries like lobar and segmental ones is present.

The objective of the study is to detalize the criteria of massive pulmonary thrombotic masses taking into account CT results to clarify the criteria for stratification of death risk in patients with PE according to the recommendations of the ESC (2014).

Materials and methods

371 patients were admitted to the National Pirogov Medical Surgical Center during the period from 2005 to 2017. 195 patients were males, and 176 patients were females. Age of patients varied from 23 to 95 years, the average age was 56.3 ± 16.1 years.

The distribution of the proximal level of pulmonary artery branches occlusion was the following: main pulmonary arteries – 8.4%, lobar pulmonary arteries – 60.6%, segmental arteries – 31%.

All patients underwent general clinical and biochemical blood tests, including determining the level of plasma concentrations of D-dimer, troponin I, brain natriuretic peptide (NT-Pro-BNP), electrocardiography (ECG), echocardiography (EchoCG), and Doppler ultrasound exam of lower extremity veins. All patients underwent Final TE diagnosis was established with CT-angiopulmonography.

The study was carried out in 2 stages. The first step was to determine the group of patients according to the risk of early death related to PE based on the criteria of the ESC (2014). Subsequently, the groups of high, moderately high, moderately low, and low risks of death were identified.

High risk of PE-related death was found in 31 patients. Between them there were 16 men and 15

women. Patients' age varied from 23 to 86 years, average age was 54.5 ± 20.2 years.

Moderately high risk of early death was present in 37 patients with PE, aged from 29 to 78 years, their average age was 59.8 ± 14.6 years. Between them there were 20 males and 17 females.

Moderately low risk of PE-associated death was detected in 52 patients (24 males, 28 females). Their age varied from 28 to 86 years, and their average age was 59.4 ± 14.9 years.

Low PE-associated death risk was found in 251 patients (135 males, 116 females). Their age varied from 28 to 95 years, average age was 55.5 ± 16.3 years.

CT angiopulmonography revealed that patients with PE of the large arteries often had not occlusion, but different degree of parietal thrombosis of the pulmonary arteries narrowing the vessel lumen. Embolic occlusion in these patients was usually located in more distal arteries. In case of parietal thrombosis of the main arteries occlusion could be found in lobar or segmental arteries. The lesions of several lobar arteries were frequently present in patients that led to impaired circulation in corresponding segmental arteries. Taking this into account, we consider necessary to evaluate the presence of thrombotic masses not in proximal (main and lobar) arteries but total reduction of circulation in distal (lobar and segmental) arteries. It is known that pulmonary arterial system consists of 20 segmental arteries. Consequently, the occlusion of main pulmonary artery leads to exclusion of 10 segmental arteries from the circulation. Lesions of such dimensions lead to pronounced hemodynamic abnormalities.

We tested this idea in patients with high, moderately high, and moderately low risk of PE-associated death. It was found that the volume of pulmonary lesions that considered total absence of circulation in segmental arteries was almost identical and its average values were 13.1 ± 2.8 , 12.9 ± 2.6 , 11.4 ± 1.5 , respectively.

At the second stage of this study we selected groups of patients depending on the total absence of circulation in the segmental arteries to clarify the assumption that significant hemodynamic disturbances corresponding to massive PE occur in the total absence of circulation in 10 or more segmental arteries. Considering this, all PE patients with different risk of early death were divided into 2 subgroups.

The first group included patients ($n=143$, 75 males, 68 females) with massive pulmonary artery lesions and total absence of circulation in 10 and more seg-

mental arteries (11.6 ± 1.3 arteries, massive PE). Patients' age varied from 23 to 85 years, their average age was 56.2 ± 15.4 years. The group of massive PE in 76.2% of cases was present with patients with high, moderately high or moderately low risk of PE-associated death.

The second subgroup (non-massive PE) included patients ($n=228$, 121 males, 107 females) with total absence of circulation in less than 10 segmental arteries (2.9 ± 2.4 in average). Patients' age varied from 27 to 95 years, their average age was 56.1 ± 16.5 years.

We compared the results of the first and the second group. In all groups the volume of thrombotic lesions of pulmonary artery branches assessed with CT-angiopulmonography was compared with the results of EchoCG, ECG, and clinical manifestations of these patients.

Results and discussion

The level of proximal occlusion with thrombotic masses was evaluated in patients with PE and different grades of early death risk and severity of pulmonary artery lesions using CT-angiopulmonography (Figure 1).

Proximal occlusion of pulmonary artery branches was found with comparable frequency in patients with massive PE and patients with high, moderately high and moderately low risk of early PE-related death according to the criteria of the ESC (2014) ($p > 0.05$). No patient with non-massive PE had occlusion of the main pulmonary artery. In this group lobar artery occlusion was statistically more frequent than in patients with the low risk of PE-associated death ($p < 0.01$). 82.4% of patients had occlusion of one lobar artery, 17.6% of patients had occlusion of two arteries one of which was superior or middle lobar artery of the right lung, consequently, total absence of circulation in segmental arteries in these patients did not exceed 9 arteries of this level.

Thus, we can assume that evaluation of the volume of pulmonary lesions with total absence of blood supply in 10 and more segmental arteries is comparable with high and moderate risk of PE-associated death, whereas absence of circulation in less than 10 segmental arteries corresponds to the low risk of early death. It was proved with correlation analysis that revealed significant correlation of this volume of lesions with high ($r=0.54$), moderately high ($r=0.68$) risk of early death from PE, and moderate degree correlation with moderately-low risk of death ($r=0.42$).

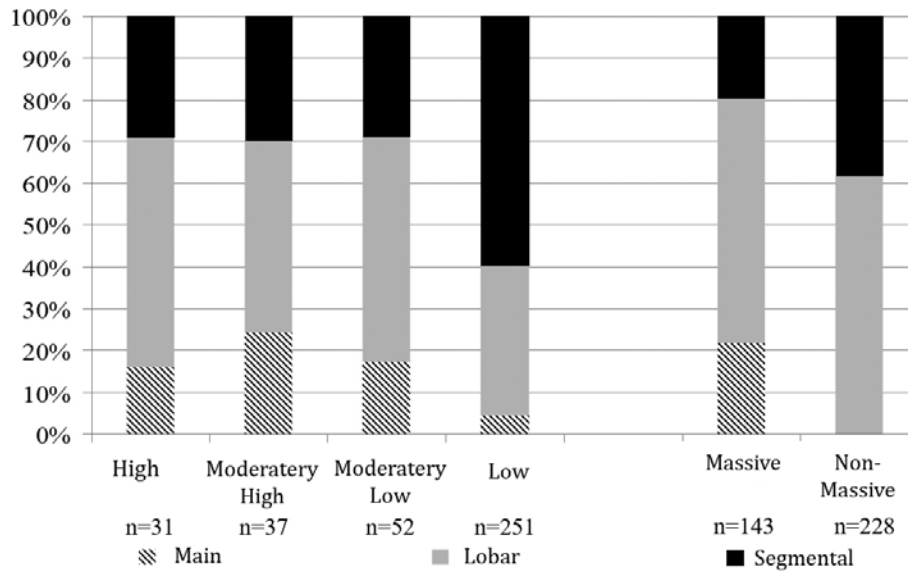


Figure 1. Distribution of the level of proximal occlusion of pulmonary artery branches in patients with PE.

Comment: Subgroups of patients: high death risk (n=31); moderatelyA high death risk (n=37); moderately low death risk (n=52); low death risk (n=251); Massive PE: total absence of circulation in 10 or more segmental arteries (n=143); Non-massive PE: total absence of circulation in less than 10 segmental arteries (n=228).

Table 1. The frequency of EchoCG criteria in PE patients with different early death risk

EchoCG parameter	Group of patients						p ₁	p ₂	p ₃	p ₄
	The risk of PE-associated death according to the ESC criteria (2014)				Considering total absence of circulation in segmental arteries					
	High risk n=31	Moderately high risk n=37	Moderately low risk n=52	Low risk n=251	Massive n=143	Non-massive n=228				
Dilatation of the RV > 3cm, %	71	56.8	82.7	6	63	10.2	0.39	0.5	<0.01	0.11
RV size, cm	3.02±0.68	3.03±0.53	3.07±0.48	2.56±0.44	2.92±0.38	2.51±0.48	0.42	0.87	0.81	0.94
RV hypokinesis, %	9.7	8.1	3.8	0	7	0	0.79	0.62	0.39	0.99
Dilatation of the right atrium > 65 mL, %	61.3	54	57.7	17.9	46	24.7	0.71	0.39	0.15	0.07
Pulmonary hypertension > 30 mm Hg, %	93.5	100	96.2	68.1	100	65.8	0.22	0.99	0.3	0.59
Average pressure in pulmonary artery, %	47.9±13.5	56.2±23.9	54.3±15.3	36.6±15.3	62.6±17.2	34.1±11.9	0.5	0.83	0.71	0.89
Tricuspid regurgitation ≥ 2 degree, %	38.7	56.8	53.4	15.9	42	19.1	0.74	0.11	0.16	0.36
Paradoxical septal movement, %	16	16.2	11.5	0	11.9	0	0.57	0.52	0.94	0.99
Cava vena inferior dilatation > 20mm, %	45.2	18.9	15.4	6	23.8	2.6	0.03	0.51	0.17	0.07

Comment: Comparison of EchoCG criteria of massive PE with the groups of: p₁ – high risk of death; p₂ – moderately high risk of death; p₃ – moderately low risk of death; p₄ – comparison with non-massive PE and low death risk PE.

Right ventricular dysfunction is one of the most important criteria of risk stratification in patients with PE. Commonly it is evaluated using such EchoCG parameters like end-diastolic size of the right ventricle (RV) >3 cm, tricuspid regurgitation > 2 degree, RV hypokinesia, pulmonary hypertension>30 mm Hg, and paradoxical septal motion.

Further we analyzed the prevalence and severity of EchoCG-criteria of PE (Table 1).

The analysis of EchoCG parameters in patients with high, moderately high, and moderately low risk of death assessed with the ESC criteria (2014) and in patients with massive lesions of pulmonary tree and total absence of circulation in 10 and more segmental arteries failed to find significant differences in any of symptoms (p>0.05), apart from vena cava inferior dilatation > 20 mm (p<0.02), that was characteristic for patients with high risk of PE-associated

Table 2. Prevalence of ECG criteria in PE patients

Groups of patients		ECG characteristic		
		S ₁ Q _{III} , %	Negative. T in V ₁ –V ₃ leads, %	RBBB, %
The risk of PE-associated death according to the ESC criteria (2014)	High risk n=31	61.3	48	19.4
	Moderately high n=37	54.1	45.9	24.3
	Moderately low risk n=52	46.2	48.1	31.5
	Low risk n=251	3.2	23.9	21.9
Considering total absence of circulation in segmental arteries	Massive n=143	46.9	48.3	27.3
	Non-massive n=228	4.4	21.9	22.9
p1		0.14	0.98	0.33
p2		0.11	0.8	0.71
p3		0.93	0.98	0.58
p4		0.49	0.6	0.79

TComment: Comparison of ECG characteristics of massive PE with the groups of: p1 – high risk of death; p2 – moderately high risk of death; p3 – moderately low risk of death; p4 – comparison with non-massive PE and low death risk PE.

death. Although it is an indirect sign for evaluation of RV disfunction, it demonstrates significantly that patients with high risk of death have more pronounced overload of the right heart.

Patients with a low risk of PE-associated death according to the ESC criteria (2014) and patients with non-massive pulmonary arterial tree lesions with absent circulation in less than 10 segmental arteries had no significant differences. All EchoCG criteria of the right heart overload were significantly less frequent in both these subgroups comparing with the other groups ($p<0.02$).

Correlation analysis revealed weak correlation in patients of the groups of high, moderately high, and moderately low risk of PE-associated death with all EchoCG-signs of PE apart from paradoxical septal movement in patients with high and moderately high risk that had significant moderate correlation ($r=0.58$, $r=0.52$). Total absence of circulation in 10 and more segmental arteries had moderate correlation with vena cava inferior dilatation ($r=0.31$) and paradoxical septal movement ($r=0.38$).

PE ECG-criteria are not used for stratification of the risk of early death in PE patients. Nevertheless, ECG-signs are important for evaluation of the right heart overload that can be expressed as S₁Q_{III}I phenomenon (deep waves S₁ and Q_{III}), T wave inversion in leads III, aVF, V₁–V₃ and complete or partial right bundle branch block (RBBB).

The frequency of the prevalence of the ECG-signs of the right heart overload in PE patients with massive lesions of pulmonary circulation was the following: deep S₁Q_{III} waves – 46.9% of cases, negative T-wave in V₁–V₃ leads – 48.3% of cases, RBBB signs – 27.3% of cases. Comparison of PE subgroups with high, moderately high, and moderately low risk of death according to the ESC criteria (2014) and pa-

tients with massive lesions of pulmonary arterial tree (total absence of circulation in 10 and more segmental arteries) did not reveal any significant differences (Table 2). The same ECG-symptoms of PE except RBBB were significantly less frequent ($p<0.01$) in the groups of patients with non-massive pulmonary artery lesions and low risk of PE-associated death.

This conclusion is supported by the results of correlation analysis that found weak ($r<0.3$) correlation between all ECG symptoms of the right heart overload and non-massive PE and low-risk of PE-associated death. High, moderately high, and moderately low risk of PE-associated death and patients with massive pulmonary artery lesions (total absence of circulation in 10 and more segmental arteries) correlated significantly with ECG-criteria of this disease ($r=0.59$, $r=0.49$, $r=0.46$, $r=0.64$, respectively).

Considering this, we can suggest that registration of ECG symptoms of the right heart overload in PE patients is likely to be related to massive PE. Such ECG signs like S₁Q_{III} phenomenon and negative T wave in V₁–V₃ leads have the highest meaning. RBBB has weaker correlation with massive PE than other ECG signs.

Increased levels of serum troponin is one of the criteria of acute myocardial lesions including RV lesions in PE. We found elevated serum troponin in 58.1% of patients with high risk of death according to the ESC criteria (2014), in 100% cases of moderately high risk, and in 38.5% of patients with massive PE (total absence of circulation in 10 and more pulmonary arteries). In majority of cases these patients were admitted to hospital within 2 days after the disease manifestation. We evaluated the dynamics of this marker concentration depending on time of PE development (Figure 2).

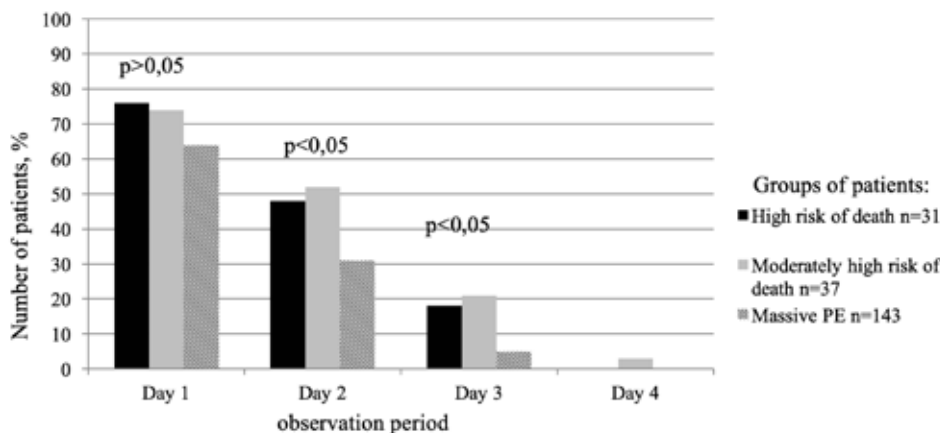


Figure 2. Distribution of elevated troponin levels in PE patients with high and moderately high risk of death and massive PE depending on the duration of the disease

Time of patient's admission to hospital influenced troponin levels and the frequency of its detection. Considering this, we can assume that a part of PE patients with moderately low risk of early death and admitted to hospital not at the first day could have had elevated serum troponin before and consequently could have been classified as patients with moderately high risk of death, and the treatment strategy of these patients could have been different.

The ESC (2014) recommended to determine the levels of brain natriuretic peptide (NT-Pro-BNP) for evaluation of the presence of RV dysfunction and severity of heart failure. Comparative analysis of aver-

age values of NT-Pro-BNP in patients of the groups of high, moderately high, moderately low, and low risk of PE-associated death demonstrated that the levels of brain natriuretic peptide were significantly lower just in the group of low risk comparing with the other groups ($p<0.01$): 2888 ± 515 pmol/L, 2962 ± 421 pmol/L, 3137 ± 652 pmol/L, and 2118 ± 419 pmol/L, respectively. It proves significantly higher right heart overload in PE patients with high, moderately high, and moderately low risk of early death. Similar results were obtained after comparison of PE patients with massive (total absence of circulation in 10 and more segmental arteries) and non-massive lesions (total absence of cir-

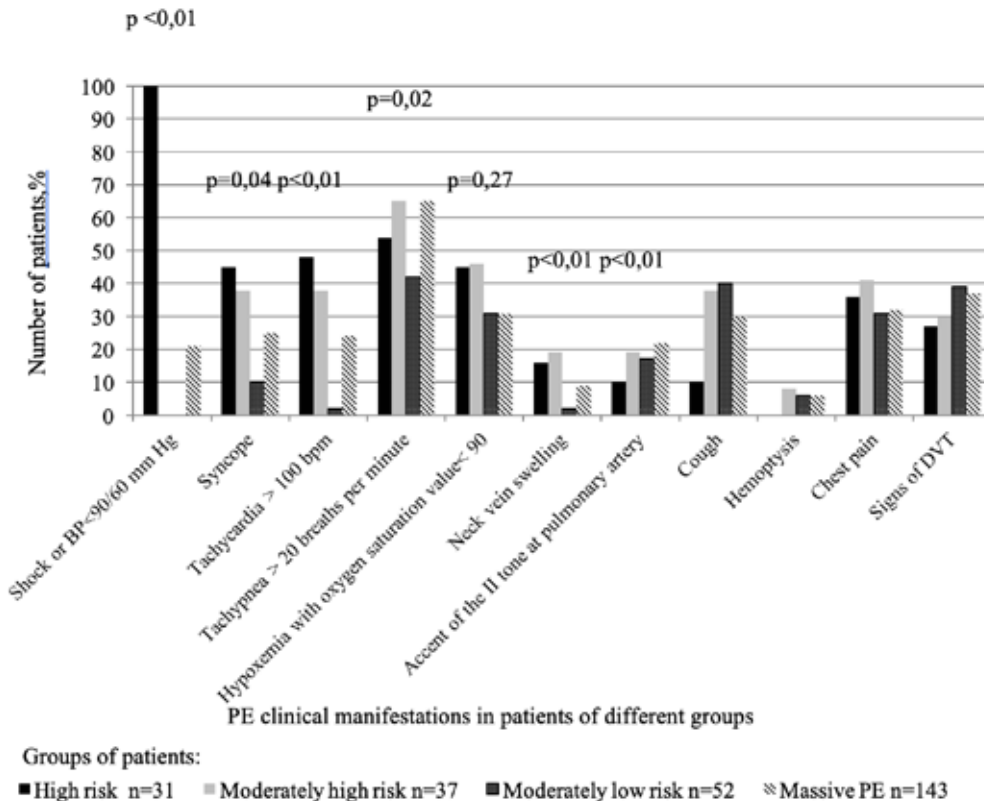


Figure 3. Distribution of symptoms in PE patients with high, moderately high, and moderately low risk of death and massive PE.

circulation in less than 10 segmental arteries) lesions of pulmonary arterial tree: $3\,857.4 \pm 281.3$ pmol/mL and 1389 ± 664.9 pmol/mL, respectively ($p < 0.01$).

The study of dynamics of brain natriuretic peptide in PE patients in all subgroups demonstrated normalization of its plasma levels by 4–5 days after the manifestation of the disease.

Complaints, anamnesis, identification of risk factors often determine the tactics of examination and treatment of patients with suspected PE. The most characteristic symptoms of PE are: shortness of breath, shock or hypotension with a blood pressure of less than 90/60 mm Hg, collaptoid state, tachycardia with a heart rate of more than 100 beats per minute, chest pain, cough and hemoptysis, cyanosis of the upper half of the body, neck veins swelling and accent of the II tone at pulmonary artery. It is generally accepted that these symptoms have low specificity and do not correlate with the massiveness of pulmonary arterial tree lesions, and their severity is often so insignificant that they remain unnoticed not only by doctors, but also by patients. We found out that patients with low TE-associated risk of death according to the criteria of the ESC (2014) and non-massive lesions (total absence of circulation in less than 10 segmental arteries) of pulmonary arterial tree had the same frequency of symptoms ($p > 0.05$) and they were significantly less frequent ($p < 0.05$) comparing with the patients with massive PE and patients with high, moderately high, and moderately low PE-related risk of death. We performed the comparative analysis of PE clinical symptoms prevalence in these patients (Figure 3).

We found out that many patients with total absence of circulation in 10 and more segmental arteries manifested with such symptoms like accent of the II tone at pulmonary artery and hemoptysis significantly more often than in patients with high risk of PE-associated death ($p < 0.01$), whereas shock or hypotension with systolic blood pressure < 90 mm Hg and pre- or syncopal conditions were less frequent between them comparing with the same group of patients ($p < 0.05$). This is reasonable, since the presence of hypotension or shock in a patient is a selection criterion in this subgroup, which makes it very difficult to assess its significance for comparative analysis. We noted that a considerable part of patients, especially with moderately high risk of early death, that were hospitalized not on the first day of the development of the disease reported episodes of weakness,

dizziness, pre- and syncopal state, which could be caused by hypotension with subsequent stabilization of hemodynamic parameters. Thus, if these patients were admitted to hospital during manifestation of these symptoms, likely they would be assigned to the group of high death risk.

This idea is indirectly confirmed by the absence of a statistically significant difference in presence of pre- or syncopal condition between the groups of high and moderately high risks of PE-associated death ($p = 0.54$). Correlation analysis revealed moderate correlation between high or moderately high risk of death and the presence of pre- or syncopal states in patients ($r = 0.39$ and $r = 0.35$, respectively). Moderate correlation between the volume of lesions and the presence of above-mentioned symptom was found in patients with massive PE ($r = 0.41$). It can be interpreted as another indirect prove of specificity of clinical symptoms in relation to disease duration for stratification of the risk of early death.

Conclusions

The size of pulmonary arterial tree lesions in patients with high, moderately high, and moderately low risk of PE-associated death according to the classification of the ESC (2014) was almost identical.

Elevated troponin and brain natriuretic peptide levels come back to normal values by 3rd and 5th days after the manifestation of the disease that restricts their significance for patients admitted to hospital at later period, since they lower the estimation of death risk and influence the choice of not fully adequate treatment tactics in these patients.

The presence of thrombotic masses in pulmonary arteries that interfere with blood flow in total of 10 out of 20 segmental arteries causes severe hemodynamic disturbances and approaches hemodynamic disturbances of massive PE.

The proposed system of evaluation of the massiveness of pulmonary arterial tree lesions in PE is comparable with the classification of the ESC (2014) from the point of view of prevalence of EchoCG and ECG criteria of this disease and clinical symptoms. Evaluation of massiveness of pulmonary lesions by total absence of distal circulation in 10 and more segmental arteries can complete the stratification of the risk of PE-associated death for determining optimal tactics of patients' management.

Conflict of interest: None declared.

References

1. Savelev V.S., Pokrovskij A.V., Zatevahin I.I., Kirienko A.I. i dr. Russian clinical recommendations for the diagnosis, treatment and prevention of venous thromboembolic complications. *Phlebology*. 2015;9-4:3-57. Russian
2. Bershtejn L.L. Pulmonary embolism: principles of diagnosis, antithrombotic therapy and prevention. Effective pharmacotherapy. *Kardiologiya i Angiologiya*. 2013;43-3:34-44. Russian
3. The Task Force Report. Guidelines on the diagnosis and management of acute pulmonary embolism. *European Heart Journal*. 2014;43-35:3033-3073.
4. Meissner M.H., Gloviczki P., Comerota A.J. et al. Early thrombus removal strategies for acute deep venous thrombosis: clinical practice guidelines of the society for vascular surgery and the american venous forum. *J. Vasc. Surg.* 2012;55-5:1449-1462
5. Gulyaeva N.V., Lipchenko A.A., Fokina E.G. Thrombolytic therapy in pulmonary embolism medium risk: efficacy, safety, expediency. *Heart*. 2009;8-5:270-289. Russian
6. Moiseev S.V. Anticoagulants in the treatment of VTEC. *Phlebology*. 2012;1:32-36. Russian
7. Ermolaev A.A., Plavunov N.F., Spiridonova E.A., Baratashvili V.L., Stazhadze L.L. Analysis of causes of pulmonary thromboembolism hypodiagnosics at the prehospital stage. *Cardiology*. 2012;52-6:40-47. Russian
8. Kirienko A.I., Andriyashkin V.V., Zolotuhin I.A. i dr. The results of a system for the prevention of venous thromboembolism in a nationwide. *Phlebology*. 2014; 8-3:4-10. Russian
9. Strazhnov I.V., Strazhnov A.I. Massive pulmonary embolism: diagnostic and therapeutic strategy in the setting of primary vascular Department. *Medical almanac*. 2017;48-3:55-57. Russian
10. Shulutko A.M., Krylov A.YU., Osmanov E.H.G. i dr. Anticoagulant therapy in the treatment of acute proximal thrombosis of the lower extremities deep veins. *Surgery*. 2011;1:52-55. Russian
11. Agnelli G., Buller H.R., Cohen A. et al. Investigators Oral Apixaban for the Treatment of Acute Venous Thromboembolism. *Engl J Med*. 2013;369:799-808.
12. Juan I Arcelus, Pere Domenech, Ricardo Guijarro, et al. Rivaroxaban in the Treatment of Venous Thromboembolism and the Prevention of Recurrences: a practical approach. *Clin. Appl. Thromb. Hemost*. 2015;21-4:297-308.
13. Shevchenko YU.L., Stojko YU.M., Zamyatin M.N. Standard and new modes of anticoagulant therapy in pulmonary embolism. *Pirogov journal*. 2014;10: 109-112. Russian
14. Yudin A.L., Uchevatkin A.A., Afanaseva N.I., Yumatova E.A., Kulagin A.L. The role of multidetector computed tomography in the diagnosis of venous thromboembolism. *Russian medical journal*. 2015;21-1: 40-43. Russian

Relationship between the degree of epicardial fat volume and severity of coronary atherosclerosis

Chumakova G.A.*^{1,2}, Pokutnev A.P.³, Veselovskaya N.G.^{1,3}, Bobrovskaya L.A.²

¹Institute for Complex Problems of Cardiovascular Disease, Kemerovo, Russia

²Altai State Medical University, Barnaul, Russia

³Altai Regional Cardiology Clinic, Barnaul, Russia

Autors

Galina A. Chumakova, M.D., Ph.D., doctor of sciences, professor of the Department of Internal Medicine, Postgraduate Medical Faculty, Altai State Medical University, senior researcher at the Institute for Complex Problems of Cardiovascular Disease; Barnaul, Kemerovo, Russia

Andrei P. Pokutnev, M.D., head of the Department of Cardiac Intensive Care, Altai Regional Cardiology Clinic, Barnaul, Russia

Nadezhda G. Veselovskaya, M.D., Ph.D., doctor of sciences, head of the Department of Cardiology №4, Altai Regional Cardiology Clinic, senior researcher at the Institute for Complex Problems of Cardiovascular Disease; Barnaul, Kemerovo, Russia

Lyudmila A. Bobrovskaya, M.D., Ph.D., associate professor of the Department of Endocrinology and Internal Medicine, Altai State Medical University, Barnaul, Russia

Summary

Background

Obesity is associated with high level of cardiovascular morbidity and mortality. During the last years it has been clarified that high cardiovascular risk correlates not only with total volume of adipose tissue, but mostly with increased amount of visceral fat tissue. Epicardial fat tissue is the most studied local visceral fat depot and a potent source of pro-inflammatory, pro-atherogenic, and neurohumoral factors.

Objective

To investigate the relationship between the degree of epicardial fat volume and coronary atherosclerosis severity

Materials and methods

This study included 156 men with coronary heart disease (CHD) aged 53.2 ± 7.6 years with obesity I–III grade, BMI 34.5 ± 5.6 kg/m². All patients underwent measurement of metabolic and additional cardiovascular risk factors and coronary angiography. Epicardial fat tissue thickness (EFT) was evaluated using transthoracic echocardiography.

Results

The highest values of EFT were observed in the group of patients with multiple stenosis of coronary arteries where EFT reached 10 (8; 10) mm. ROC-analysis revealed EFT as a predictor of significant coronary atherosclerosis in patients with CHD. Sensitivity and specificity of this marker were 80.4 % and 67.6 %, respectively (cut-off value=6 mm). It was found that EFT correlated significantly with the presence and severity of coronary atherosclerosis together with age, leptin and resistin levels, and waist circumference.

Conclusions

Our results prove the necessity of addition of obesity-correcting measures, targeting first of all visceral obesity, into programs of atherosclerosis prevention including coronary atherosclerosis.

Key words

Epicardial fat tissue, coronary atherosclerosis

Obesity has become one of the major health problems in the world because it is associated with a high level of cardiovascular morbidity [1]. The prevalence of obesity in the world has grown more than twice during the period from 1980 till 2014 [2]. According to the ESSE study, the obesity takes the third place among cardiovascular risk factors after dyslipidemia and hypertension [3]. Obesity is also regarded as a risk factor for the high level of mortality among general population. The lowest level of mortality is shown when the BMI is in the range of 20–24 kg/m² (non-smokers in American and Russian populations) and starts getting higher if the BMI is below or above that range [4].

During the last years it has become clear that the high cardiovascular risk is associated not only with the total adipose tissue volume, but especially with the increase of visceral adipose tissue (VAT) amount which is concentrated in local fat depots. The best-studied local fat depot of visceral adipose tissue is EAT which lies between visceral pericardium and myocardium [5]. Due to the close anatomical and functional relationships with the myocardium, EAT has a direct impact on the coronary vessels morphology through paracrine mechanisms [6, 7]. There is no anatomical barrier between the EAT layer and the myocardium, but there are common systems of blood supply (coronary vessels) and of microcirculation. Many neurohumoral factors produced by VAT and in particular by EAT, such as, adipokines, cyto-

kines, proteins which control lipid metabolism, have a potent pro-atherogenic effect and can stimulate the development of coronary artery atherosclerosis [8, 9].

The **objective of the research** is to study the relationship between the grade of epicardial obesity and the severity of coronary atherosclerosis.

Materials and methods: the study was conducted in Altai regional cardiologic clinic in the period from 2011 till 2016. The study's protocol was approved by the ethics committee. The study included 156 men with ischemic heart disease (IHD) in the age of 53.2 ± 7.6 and with the obesity of I–III grades. All patients underwent coronary angiography. Patients with diabetes mellitus type 2 and those who had undergone the acute myocardial infarction were excluded from the study.

The laboratory exams were held: total cholesterol (TC), serum triglycerides (TG) measured by the enzymatic method using test kits; high density lipoprotein cholesterol (HDL cholesterol) in supernatant plasma. The cholesterol of low-density lipoproteins (LDL cholesterol) was calculated using the Friedwald formula. The glucose content in capillary blood was determined by the glucose oxidase method. The serum leptin and resistin levels were determined by enzyme immunoassay (BioSource sets, Belgium). The determination of the main apolipoproteins—apolipoprotein A1 (ApoA1) and apolipoprotein B (ApoB)—was carried out by immunoprecipitation method using a Konelab analyzer.

Anthropometric measurements were performed to estimate total obesity by body mass index (BMI) and abdominal obesity by waist circumference (WC). Epicardial obesity was assessed by transthoracic echocardiography in B-mode on a Vivid 5 device with a 3.5 MHz mechanical sector sensor. Three cardiac cycles were registrated in parasternal positions on the long and short axes of the left ventricle [10]. The maximum thickness of epicardial fat was visualized behind the free wall of the right ventricle when the measurement was performed along the perpendicular to the aortic ring, which was used as an anatomical landmark. All patients underwent diagnostic CAG using the Philips Integris 3000 device (USA).

Statistical data processing was performed using the program STATISTICA 6.1., MedCalc 5.4. For each of the continuous values of normal distribution, the mean (M) and standard deviation (SD) are given; for the quantities with abnormal distribution, the median (Med) and the upper and lower quartiles (UQ; LQ) are shown. The normal distribution hypothesis was tested using the Shapiro-Wilk criterion. The hypothesis of mean tEAT values equality in different groups was tested using the Kruskal-Wallis method. The statistical description of the relationship between the various parameters was carried out by calculating the Spearman's rank correlation coefficient. A ROC-curve was constructed to estimate the sensitivity and

specificity of tEAT as a prognostic criterion. The univariate binary logistic regression method was used to evaluate the effect of various predictors on the development of hemodynamically significant coronary atherosclerosis. The level of statistical significance was $p < 0.05$.

Results and discussion: we performed the evaluation of the relationship between the EAT thickness (tEAT) and main and additional metabolic risk factors (RF), the age and BMI using correlation analysis. We have found out that tEAT correlates significantly with plasma lipids: TG ($r = 0.396$; $p < 0.001$), HDL ($r = -0.295$; $p = 0.004$), ApoA ($r = -0.317$; $p = 0.002$), and ApoB ($r = 0.357$, $p < 0.001$). In addition, a positive relationship was showed between the tEAT value and some proatherogenic neurohumoral factors of visceral fat such as leptin ($r = 0.592$; $p < 0.001$) and resistin ($r = 0.247$; $p = 0.023$) (Figure 1).

No significant relationship was showed between tEAT and the level of systolic and diastolic blood pressure (SBP and DBP), as well as the glucose level, which can possibly be explained by the fact that most patients with arterial hypertension were getting an adequate antihypertensive therapy and patients with impaired carbohydrate metabolism were not included in the study. We also found no relationship between tEAT and BMI ($r=0.135$; $p=0.114$). It can be explained by the fact that BMI reflects the total obesity degree

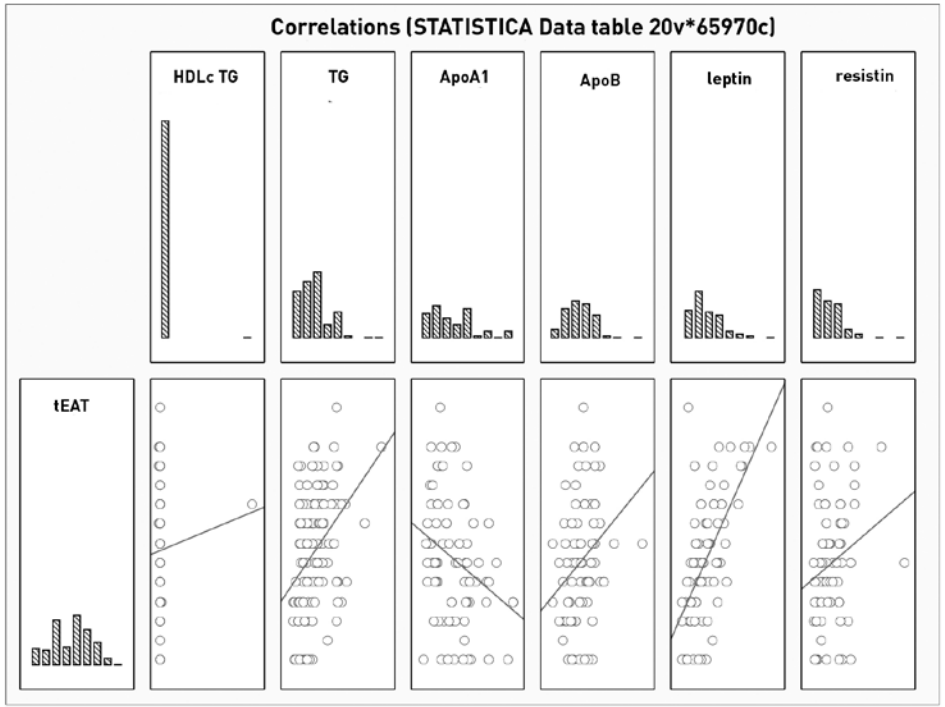


Figure 1. The relationship between tEAT and metabolic risk factors (Spearman correlation analysis) (HDLc — high density lipoprotein cholesterol, TG — triglycerides, ApoA1 — apoprotein A1, ApoB — apoprotein B, tEAT — thickness of epicardial adipous tissue)

when a significant part of adipose tissue is represented by the inert subcutaneous fat which does not produce adipokines and other proatherogenic neurohumoral factors, in contrast to the neurohumorally active visceral adipose tissue. That's why, possibly, the BMI obesity was not shown to be associated with the cardiovascular risk increase in most studies [10.11]. But visceral adipose tissue, including epicardial adipose tissue, is a source of pro-inflammatory and pro-thrombotic cytokines, such as, tumor necrosis factor (TNF α), monocyte chemoattractant protein (MCP-1), interleukins 1 and 6 (IL-1, IL-6), resistin, omentin, leptin, visfatin, inhibitor of tissue plasminogen activator (PAI-1) and angiotensinogen [12.13]. Thus, the hormonal activity of epicardial adipose tissue was studied in 42 patients who underwent coronary artery bypass grafting surgery, and it was found that EAT produces proinflammatory cytokines IL-1, IL-6 and TNF α , as well as chemokine MCP-1, having a potent effect on the bloodstream [14]. It was also found that the EAT thickness increase of more than 7 mm in women was associated with subclinical coronary arteries atherosclerosis [15]. In another study ($n = 998$), it was proved that the EAT volume increase, assessed by computed tomography, was associated with a high risk of coronary heart disease development during 5 years of observation, regardless of gender [18].

After that we performed the analysis of the relationship between the degree of epicardial obesity and the prevalence and the severity of coronary vessel impairment. According to the results of the performed

CAG, several groups of patients were identified on the grounds of the quantity of impaired arteries. The first group included patients with single-vessel coronary lesion ($n=27$), the second — two-vessel lesion ($n=54$), the third — three-vessel lesion ($n=54$), and the fourth group consisted of patients with multiple coronary stenosis and the diffuse impairment of coronary vessels ($n=18$). Analyzing the mean values of tEAT, it was found that the highest mean tEAT values were in the group of patients with multiple coronary stenosis and were 10 [8;10] mm, the lowest mean tEAT values were in patients with single-vessel and two-vessel lesions and were 3 [2;5] mm and 4 [2;8] mm respectively. Thus, the difference between the groups was statistically significant ($p=0.004$) (figure 2).

Figure 3 and 4 show a coronary angiogram and an echocardiogram of a patient with multiple coronary stenosis and significant epicardial obesity with the tEAT of 13 mm.

Taking in consideration the found relationship between tEAT and coronary vessels impairment in patients with obesity, we performed the evaluation of tEAT informativity in detecting hemodynamically significant stenosis of CA ($>70\%$) using ROC-analysis (figure 5).

As a criterion for diagnostic effectiveness, the area under the ROC curve (AUC) was measured (figure 5). It was 0.740 and this indicates a good classification quality of tEAT ($p=0.001$). The obtained AUC value differs significantly from the area above the diagonal (0.5) with $p = 0.0001$. The sensitivity of the ROC model

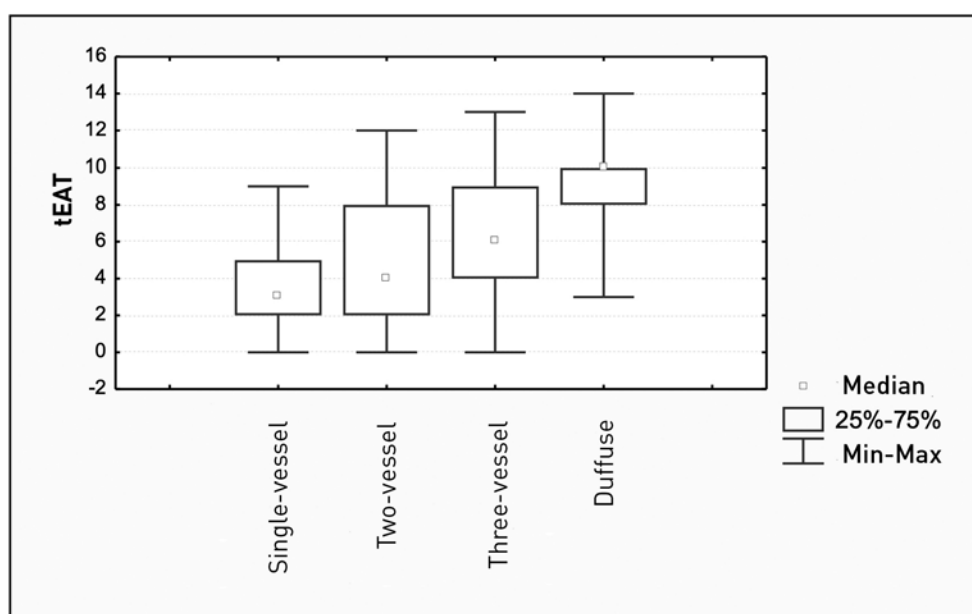


Figure 2. tEAT values in patients with different degrees of coronary vessels impairment

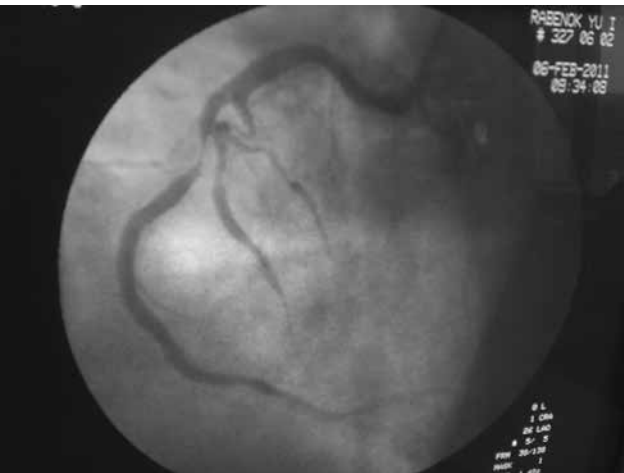


Figure 3. Coronary angiogram of N patient

(the fraction of truly positive classification results which is the presence of a severe stenosis) is 80.4 %, the specificity (the fraction of truly negative classification results which is the absence of any significant stenosis) is 67.6%. The cut-off value for tEAT was found to be 6 mm. Thus, a tEAT ≥ 6mm is a predictor of significant coronary atherosclerosis in patients with CHD.

The obtained data are confirmed by another study conducted in Corea (n=557) which showed that the tEAT increase of more than 3 mm was an independent risk factor of coronary atherosclerosis with more than 50 % stenosis presence [16].

After that we studied the influence of different predictors on the development of severe coronary atherosclerosis, using univariate binary logistic analysis. In addition to tEAT, there were age and main metabolic risk factors among the predictors: WC, TG, HDL cholesterol, glucose, systolic and diastolic blood pressure (SBP, DBP), and some additional cardiovascular risk factors, such as ApoA1, ApoB, leptin and resistin.

Table 1. Results of univariate binary logistic analysis of coronary atherosclerosis predictors

Predictors	OR	95 %CI	χ^2	p
Age	6.52	2.61–15.9	10.06	<0.001
tEAT	4.41	2.02–9.43	22.31	<0.001
Leptin	3.50	1.46–8.37	11.65	<0.001
Resistin	3.13	1.32–7.42	10.89	<0.001
WC	1.72	0.76–3.74	5.63	<0.01

Note: OR — odds ratio; CI — confidence interval; WC — waist circumference; tEAT — epicardial adipose tissue thickness

The performed analysis showed that tEAT, together with age, resulted in being the significant predictor of coronary atherosclerosis in patients included in the study (table 1). Moreover, the similar relationship was demonstrated with leptin, resistin and WC levels.



Figure 4. Echocardiogram of N patient. EAT is indicated by the arrow.

Note: Area under the ROC curve (AUC) — 0.740; Standard error — 0.0437; 95 % Confidence interval 0.653 to 0.814; z statistic — 5.487 Significance level P (Area=0.5) — 0.0001

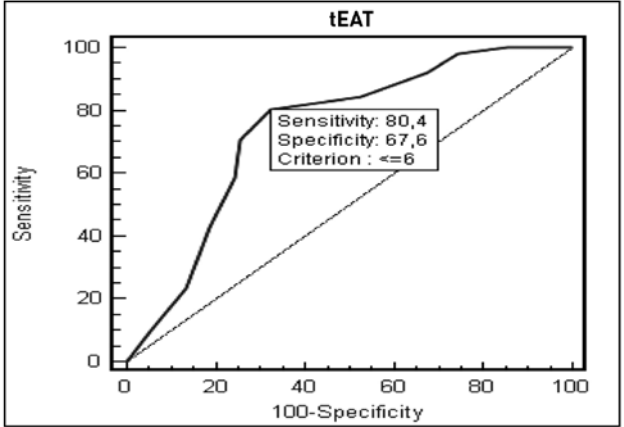


Figure 5. ROC-curve for estimating the informativity of tEAT as the stenosing coronary atherosclerosis predictor (tEAT — epicardial adipose tissue thickness).

It is important that when comparing epicardial and abdominal obesity (using the WC value) as coronary atherosclerosis predictors, the tEAT resulted in being more significant (OR 4.44; 95 % CI 2.06–9.59; p<0.001) than WC (OR 1.65; 95 %CI 0.72–3.80; p=0.018). The lipid metabolism markers (TG, HDL cholesterol, ApoA1, ApoB), SBP and DBP levels were not informative as predictors, probably because patients were getting an adequate hypolipidemic and hypotensive therapy in the course of 1–6 months.

Thus, our study found out the relationship of tEAT with plasma level (HDL cholesterol, TG), apolipoproteins (ApoA1, ApoB), visceral fat hormones (leptin, resistin). It was also found that patients with severe coronary impairment had higher average tEAT values. It was also showed that according to ROC-curve the tEAT ≥ 6 mm in patients with obesity and CHD was informative for diagnostics of stenosing coronary atherosclerosis, which was proved by univariate binary logistic analysis. The gotten results demonstrate the necessity of obesity correction measures, especially

those regarding visceral obesity, in atherosclerosis (including coronary atherosclerosis) prevention programs.

Conflict of interest: None declared

References

1. Bastien M., Poirier P., Lemieux I., et al. Overview of epidemiology and contribution of obesity to cardiovascular disease. *Prog Cardiovasc Dis* 2014; 56 (4): 369–81.
2. WHO. Obesity and overweight. Fact sheet N 311. Updated January 2015. Available at: <http://www.who.int/mediacentre/factsheets/fs311/en/> Checked by 10/08/2016
3. Muromtseva GA, Kontsevaya AV, Konstantinov VV, et al. The prevalence of risk factors noninfectious diseases in Russian population in 2012–2013. Survey ESSAY-RF. *Cardiovascular Therapy and Prevention* 2014; 13 (6): 4–11. Russian
4. Berrington de Gonzalez A, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med*. 2010;363 (23): 2211–9.
5. Iacobellis G, Malavazos AE, Corsi MM. Epicardial fat: from the biomolecular aspects to the clinical practice. *Int J Biochem Cell Biol* 2011; 43: 1651–4.
6. Iacobellis G., Willens H.J. Echocardiographic Epicardial Fat: A Review of Research and Clinical Applications *JASE* 2009; 22:1311–1319.
7. Chumakova GA, Veselovskaya NG. Clinical significance of visceral obesity. Moscow. GEOTAR-Media. 2016. — 160. Russian
8. Xu Y, Cheng X, Hong K, Huang C, Wan L. How to interpret epicardial adipose tissue as a cause of coronary artery disease: a metaanalysis. *Coron Artery Dis* 2012; 23: 227–33.
9. Veselovskaya NG, Chumakova GA, Elykomov VA, et al. Risk factors for restenosis after coronary stenting in patients with obesity. *Cardiovascular Therapy and Prevention* 2013; 3:4–9. Russian
10. Kalantar-Zadeh K, Streja E, Kovesdy CP, et al. The obesity paradox and mortality associated with surrogates of body size and muscle mass in patients receiving hemodialysis. *Mayo Clin Proc* 2010;85 (11): 991–1001.
11. De Schutter A, Lavie CJ, Patel DA, et al. Obesity paradox and the heart: which indicator of obesity best describes this complex relationship? *Curr Opin Clin Nutr Metab Care* 2013;16 (5): 517–24.
12. Iacobellis G, Malavazos AE, Corsi MM. Epicardial fat: from the biomolecular aspects to the clinical practice. *Int J Biochem Cell Biol* 2011; 43: 1651–4
13. Xu Y, Cheng X, Hong K, Huang C, Wan L. How to interpret epicardial adipose tissue as a cause of coronary artery disease: a metaanalysis. *Coron Artery Dis* 2012; 23: 227–33.
14. Eroglu S., Sade L.E., Yildirim A. et al. Epicardial adipose tissue thickness by echocardiography is a marker for the presence and severity of coronary artery disease *Nutr Metab Cardiovasc Dis* 2009; 19:211–217.
15. Ding J., Hsu F.C., Harris T.B. The association of pericardial fat with incident coronary heart disease: the Multi-Ethnic Study of Atherosclerosis (MESA) 1.2.3 *Am J Clin Nutr* 2009; 90: 499–504
16. Ahn S.G., Lim H.S., Joe D.Y. Relationship of epicardial adipose tissue by echocardiography to coronary artery disease *Heart* 2008; 94: 7–13.

Treatment of Hypertension

Wilbert S. Aronow*

Autor

Wilbert S. Aronow, MD, FACC, FAHA, Cardiology Division, and the Department of Medicine, Westchester Medical Center and New York Medical College, Valhalla, NY, USA

Abstract

Automated validated devices should be used to measure blood pressure (BP). A systolic BP between 120–129 mm Hg with a diastolic BP < 80 mm Hg should be treated by lifestyle measures. Treat with lifestyle measures plus BP lowering drugs for secondary prevention of recurrent cardiovascular disease events in patients with clinical cardiovascular disease (coronary heart disease, congestive heart failure, and stroke) and an average systolic BP of ≥ 130 mm Hg or an average diastolic BP ≥ 80 mm Hg. Treat with lifestyle measures plus BP lowering drugs for primary prevention of cardiovascular disease in patients with an estimated 10-year risk of atherosclerotic cardiovascular disease $\geq 10\%$ and an average systolic BP ≥ 130 mm Hg or an average diastolic BP ≥ 80 mm Hg. Treat with lifestyle measures plus BP lowering drugs for primary prevention of cardiovascular disease in patients with an estimated 10-year risk of atherosclerotic cardiovascular disease of < 10% and an average systolic BP ≥ 140 mm Hg or an average diastolic BP ≥ 90 mm Hg. Treat with antihypertensive drug therapy with 2 first-line drugs from different classes either as separate agents or in a fixed-dose combination in patients with a BP $\geq 140/90$ mm Hg or with a BP > 20/10 mm Hg above their blood pressure target. White coat hypertension must be excluded before starting treatment with antihypertensive drugs in patients with hypertension at low risk for atherosclerotic cardiovascular disease. Antihypertensive drug therapy for different disorders is discussed.

Keywords

Hypertension; systolic blood pressure; diastolic blood pressure; antihypertensive drugs; lifestyle measures

INTRODUCTION

Hypertension is the most common modifiable risk factor for cardiovascular events and mortality in the world. [1] The prevalence of hypertension is 69% in persons with a first myocardial infarction [2, 77% in persons with a first stroke [2, 74% in persons with

congestive heart failure [2, and 60% in persons with peripheral arterial disease. [3] Hypertension is also a major risk factor for sudden cardiac death, a dissecting aortic aneurysm, angina pectoris, left ventricular hypertrophy, thoracic and abdominal aortic aneurysms, chronic kidney disease, atrial fibrillation,

* Corresponding author. Tel.: (914) 493-5311, E-mail: wsaronow@aol.com

diabetes mellitus, the metabolic syndrome, vascular dementia, Alzheimer's disease, and ophthalmologic disease [4]. A meta-analysis of 61 prospective studies with 1 million persons without prior cardiovascular disease demonstrated that cardiovascular risk increases progressively from a blood pressure level of 115/75 mm Hg with a doubling of the incidence of coronary heart disease and of stroke for every 20/10 mm Hg increase [5]. Numerous randomized prospective, double-blind, placebo-controlled studies have shown that antihypertensive drug treatment reduces cardiovascular events and mortality [4,6,10].

2017 ACC/AHA HYPERTENSION GUIDELINES

The 2017 United States hypertension guidelines were written by members from 11 professional societies. [11] These guidelines stated that common modifiable risk factors present in persons who have hypertension are current cigarette smoking, passive smoking, diabetes mellitus, dyslipidemia/hypercholesterolemia, overweight/obesity, physical inactivity/low fitness, and unhealthy diet [11].

The new 2017 hypertension guidelines reported that a normal blood pressure is below 120/80 mm Hg. [11] An elevated blood pressure is 120–129/<80 mm Hg. Stage 1 hypertension is a systolic blood pressure of 130–139 mm Hg or a diastolic blood pressure of 80–89 mm Hg. Stage 2 hypertension is a systolic blood pressure of 140 mm Hg and higher or a diastolic blood pressure of 90 mm Hg and higher [11]. Automated validated devices should be used to measure blood pressure. Using these new criteria, the prevalence of hypertension in the United States of America is 31 % of men and 18 % of women aged 20 to 44 years, 52 % of men and 46 % of women aged 45 to 54 years, 68 % of men and 65 % of women aged 55 to 64 years of age, 75 % of men and 78 % of women aged 65 to 74 years of age, and 83 % of men 86 % of women aged 75 years and older [11]. The overall prevalence of hypertension in the United States of America is 49 % in non-Hispanic white men and 47 % in non-Hispanic white women, 59 % in non-Hispanic African-American men and 60 % in non-Hispanic African-American women, and 46 % in Hispanic men and 41 % in Hispanic women [11].

These hypertension guidelines also reported that the absolute cardiovascular risk reduction caused by blood pressure lowering is greater at higher absolute levels of cardiovascular disease risk [11]. Antihypertensive drug therapy should be guided by

predicted cardiovascular disease risk in conjunction with blood pressure. [11–14] Hypertensive persons with a 10-year atherosclerotic cardiovascular risk less than 15 % with a systolic blood pressure between 120–159 mm Hg and a coronary artery calcium score greater than 100 also have an increased risk for cardiovascular events and should be considered for intensive blood pressure lowering [15].

A systolic blood pressure between 120–129 mm Hg with a diastolic blood pressure below 80 mm Hg should be managed by lifestyle measures. [11, [16] Persons with an untreated systolic blood pressure between 131–159 mm Hg or a diastolic blood pressure between 81–99 mm Hg, should be screened for white coat hypertension using either daytime ambulatory blood pressure monitoring or home blood pressure monitoring [11, 17].

The new hypertension guidelines recommended lifestyle measures plus blood pressure lowering drugs for secondary prevention of recurrent cardiovascular disease events in persons with clinical cardiovascular disease (coronary heart disease, congestive heart failure, and stroke) and an average systolic blood pressure of 130 mm Hg and higher or an average diastolic blood pressure of 80 mm Hg and higher [11, 18, 19]. These guidelines recommended lifestyle measures plus blood pressure lowering drugs for primary prevention of cardiovascular disease in persons with an estimated 10-year risk of atherosclerotic cardiovascular disease $\geq 10\%$ [20] and an average systolic blood pressure of 130 mm Hg and higher or an average diastolic blood pressure of 80 mm Hg and higher [11, 21]. These guidelines recommended lifestyle measures plus blood pressure lowering drugs for primary prevention of cardiovascular disease in persons with an estimated 10-year risk of atherosclerotic cardiovascular disease of $< 10\%$ [20] and an average systolic blood pressure of 140 mm Hg and higher or an average diastolic blood pressure of 90 mm Hg and higher [5, 11, 21]. These guidelines recommended treatment with antihypertensive drug therapy with 2 first-line drugs from different classes either as separate agents or in a fixed-dose combination in persons with a blood pressure of 140/90 mm Hg and higher or with a blood pressure more than 20/10 mm Hg above their blood pressure target [11, 22]. White coat hypertension must be excluded before using antihypertensive drugs in persons with hypertension at low risk for atherosclerotic cardiovascular disease. [11]

Secondary hypertension should be suspected if there is new onset or uncontrolled hypertension in

adults [11, 23]. Screen for secondary hypertension if there is drug-resistant /induced hypertension, abrupt onset of hypertension, onset of hypertension in a person younger than 30 years, exacerbation of previously controlled hypertension, disproportionate target organ damage for the degree of hypertension, accelerated/malignant hypertension, onset of diastolic hypertension in older persons, or unprovoked or excessive hypokalemia [11, 23]. Common causes of secondary hypertension include renal parenchymal disease, renovascular disease, primary aldosteronism, obstructive sleep apnea, and drug- or alcohol-induced hypertension [11]. Uncommon causes of secondary hypertension include pheochromocytoma/paraganglioma, Cushing's syndrome, hypothyroidism, hyperthyroidism, aortic coarctation, primary hyperparathyroidism, congenital adrenal hyperplasia, mineralocorticoid excess syndromes, and acromegaly [11].

The new hypertension guidelines recommended that the blood pressure should be lowered to less than 130/80 mm Hg in persons with ischemic heart disease [9–11, 19, 24] in persons with heart failure with a decreased left ventricular ejection fraction [11, 25], in persons with heart failure with a preserved left ventricular ejection fraction [11, 25], in persons with chronic kidney disease [11, 26], in persons after renal transplantation [11], in persons with lacunar stroke [11, 27], in persons with peripheral arterial disease [11, 18], in persons with diabetes mellitus [11, 28–31], in noninstitutionalized ambulatory community-dwelling persons older than 65 years of age. [9–11], and for secondary stroke prevention [11, 32].

ANTIHYPERTENSIVE DRUG TREATMENT RECOMMENDED

The new hypertension guidelines recommended for white and other non-black persons younger than 60 years of age with primary hypertension, the first antihypertensive drug should be an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, the second drug a thiazide diuretic (preferably chlorthalidone) or a calcium channel blocker, and if a third antihypertensive drug is needed, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus a thiazide diuretic plus a calcium channel blocker should be given [11]. For white and other non-black persons aged 60 years of age and older with primary hypertension, the first antihypertensive drug should be a thiazide diuretic (preferably chlorthalidone) or a calcium channel blocker, and if

a third antihypertensive drug is required, a thiazide diuretic plus a calcium channel blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker should be given [11]. For African-Americans with primary hypertension, the first antihypertensive drug should be a thiazide diuretic (preferably chlorthalidone) or a calcium channel blocker, and if a third antihypertensive drug is needed, a thiazide diuretic plus a calcium channel blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker should be administered [11].

Persons with stable ischemic heart disease and hypertension should be treated with a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and if a third antihypertensive drug is needed, a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus a thiazide diuretic or a calcium channel blocker should be administered. [8, 11, 33–44]. If a fourth antihypertensive drug is needed to adequately control hypertension, a mineralocorticoid receptor antagonist should be added [11]. In persons with stable ischemic heart disease who have angina pectoris despite beta blocker therapy and persistent uncontrolled hypertension, a dihydropyridine calcium channel blocker should be added [8, [11, 33, 45]. Beta blockers which should be administered in treating ischemic heart disease with hypertension include carvedilol, metoprolol tartrate, metoprolol succinate, bisoprolol, nadolol, propranolol, and timolol [11]. Atenolol should not be given [8, 11, 35, 46, 47]. Nondihydropyridine calcium channel blockers such as verapamil and diltiazem are contraindicated if there is left ventricular systolic dysfunction. [11] If there is left ventricular systolic dysfunction, the beta blockers that should be administered are carvedilol, metoprolol succinate, or bisoprolol [8, 11, 34].

If hypertension persists after treatment with a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in patients with an acute coronary syndrome, a long-acting dihydropyridine calcium channel blocker should be added to the therapeutic regimen [8, 11]. Aldosterone antagonists should be administered to patients treated with beta blockers plus angiotensin-converting enzyme inhibitors or angiotensin receptor blockers after myocardial infarction who have left ventricular systolic dysfunction and either heart failure or diabetes mellitus if their serum potassium is less than 5.0 meq/L and if their serum creatinine is ≤ 2.5 mg/dL in men and ≤ 2.0 mg/dL in women [8, 11, 48, 9].

Patients with hypertension who have heart failure with a decreased left ventricular ejection fraction should be treated with a beta blocker (carvedilol, metoprolol succinate, or bisoprolol) plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker or preferably an angiotensin receptor–nephrolysin inhibitor plus a diuretic and if indicated with a mineralocorticoid receptor antagonist [11, 25, 35, 48, 49]. Nondihydropyridine calcium channel blockers are contraindicated in patients with heart failure and a decreased left ventricular ejection fraction. [11, 25, 50, 51].

Patients with hypertension and heart failure with a preserved left ventricular ejection fraction should have their volume overload treated with diuretics, their other comorbidities treated, and their hypertension treated with a beta blocker plus an angiotensin converting enzyme inhibitor or angiotensin blocker plus a mineralocorticoid receptor antagonist. [11, 25, 52, 53].

Patients with hypertension and chronic kidney disease stage 3 or higher or stage 1 or 2 chronic kidney disease with albuminuria ≥ 300 mg per day should be treated with an angiotensin-converting enzyme inhibitor to slow progression of chronic kidney disease [11, 26, 54–56]. If an angiotensin-converting enzyme inhibitor is not tolerated, these patients should be treated with an angiotensin receptor blocker [11]. Patients with stage 1 or 2 chronic kidney disease who do not have albuminuria may be treated with usual first-line antihypertensive drugs [11]. If 3 antihypertensive drugs are necessary, these patients should be treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus a thiazide diuretic plus a calcium channel blocker. After kidney transplantation, treat hypertension with a calcium channel blocker to improve glomerular filtration rate and kidney survival [11, 57].

Patients with hypertension and a prior stroke or transient ischemic attack should receive treatment with a thiazide diuretic or angiotensin-converting enzyme or angiotensin receptor blocker [11, 58–60]. If a third antihypertensive drug is needed, these patients should be treated with a thiazide diuretic plus an angiotensin-converting enzyme or angiotensin receptor blocker plus a calcium channel blocker.

Patients with hypertension and peripheral arterial disease should be treated with an angiotensin-converting enzyme or angiotensin receptor blocker or a calcium channel blocker or thiazide diuretic or beta blocker [11, 61]. There is no evidence that any

one class of antihypertensive drugs is superior to treat hypertension in patients with peripheral arterial disease [11, 61]. Thiazide diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers are effective antihypertensive drugs. In patients with hypertension and diabetes mellitus and may be used as initial therapy. [11, 62–64]. Angiotensin-converting enzymes or angiotensin receptor blockers should be used for treating diabetics with hypertension and persistent albuminuria. [11, 65, 66]. Chlorthalidone was better than lisinopril, amlodipine, and doxazosin in reducing cardiovascular disease and renal outcomes in nondiabetic s with hypertension and the metabolic syndrome [11, 67].

Beta blockers are the preferred antihypertensive drugs in patients with hypertension and thoracic aortic aneurysm [11, 68]. Beta blockers also improve survival in adults with type A and with type B acute and chronic thoracic aortic dissection [11, 69, 70]. If thoracic aorta dissection develops, beta blockers are the initial drug of choice for reducing blood pressure, ventricular rate, dP/dt , and stress on the aorta [68, 71, 72]. Systolic blood pressure should be lowered to 100 to 120 mm Hg and the ventricular rate decreased to less than 60 beats/minute by intravenous propranolol, metoprolol, labetalol, or esmolol [68, 72].

Pregnant women with hypertension should not receive treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, direct renin inhibitors, or atenolol because these drugs are fetotoxic [11, 73–75]. Pregnant women with hypertension should be treated with methyldopa, nifedipine, and/or labetalol [11, 76, 77].

Resistant hypertension is diagnosed if the blood pressure is not controlled despite adequate doses of 3 first-line classes of antihypertensive drugs including a thiazide diuretic or if adequate blood pressure control needs 4 or more antihypertensive drugs from different classes [11, 78]. Therapy of resistant hypertension includes improving compliance with use of medication, detection and treatment of secondary hypertension, use of lifestyle measures, and treatment of obesity and other comorbidities [11, 16]. If a fourth antihypertensive drug is needed to control blood pressure in persons treated with adequate doses of antihypertensive drugs from different classes including a thiazide diuretic, a mineralocorticoid receptor antagonist should be added to the therapeutic regimen [11, 79].

Hypertensive emergencies are diagnosed if the systolic blood pressure is higher than 180 mm Hg or if

the diastolic blood pressure is higher than 120 mm Hg with the presence of acute target organ damage [11, 80]. Patients with a hypertensive emergency should be admitted to an intensive care unit for continuous monitoring of blood pressure and target organ damage and for intravenous administration of appropriate antihypertensive drugs. The drugs of choice for treating hypertensive emergencies caused by different disorders are extensively discussed elsewhere [11, 80].

In patients with hypertension, blood pressure lowering is reasonable to prevent cognitive decline and dementia [11, 81, 82]. We are awaiting the results from the Systolic Blood Pressure Intervention Trial (SPRINT) which is adequately powered to test whether intensive blood pressure control reduces dementia [11].

Patients with hypertension on beta blockers undergoing major surgery should continue treatment with beta blockers [11]. Beta blockers should not be started on the day of surgery in beta-blocker naïve patients [11]. Abrupt preoperative discontinuation of beta blockers or clonidine is potentially harmful [11, 83, 84]. Patients undergoing major elective surgery should have their blood pressure controlled with a target blood pressure goal of less than 130/80 mm Hg [11]. Patients undergoing major elective surgery with a systolic blood pressure of ≥ 180 mm Hg or a diastolic blood pressure of ≥ 110 mm Hg should have their surgery deferred [11, 85]. Management of hypertension in patients undergoing surgery is discussed elsewhere. [86].

REFERENCES

1. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2224–2260.
2. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics-2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009; 119: e21–e181.
3. Aronow WS, Ahmed MI, Ekundayo OJ, et al. A propensity-matched study of the association of PAD with cardiovascular outcomes in community-dwelling older adults. *Am J Cardiol* 2009; 103:130–135.
4. Aronow WS, Fleg JL, Pepine CJ, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. *J Am Coll Cardiol*. 2011; 57: 2037–2114.
5. Lewington S, Clarke R, Qizilbash N, et al. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360: 1903–1913.
6. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *N Eng J Med* 2008; 358: 1887–1898.
7. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016; 387: 957–967.
8. Rosendorff C, Lackland DT, Allison M, Aronow WS, et al. AHA/ACC/ASH scientific statement. Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension. *J Am Coll Cardiol* 2015; 65:1998–2038
9. Wright JT, Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015; 373: 2103–2116.
10. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥ 75 years. A randomized clinical trial. *JAMA* 2016; 315: 2673–2682.
11. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation and management of high blood pressure in adults. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017; 70: November 13 [Epub ahead of print]
12. Navar AM, Pencina MJ, Peterson ED. Assessing cardiovascular risk to guide hypertension diagnosis and treatment. *JAMA Cardiol* 2016; 1: 864–871.
13. Karmali KN, Lloyd-Jones DM. Global risk assessment to guide blood pressure management in cardiovascular disease prevention. *Hypertension* 2017; 69: e2–e9.
14. Muntner P, Whelton PK. Using predicted cardiovascular disease risk in conjunction with blood pressure to guide antihypertensive medication treatment. *J Am Coll Cardiol* 2017; 69: 2446–2456.
15. McEvoy JW, Martin SS, Dardari ZA, et al. Coronary artery calcium to guide a personalized risk-based approach to initiation and intensification of antihypertensive therapy. *Circulation* 2017; 135: 153–165.

16. Aronow WS. Lifestyle measures for treating hypertension. *Arch Med Sci* 2017; 13: 1241–1243.
17. Mancia G, Bombelli M, Brambilla G, et al. Long-term prognostic value of whitecoat hypertension: an insight from diagnostic use of both ambulatory and home blood pressure measurements. *Hypertension* 2013; 62: 168–174.
18. Thompson AM, Hu T, Eshelbrenner CL, et al. Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: a meta-analysis. *JAMA* 2011; 305: 913–922.
19. Czernichow S, Zanchetti A, Turnbull F, et al. The effects of blood pressure reduction and of different blood pressure-lowering regimens on major cardiovascular events according to baseline blood pressure: meta-analysis of randomized trials. *J Hypertens* 2011; 29: 4–16.
20. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 63: 2935–2959.
21. Blood Pressure-Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. *Lancet* 2014; 384: 591–598.
22. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC 7 Report. *JAMA* 2003;289:2560–2572.
23. Chiong JR, Aronow WS, Khan IA, et al. Secondary hypertension: current diagnosis and treatment. *Int J Cardiol* 2008; 124: 6–21.
24. Bundy JD, Li C, Stuchlik P, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review of cardiovascular disease and mortality: a systematic review and network meta-analysis. *JAMA Cardiol* 2017; 2: 775–781.
25. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure. A report of the American College of Cardiology /American Heart Association Task Force on clinical Practice Guidelines and the Heart Failure Society of America. Developed in collaboration with the American Academy of Family Physicians, the American College of Chest Physicians, and International Society for Heart and Lung Transplantation. *J Am Coll Cardiol* 2017; 70: 776–803.
26. Upadhyay A, Earley A, Haynes SM, Uhlig K. Systematic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier. *Ann intern Med* 2011; 154: 541–548.
27. SPS3 Study Group, Benavente OR, Coffey CS, et al. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet* 2013; 382: 507–515.
28. Emdin CA, Rahimi K, Neal B, et al. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2015; 313: 603–615.
29. Margolis KL, O'Connor PJ, Morgan TM, et al. Outcomes of combined cardiovascular risk factor management strategies in type 3 diabetes: The ACCORD randomized trial. *Diabetes Care* 2014; 37: 1721–1728.
30. Soliman EZ, Byington RP, Bigger JT, et al. Effect of intensive blood pressure lowering on left ventricular hypertrophy in patients with diabetes mellitus: Action to Control Cardiovascular Risk in Diabetes Blood Pressure Trial. *Hypertension* 2015; 66: 1123–1129.
31. Aronow WS. Orthostatic hypotension in diabetics in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) blood pressure trial. *Hypertension* 2016; 68: 851–852.
32. Wang WT, You LK, Chiang CE, et al. Comparative effectiveness of blood pressure-lowering drugs in patients who have already suffered from stroke: traditional and Bayesian network meta-analysis of randomized trials. *Medicine* 2016; 95: e3302.. Law MR, Morris JK, Wald NJ. Use of BP lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009; 338:b1665.doi.10.1136/bmj.b1665.
33. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease:2011 update. A guideline from the American Heart Association and American College of Cardiology Foundation. Endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. *J Am Coll Cardiol* 2011; 58: 2432–2446.
34. Aronow WS. Current role of beta blockers in the treatment of hypertension. *Expert Opin Pharmacotherap* 2010; 11:2599–2607.
35. Gundersen T, Abrahamsen AM, Kjekshus J, Ronnevik PK. Timolol-related reduction in mortality and reinfarction in patients ages 65–75 years surviving acute myocardial infarction. *Circulation* 1982; 66:1179–1184.
36. Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. *JAMA* 1982; 247:1707–1714.
37. Aronow WS, Ahn C, Kronzon I. Effect of beta blockers alone, of angiotensin-converting enzyme inhibitors alone, and of beta blockers plus angiotensin-converting enzyme inhibitors on new coronary events and on congestive heart failure in older persons with healed myocardial infarcts and asymptomatic left ventricular systolic dysfunction. *Am J Cardiol*. 2001;88:1298–1300.
38. Aronow WS, Ahn C. Incidence of new coronary events in older persons with prior myocardial infarction and systemic hypertension treated with beta blockers, angiotensin-converting

- enzyme inhibitors, diuretics, calcium antagonists, and alpha blockers. *Am J Cardiol* 2002; 89:1207–1209.
39. The CAPRICORN Investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001; 357:1385–1390.
 40. Freemantle N, Cleland J, Young P, et al. Beta blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999; 318: 1730–1737.
 41. HOPE [Heart Outcomes Prevention Evaluation] Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; 342:145–153.
 42. The European trial on reduction of cardiac events with perindopril in stable coronary artery disease investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003; 362: 782–788.
 43. Pfeffer MA, Braunwald E, Moya LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1992;327:669–677.
 44. Leon MB, Rosing DR, Bonow RO, et al. Clinical efficacy of verapamil alone and combined with propranolol in treating patients with chronic stable angina pectoris. *Am J Cardiol* 1981; 48: 131–139.
 45. Aronow WS. Might losartan reduce sudden cardiac death in diabetic patients with hypertension? *Lancet* 2003; 362: 591–592.
 46. Carlberg B, Samuelson O, Lindholm LH. Atenolol in hypertension: is it a wise choice? *Lancet* 2004; 364: 1684–1689.
 47. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709–717.
 48. Pitt B, White H, Nicolau J, et al. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *J Am Coll Cardiol* 2005; 46:425–431.
 49. Elkayam U, Amin J, Mehra A, et al. A prospective, randomized, double-blind, crossover study to compare the efficacy and safety of chronic nifedipine therapy with that of isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. *Circulation* 1990;82:1954–1961.
 50. Goldstein RE, Boccuzzi SJ, Cruess D, Nattel S. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. *Circulation* 1991;83:52–60.
 51. Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction > or = 40% treated with diuretics plus angiotensin-converting enzyme inhibitors. *Am J Cardiol* 1997; 80: 207–209.
 52. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation* 2015; 131: 34–42.
 53. Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 2002; 288: 2421–2431.
 54. Jafar TH, Stark PC, Schmid CH, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Ann Intern Med* 2003; 139: 244–252.
 55. Appel LJ, Wright JT Jr, Greene T, et al. Intensive blood pressure control in hypertensive chronic kidney disease. *N Engl J Med* 2010; 363: 918–929.
 56. Cross NB, Webster AC, Masson P, et al. Antihypertensives for kidney transplant recipients: systematic review and meta-analysis of randomized controlled trials. *Transplantation* 2009; 88: 7–18.
 57. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6.105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; 358: 1033–1041.
 58. Liu L, Wang Z, Gong L, Zhang Y, et al. Blood pressure reduction for the secondary prevention of stroke: a Chinese trial and a systematic review of the literature. *Hypertens Res* 2009; 32: 1032–1040.
 59. Lakhan SE, Sapko MT. Blood pressure lowering treatment for preventing stroke recurrence: a systematic review and meta-analysis. *Int Arch Med* 2009; 2: 30.
 60. Bavry AA, Anderson RD, Gong Y, et al. Outcomes among hypertensive patients with concomitant peripheral and coronary artery disease: findings from the INternational VERapamil-SR/Trandolapril STudy. *Hypertension* 2010; 55: 48–53.
 61. Turnbull F, Neal B, Algert C, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med* 2005; 165: 1410–1419.
 62. Emdin CA, Rahimi K, Neal B, et al. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2015; 313: 603–615.
 63. Whelton PK, Barzilay J, Cushman WC, et al. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 2005; 165: 1401–1409.
 64. Palmer SC, Mavridis D, Navarese E, et al. Comparative efficacy and safety of blood pressure-lowering agents in adults with

- diabetes and kidney disease: a network meta-analysis. *Lancet* 2015; 385: 2047–2056.
65. Schmieder RE, Hilgers KF, Schlaich MP, Schmidt BM. Renin-angiotensin system and cardiovascular risk. *Lancet* 2007; 369: 1208–1219.
 66. Black HR, Davis B, Barzilay J, et al. Metabolic and clinical outcomes in nondiabetic individuals with the metabolic syndrome assigned to chlorthalidone, amlodipine, or lisinopril as initial treatment for hypertension: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Diabetes Care* 2008; 32: 353–360.
 67. Hiratzka LF, Bakris GL, Beckman JA, et al. ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol* 2010; 55: e27–e12
 68. Genoni M, Paul M, Jenni R, et al. Chronic beta-blocker therapy improves outcome and treatment costs in chronic type B aortic dissection. *Eur J Cardiothorac Surg* 2001; 19: 606–610.
 69. Suzuki T, Isselbacher EM, Nienaber CA, et al. Type-selective benefits of medications in treatment of acute aortic dissection (from the International Registry of Acute Aortic Dissection [IRAD]). *Am J Cardiol* 2012; 109: 122–127.
 70. Braverman AC. Acute aortic dissection. Clinician update. *Circulation* 2010; 122: 184–188.
 71. Tsai TT, Nienaber CA, Eagle KA. Acute aortic syndromes. *Circulation* 2005; 112: 3802–3813.
 72. Pucci M, Sarween N, Knox E, et al. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in women of childbearing age: risks versus benefits. *Expert Rev Clin Pharmacol* 2015; 8: 221–231.
 73. Ferrer RL, Sibai BM, Mulrow CD, et al. Management of mild chronic hypertension during pregnancy: a review. *Obstet Gynecol* 2000; 96 (Pt 2): 849–860.
 74. Moretti ME, Caprara D, Drehuta I, et al. The fetal safety of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers. *Obstet Gynecol Int* 2012; 2012: 658310.
 75. James PR, Nelson-Piercy C. Management of hypertension before, during, and after pregnancy. *Heart* 2004; 90: 1499–1504.
 76. Hypertension in pregnancy. Report of the American College of Obstetrics and Gynecologists' Task force on Hypertension in Pregnancy. *Obstetrics and Gynecology* 2013; 122: 1122–1131.
 77. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation* 2008; 117: e510–e526.
 78. Tataru AP, Barry AR. A systematic review of add-on pharmacologic therapy in the treatment of resistant hypertension. *Am J Cardiovasc Drugs* 2017; 17: 311–318.
 79. Aronow WS. Treatment of hypertensive emergencies. *Ann Translational Med* 2017; 5 (Suppl 1): S5. doi: 10.21037/atm.2017.03.34.
 80. Forette F, Seux ML, Staessen JA, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. *Arch Intern Med* 2002; 162: 2046–2052.
 81. Tzourio C, Anderson C, Chapman N, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med* 2003; 163: 1069–1075.
 82. Hart GR, Anderson RJ. Withdrawal syndromes and the cessation of antihypertensive therapy. *Arch Intern Med* 1981; 141: 1125–1127.
 83. Shammash JB, Trost JC, Gold JM, et al. Perioperative beta-blocker withdrawal and mortality in vascular surgical patients. *Am Heart J* 2001; 141: 148–153.
 84. Fleisher LA. Preoperative evaluation of the patient with hypertension. *JAMA* 2002; 287: 2043–2046.
 85. Aronow WS. Management of hypertension in patients undergoing surgery. *Ann Translational Med* 2017; 5 (10): 227. doi: 10.21037/atm.2017.03.54

Congress of the American College of Cardiology: results of clinical trials

Kanorskii S.G.*

Kuban State Medical University, Krasnodar, Russia

Author

Sergey G. Kanorskii, MD, PhD, doctor of sciences, professor, head of the Department of Therapy № 2, Faculty of Advanced Training and Professional Retraining of Specialists, Kuban State Medical University, Krasnodar, Russia.

Summary

The 67th annual congress of the American College of Cardiology was held in Orlando (USA) on March 10–12, 2018. It was attended by 18.300 people, including 13.000 professionals and opinion leaders from 137 countries.

Traditionally, new results of large clinical trials that could influence clinical practice, in particular, the ones summarized in this article, generated distinct interest. Data obtained in studies ANNEXA-4, A Cluster-Randomized Trial of Blood-Pressure Reduction in Black Barbershops, CARES, HER2, INDIE-HFpEF, MOMENTUM-3, SECURE, SMART-DATE, STOP PAD, TREAT, TRIUMPH, registers and studies of real practice like ARTEMIS, GWTG-HF, POICE, subanalysis of recently presented major projects CANTOS, CANVAS, COMPASS, CVD-REAL 2, FOURIER were of great importance.

The results of clinical trials presented at the scientific sessions of the American College of Cardiology in 2018 demonstrated new possibilities of antithrombotic therapy, treatment of atherosclerosis, coronary heart disease, cardiac arrhythmias, heart failure and arterial hypertension that will certainly help to optimize the management of patients with common cardiovascular diseases.

Key words

Clinical trials, cardiovascular diseases, congress of the American College of Cardiology.

The 67th annual congress of the American College of Cardiology was held in Orlando (USA) in the period from 10 till 12 March 2018. It was attended by 18.300 people, including 13.000 professionals and opinion leaders from 137 countries. The exposition consisted of 280 exponents. 375 journalists from 174 mass media covered this major scientific event.

As usually, the point of highest interest consisted in new results of large clinical studies which could influence the clinical practice; in particular, some of these results are given in this article. A significant role belongs also to the data gotten in the ANNEXA-4, A Cluster-Randomized Trial of Blood-Pressure Reduction in Black Barbershops, CARES, HER2, INDIE-HFpEF, MOMENTUM-3, SECURE, SMART-DATE, STOP PAD, TREAT, TRIUMPH, in registers and in practical studies ARTEMIS, GWTG-HF, POICE, subanalyses of recently presented large projects CANTOS, CANVAS, COMPASS, CVD-REAL 2, FOURIER.

The patients who underwent the myocardium infarction (MI) have a high risk of cardiovascular complications during the subsequent years, despite the modern measures of secondary prevention including intensive statin therapy. Thus, additional treatment is required to decrease this residual risk and to improve the prognosis of these patients.

The long-term efficacy and safety of alicrocumab, a PCSK9 inhibitor that significantly decreases the level of low density lipoproteins (LDL), was evaluated in the ODYSSEY OUTCOMES study. The trial included patients who had undergone acute coronary syndrome (MI or unstable angina) 1–12 months before randomization. All patients received high-intensity statin therapy (atorvastatin 40–80 mg/day or rosuvastatin 20–40 mg/day or the maximum tolerated dose of one of these drugs for 2 weeks), but did not reach the lipid profile target range (LDL level remained ≥ 70 mg / dL or ≥ 1.8 mmol/L, and apolipoprotein B level was ≥ 80 mg / dL). 18.924 patients were randomized for additional subcutaneous administration of alicrocumab (75 or 150 mg 1 time per 2 weeks) or placebo with a median observation time of 2.8 years. The goal of treatment was to achieve a LDL level of 25–50 mg/dL with an acceptable decrease to 15 mg/dL.

The average decrease of LDL level in the alicrocumab group was 62.7% in 4 months time (55.7 mg/dL less compared to placebo) and 54.7% in 48 months time after randomization (48.1 mg/dL lower than for placebo). Alicrocumab treatment was accompanied by a decrease in the incidence of reaching the primary efficacy endpoint (death caused by coronary heart

disease — CHD, nonfatal MI, ischemic stroke, or unstable angina requiring hospitalization) by 15% (relative risk — RR 0.85 with 95% confidence interval — CI in the range from 0.78 till 0.93; $p = 0.0003$; absolute risk reduction — 1.7%). Among the primary endpoint components, coronary artery disease mortality did not significantly decrease (RR 0.92 with 95% CI in the range from 0.76 till 1.11; $p = 0.38$), in contrast to the non-fatal MI incidence (RR 0.86 with 95% CI in the range from 0.77 to 0.96; $p = 0.006$), ischemic stroke (RR 0.73 with 95% CI in the range from 0.57 till 0.93; $p = 0.01$) and unstable angina (RR 0.61 with 95% CI in the range from 0.41 till 0.92; $p = 0.02$).

All-cause mortality was significantly reduced in alicrocumab group compared with placebo (RR 0.85 with 95% CI in the range from 0.73 till 0.98; $p = 0.026$; absolute risk reduction — 0.6%), but this indicator did not concern the primary endpoint. Analysis of a subgroup of patients with baseline LDL ≥ 100 mg / dL showed the greatest benefit of using alicrocumab — it reduced the primary endpoint incidence by 24% (RR 0.76 with 95% CI in the range from 0.65 till 0.87; absolute risk reduction — 3.4%) and all-cause mortality by 29% (RR 0.71 with 95% CI from 0.56 to 0.90; absolute risk reduction — 1.7%). The diabetes incidence, worsening or complications, allergic reactions and neurocognitive disorders in the groups of the PCSK9 inhibitor and placebo did not differ significantly. The patients treated with alicrocumab were more likely to have skin reactions at the injection site (3.8% vs. 2.1% in the placebo group).

Myocardial damage after non-cardiac surgery includes MI and an isolated troponin level increase in the blood that occur during the first 30 days after surgery. Such myocardial damage is independently associated with an increased risk of cardiovascular events and death during the first two years after surgery. Anticoagulant therapy is useful for patients with an increased risk of thrombotic complications, but has not been previously estimated for the prevention of myocardial damage as a result of non-cardiac surgery.

In the randomized MANAGE trial ($n = 1754$, mean age 70 years), prophylactic efficacy of the direct thrombin inhibitor dabigatran on the vascular complications after non-cardiac surgery was evaluated (110 mg 2 times a day), compared with placebo. Patients who were not taking proton pump inhibitors were randomized to receive omeprazole, 20 mg per day, or placebo (factorial design 2×2). The primary composite efficacy endpoint included vascular death, non-fatal MI, non-hemorrhagic stroke, peripheral

arterial thrombosis, amputation, and symptomatic venous thromboembolism. The primary composite safety endpoint included bleeding (life threatening, major or critical organ bleeding). During the 2 years follow-up, 46% of patients in the dabigatran group and 43% of patients in the placebo group stopped the prescribed treatment, mainly at their personal request. The primary efficacy endpoint was registered in 11% of patients randomized to receive dabigatran, and in 15% of the placebo group (RR 0.72 with 95% CI in the range from 0.55 to 0.93; $p = 0.012$). There was no significant influence of omeprazole on the dabigatran effects in terms of effectiveness (p value for interaction = 0.79). There were no significant differences in the onset of the primary safety endpoint events between the dabigatran and placebo groups (RR 0.92 with 95% CI in the range from 0.55 to 1.53; $p = 0.79$). Omeprazole had no influence on the safety of dabigatran.

The risk of atrial fibrillation (AF) onset over the age of 55 is more than 1/3, which is associated with a 5-fold increase in the incidence of stroke. If AF is identified, anticoagulant therapy can reduce the risk of stroke by about 65% and mortality by 30%. The clinical value of screening for determining the AF presence is still poorly studied. The aim of the mSToPS study was to determine the effectiveness of this arrhythmia diagnostics by patient self-recording of electrocardiogram in comparison to the usual follow-up of 2655 patients without previously diagnosed AF. The iRhythm Zio device was used for active monitoring at home. The primary endpoint was the number of participants with the newly detected AF in the course of a year. The recurrence of the newly diagnosed AF was 6.3% in the active control group compared to 2.3% of those with standard follow-up (RR 2.8 with 95% CI in the range from 2.1 to 3.7; $p < 0.0001$).

The median of total AF duration in the monitoring group was 0.9%, and the mean duration of the longest AF episode was 185.5 min (92.8% episodes of >5 min, 37.7% episodes of >6 hours). Active monitoring was associated with an increase in the incidence of anticoagulant therapy onset in comparison to the standard follow-up group (5.4% vs 3.4%, $p = 0.0004$). Though, there were no differences in clinical outcomes (stroke, MI, systemic thromboembolism) between the active control group and the standard follow-up group.

The effectiveness of clopidogrel antiplatelet therapy in patients with ACS may decrease due to individual variability of the response to treatment with this

drug. The choice of a P2Y₁₂ receptor blocker therapy is usually based on the physician's assessment of the risk of ischemic events on the one side and the risk of uncontrolled bleeding on the other. It has been shown that there are several genes which affect enzymes controlling clopidogrel's antiplatelet efficacy. There has been developed an easy-to-use genetic screening system ST Q3 which is transportable within a medical center and in 70 minutes can provide information on these genes from a blood sample at the bedside of the patient.

The PHARMCLO study was aimed to evaluate a personalized approach to the P2Y₁₂ receptor blocker choice in patients with ACS. The study combined clinical characteristics and genetic data to provide information for the drug choice. Patients from 13 medical centers in Italy who were admitted in hospital because of ACS ($n = 888$) were randomized for two types of treatment: the standard one which included the prescription of clopidogrel, ticagrelor or prasugrel only on the grounds of patients' clinical characteristics, and the treatment based on the genetic test data (tested on ABCB1, 2C19 * 2, 2C19 * 17). The genetic test results were taken in consideration together with clinical characteristics before the antiplatelet therapy prescription. The primary composite endpoint included MI, stroke, death from cardiovascular causes, or significant bleeding (BARC 3–5).

After 12 months, 50.7% of patients from the standard treatment group received clopidogrel, 8.4% received prasugrel, 32.7% received ticagrelor, and 8.2% did not received any P2Y₁₂ receptor inhibitor. In the genetic test group, 43.3% of patients received clopidogrel, 7.6% received prasugrel, 42.6% received ticagrelor, and 6.5% did not receive any P2Y₁₂ receptor inhibitor. The primary endpoint was registered in 15.9% of patients from the pharmacogenomics group and in 25.9% of patients from the standard treatment group (RR 0.58 with 95% CI in the range from 0.43 till 0.078; $p < 0.001$), which was mainly due to a decrease in the non-fatal myocardial infarction incidence (RR 0.42 with 95% CI in the range from 0.25 till 0.70). Among those treated with clopidogrel, the primary endpoint was reached 32% less frequently in the pharmacogenomics group compared to the control group (RR 0.68, 95% CI in the range from 0.47 till 0.97; $p = 0.03$).

The realization of genotyping for the choice of antiplatelet therapy in ACS is possible in actual practice and leads to changes in the drug administration regimen. The personalized choice of anti-platelet

therapy can lead to a clinically significant reduction in the incidence of ischemic and hemorrhagic complications. It is necessary to confirm these data about genotype-based antiplatelet therapy in future studies and to clarify the economic efficiency of genotyping in a complex situation of providing medical care in ACS, when the test cannot be delegated to any centralized genetic laboratory because of the lack of time.

The incidence of sudden cardiac death (SCD) after MI is higher in patients with low left ventricular ejection fraction (LVEF). Implantable cardioverter-defibrillators (ICDs) are not introduced into the body of patients during the first 40–90 days after the date of myocardial infarction, depending on the revascularization method and several other reasons. First, large randomized clinical trials did not demonstrate that ICD implantation during this period could lead to a long-term mortality reduction. Secondly, in many cases LVEF improves in the course of the following months after MI. Thirdly, there is a competing risk of death from other causes that cannot be prevented by ICD.

The task of the multicenter randomized VEST study was to answer the question about the possibility of reducing the SCD risk by the usage of a wearable cardioverter-defibrillator (WCD) during the first period after MI (up to 90 days) in patients with reduced LVEF.

Patients who had recently underwent myocardial infarction, with LV EF $\leq 35\%$ and an adequate drug therapy, were randomized in a 2: 1 ratio for usage or non-usage of WCD on hospital discharge. The primary endpoint was SCD in the course of 3 months; the secondary endpoint was death from any other cause and non-fatal outcomes. During a mean observation period of 84.3 ± 15.6 days, no significant differences were shown in the primary endpoint incidence between the WCD group ($n = 1524$) and the control group ($n = 778$) — 1.6% vs 2.4% ($p = 0.18$). There were also no significant differences in the association with the causes of death and nonfatal outcomes between the two groups. However, the overall mortality was significantly lower in the WCD group (3.1% compared to 4.9% in the control group, $p = 0.04$). Among the side effects of the NCD usage, there were skin manifesta-

tions in the form of rash and itching, more likely on chest region.

The results of clinical trials presented at the scientific sessions of the American College of Cardiology in 2018 demonstrated new possibilities of antithrombotic therapy, treatment of atherosclerosis, coronary heart disease, cardiac arrhythmias, heart failure and arterial hypertension that will certainly help to optimize the management of patients with common cardiovascular diseases.

More information about the scientific event held in March 2018 in Orlando is presented on the official website <http://www.acc.org/acc2018>

Conflict of interest: None declared.

References

1. Steg P., Szarek M., Bhatt D. et al. Cardiovascular Outcomes with Alirocumab After Acute Coronary Syndrome: Results of the ODYSSEY Outcomes Trial. ACC Scientific Sessions, March 10, 2018, Orlando, Florida. <https://www.medscape.com/cardiology>
2. Kumbhan D.J. Management of Myocardial Injury After Noncardiac Surgery—MANAGE. ACC Scientific Sessions, March 11, 2018, Orlando, Florida. <https://www.medscape.com/cardiology>
3. Steinhubl S.R., Waalen J., Edwards A. et al. A Digital End-to-End, Nationwide, Pragmatic Trial of Screening for Undiagnosed Atrial Fibrillation Within a Health Insurance System Using a Self-Applied ECG Patch: Primary Results of the mHealth Screening to Prevent Strokes (mSToPS) Trial. ACC Scientific Sessions, March 10, 2018, Orlando, Florida. <https://www.medscape.com/cardiology>
4. Notarangelo F.M., Maglietta G., Bevilacqua P. et al. Pharmacogenomic Approach to Selecting Antiplatelet Therapy in Acute Coronary Syndromes: PHARMCLO trial. J Am Coll Cardiol. 2018 Feb 24. pii: S0735-1097 (18) 33306-0. doi: 10.1016/j.jacc.2018.02.029. [Epub ahead of print]
5. Olgin J.E., Pletcher M., Vittinghoff E. et al. Efficacy of a Wearable Cardioverter-Defibrillator after Myocardial Infarction: Results of the Vest Prevention of Early Sudden Death Trial (VEST). ACC Scientific Sessions, March 10, 2018, Orlando, Florida. <https://www.medscape.com/cardiology>

Results of the VII International Forum of cardiology and internal medicine

The VII International Forum of cardiology and internal medicine was held in Moscow, in the Russian Academy of Science building, on 21–23 March 2018. Traditionally, it represents a major scientific and educational event which is organized with the support from the Ministry of Health of the Russian Federation, the Russian Academy of Sciences, the World Heart Federation, National medical research center for preventive medicine of the Ministry of Health of Russia and the cardiology development assistance foundation «Cardioprogress».

According to the Forum's results, about 1200 delegates took part in this event, including speakers from 67 Russian subjects and from foreign countries (USA, Turkey, Korea, Israel, Czech Republic, Belarus, Moldova, Uzbekistan, Kazakhstan, Kirgizia and Azerbaijan).

Leading experts in cardiology, cardiosurgery, neurology, pulmonology, endocrinology, as well as nephrologists, rheumatologists, gastroenterologists and general practitioners participated in the scientific program of the Forum. Particular attention was paid to the issues of preventive measures for the general population and to the cardiology assistance organization, to risk factors, intervention cardiology, surgical treatment, arrhythmias, rehabilitation, as well as to associated diseases which are constantly increasing in number, also due to population ageing and the improvement in chronic and acute situations management effectiveness. Symposia for military medical practitioners were also organized within the Forum's work.

Key statistics on the scientific program of the Forum:

- 45 symposia, workshops, master classes, round tables and clinical seminars.

- 214 speakers including 8 academicians, 3 corresponding members of RAS and 150 professors.

- 5 joint symposia with representatives from near- and far-abroad countries

Also traditionally, within the scientific program of the Forum, two symposia of young scientists were held, where 16 speakers in the age younger than 35 from different cities of Russia and of CIS countries took part.

The Coordination Council of the Ministry of Health of the Russian Federation awarded the Forum 18 credit hours of continuing medical education.

The compendium of scientific materials included 450 abstracts by researchers from 11 countries of the world and from 52 cities of the Russian Federation. The represented scientific publications were dedicated to the study of various aspects of somatic diseases: arterial hypertension, lipid metabolism disorders, obesity/diabetes mellitus, arrhythmias, coronary heart disease, chronic heart failure, kidney diseases, gastrointestinal tract diseases and chronic obstructive pulmonary disease. The Forum materials are presented on the official website and in the supplement to the «Cardiovascular Therapy and Prevention» journal, which is included to the list of scientific journals recognized by the Higher Attestation Commission.

Detailed information about the forum, including the scientific program and the compendium of publications, is presented on the official website www.cardioprogress.ru.

The organizers hope that the participation of medical practitioners in the Forum would allow them to acquire and systematize new knowledge in the field of treatment and prevention of cardiovascular pathology and other internal organs disorders, which will increase the efficiency of their daily work.

Guidelines for authors

International Heart and Vascular Disease Journal Requirements for Submission and Publication

(version 2017)

The requirements for submission and publication in the **International Heart and Vascular Disease Journal** are based on the 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals', developed by the *International Committee of Medical Journal Editors* (ICMJE), which can be found at www.ICMJE.org

These requirements form the basis for relations between the Editors of the **International Heart and Vascular Disease Journal**, further called «the Editors», and an author who submits a manuscript for publication, further called «the Author».

The **International Heart and Vascular Disease Journal** publishes reviewed articles that cover all aspects of cardiovascular diseases, including original clinical research, experimental research with clinical relevance, reviews on current problems in cardiology, and clinical case studies. Usually 4 issues are published annually (one issue every 3 months).

This is an open access journal, which means that all content is freely available without charge to the user or his/her institution. Users are allowed to read, download, copy, distribute, print, search, or link to the full texts of the articles in this journal without asking prior permission from the publisher or the author. This is in accordance with the *Budapest Open Access Initiative* (BOAI) definition of open access.

1. Submission requirements and publishing policy

1.1. A manuscript should be submitted to the following e-mail address: submissions@inbox.ru

Editorial Office tel.: +7(965) 236-16-00

1.2. A manuscript is accepted for further consideration only if the manuscript, or any substantively similar version, has not been submitted to and published in any other journal, or disseminated via any other media, such as the Internet.

1.3. The Author, submitting the manuscript to the Editor, assigns the Editor to publish it. The Editors have the right to incorporate within the manuscript any illustrated or text material, including advertisements. The Editors may allow third parties to put such content into the manuscript.

1.4. Submission of the manuscript to the Editors implies that the Author agrees to transfer the exclusive property rights for the manuscript and other objects of the copyright, like photos, drawings, graphics, tables, etc., to the Editors. The Editors obtain the right to reproduce (partly or fully) all the content submitted, including objects of the copyright, in press and

on the Internet; to distribute; to translate the manuscript and other provided content into any language; to export and import copies of the issue where the article of the Author was published; and to revise the manuscript.

1.5. The Author transfers the rights specified in clauses 1.3 and 1.4 to the Editors without any time limitations or territory restrictions, including the territories of the Russian Federation.

1.6. The Editors have the right to transfer the rights received from the author to a third party or to prohibit any use of materials published in the journal by a third party.

1.7. The Author guarantees that he or she holds the copyright to all materials submitted to the **International Heart and Vascular Disease Journal**. In case of violation of this guarantee by the Author and consequent claims to the Editors, the Author is obliged to settle all the claims at his/her own expense. The Editors are not responsible for copyright violation by the Author.

1.8. The Author retains the right to use the published material or its parts for personal use, includ-

ing scientific and educational purposes. The Author retains the right to publish extracts from the published material or its parts in other journals, on the condition that reference is made to the original publication in the **International Heart and Vascular Disease Journal**.

1.9. The copyright is considered transferred to the Editors once confirmation has been sent to the author confirming the manuscript has been accepted for publication.

1.10. Reprinting of an article published in the **International Heart and Vascular Disease Journal** by third parties is only permitted with written permission from the Editors. If permission is granted, reference to the issue of the **International Heart and Vascular Disease Journal** in which the article was published and to the year of publication is obligatory.

1.11. The Editors are obliged to provide the Author with one copy of the issue in which the article is published. The Author(s) should provide his/her full postal address(es) including post code(s) at the end of the manuscript.

1.12. Manuscripts may be reviewed by independent experts. Manuscripts which are reviewed will be reviewed on a double blind basis: Authors will not know the identity of reviewers and reviewers will not know the identity of Authors. The name of the institution where an Author works or conducts research also remains confidential. The reviewer(s) comments and opinions will be sent to the Author and the Author invited to make any changes and/or corrections. In the case of an Author not returning changes and/or corrections to the Editors by an agreed date, the Editors have the right to make their own changes and/or corrections, or permit changes and/or corrections suggested by the reviewers, or to refuse to publish the manuscript. Editing, shortening and correction of the manuscript, and changes to a graph, picture or table design are made in order they comply the format and standards of the **International Heart and Vascular Disease Journal**.

1.13. The Editors are not responsible for the accuracy of information presented in the manuscripts.

1.14. The Editors recommend that submitted manuscripts conform with the 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals', developed by the *International Committee of Medical Journal Editors* (ICMJE), and available on the **International Heart and Vascular Disease Journal** website www.cardioprogess.ru, in the 'For Authors' section.

1.15. Adhering to the standards outlined in this document will lead to faster reviewing, editing, and publishing of manuscripts accepted for publication. Manuscripts submitted outside the standards on design and formatting for this journal may not be accepted by the Editors.

2. General recommendations for submission of original scientific works

2.1. The Editors recommend that results of randomized controlled trials conform to the 'Consolidated Standards of Reporting Trials' (CONSORT) guidelines. Information on these standards are available on the CONSORT website: www.consort-statement.org

2.2. A manuscript should be typed using the Times New Roman font (12 points, double spacing; with 2 cm at the top, bottom, left and right margins). The length of a manuscript, including references, schedules, drawings and tables, should not exceed 12 standard typewritten pages (1 page is 1800 letters or symbols, including spaces). A case study should not exceed 6 standard pages. Reviews and lectures should not exceed 25 standard pages.

2.3. Manuscripts should be organized as follows: 1) title page; 2) structured summary and keywords; 3) list of abbreviations; 4) text; 5) acknowledgements (if applicable); 6) references; 7) names and legends of pictures, tables, graphics, and photocopies in the order they appear in the manuscript; 8) drawings, tables, graphics, and photocopies should be submitted on separate pages in the order they appear in the manuscript. Numeration of pages should begin from the title page.

2.4. If the manuscript contains pictures, tables, graphics, or photocopies that have been published previously, reference to the author(s) and publication is necessary. It is the Author's responsibility for determining whether permission is required for the duplication of material, and for obtaining relevant permission.

2.5. Manuscripts based on reviews of original research works should contain the following sections: Introduction (reflecting the urgency of a problem and research goals); Material and methods; Results; Discussion of the obtained results and Conclusion. The text should be clear, brief and without repetition.

3. Publication of uncontrolled trials results

3.1. An uncontrolled trial is a research without a control group.

3.2. Manuscripts based on uncontrolled trials results will be accepted for publication in the 'Practical Experience' column only if the uncontrolled design of the study is described in the Material and methods and Discussion sections. It is important not to exaggerate the significance of results in the Conclusion' section.

4. Ethical aspects

4.1. Trials should be conducted in accordance with principles of «good clinical practice». Participants of a trial should be informed about the purpose and main aims of the trial. They must sign to confirm their written informed consent to participate in the trial. The

«Material and methods» section must contain details of the process of obtaining participants informed consent, and notification that an Ethics Committee has approved conducting and reporting the trial. If a trial includes radiological methods it is desirable to describe these methods and the exposure doses in the «Material and methods» section.

4.2. Patients have the right to privacy and confidentiality of their personal data. Therefore, information containing pictures, names, and initials of patients or numbers of medical documents should not be presented in the materials. If such information is needed for scientific purposes, it is necessary to get written informed consent from the research participant (or their parent, their trustee, or a close relative, as applicable) prior to publication in print or electronically. Copies of written consent may be requested by the Editors.

4.3. Animal trials must conform to the 'International Guiding Principles for Biomedical Research Involving Animals', adopted by the Council for International Organizations of Medical Sciences (CIOMS) in 1985.

5. Authorship

5.1. Each author should significantly contribute to the work submitted for publication.

5.2. If more than 4 authors are indicated in the author's list, it is desirable to describe the contribution of each author in a covering letter. If the authorship is attributed to a group of authors, all members of the group must meet all criteria for authorship. For economy of space, members of the group may be listed in a separate column at the end of the manuscript. Authors can participate in the submitted manuscript in the following ways: 1) contributing to the concept and research design or analyzing and interpreting

data; 2) substantiating the manuscript or checking the intellectual content; 3) providing final approval for the manuscript. Participation solely in collection of data does not justify authorship (such participation should be noted in the Acknowledgements section). Manuscripts should be submitted with a covering letter containing the following information: 1) the manuscript has not been submitted to any other media; 2) the manuscript has not been published previously; 3) all authors have read and approved the manuscript's content; 4) the manuscript contains full disclosure of any conflict of interests; 5) the author/authors confirm responsibility for the reliability of the materials presented in the manuscript. The author responsible for the correspondence should be specified in the covering letter.

6. Conflict of interests/financing

6.1. It is desirable for authors to disclose (in a covering letter or on the title page) any relationships with industrial and financial organizations, which might be seen as a conflict of interest with regard to the content of the submitted manuscript. It is also desirable to list all sources of financing in a footnote on the title page, as well as workplaces of all authors (including corporate affiliations or employment).

7. Manuscript content

7.1. Title page

7.1.1. It should include the name of the article (in capital letters); initials and last names of the authors; the full name of the institution which supported the manuscript, together with the city and country, and full mailing address with postal code of that institution.

7.1.2. A short title of the article (limited to 45 letters or symbols).

7.1.3. Information about the authors, including full names (last name, first name, patronymic name, if applicable; scientific degrees and titles, positions at main and secondary jobs, including corporate posts).

7.1.4. Full name, full postal address, e-mail address, and telephone number of the "Corresponding author" who will be responsible for any contact with the Editors.

7.1.5. The manuscript (or the covering letter) should be signed by all authors.

7.1.6. It is desirable to provide information about grants, contracts and other forms of financial support, and a statement about any conflict of interests.

7.2. Summary

7.2.1. Summary (limited to 300 words) should be attached to the manuscript. It should include the full title of the article, last names and initials of the authors, the name of the institution that supported the manuscript, and its full postal address. The heading of the summary should contain the international name(s) of any drug(s) mentioned.

7.2.2. Original studies summary should contain the following sections: Aim, Material and methods, Results, and Conclusion. The summary of a review should provide the main themes only. A manuscript must contain all data presented in the summary.

7.2.3. 5-6 keywords of the article should be given at the end of the abstract.

7.3. List of abbreviations and their definitions

7.3.1. To conserve space in the journal, up to 10 abbreviations of general terms (for example, ECG, ICV, ACS) or names (GUSTO, SOLVD, TIMI) can be used in a manuscript. List of abbreviations and their definitions should be provided on a separate page after the structured summary (for example, ACS – aortocoronary shunting). Only words generally accepted in scientific literature should be used.

7.4. Text

7.4.1. Original studies should be structured as follows: Introduction, Material and methods, Results, Discussion and Conclusion.

7.4.2. Case studies, reviews and lectures may be unstructured, but it is desirable to include the following paragraphs: Discussion and Conclusion (Conclusions and Recommendations).

7.4.3. Please, use international names of drugs in the title. Exceptions are possible when use of trade names is well-founded (for example, in studies of bio- or therapeutic equivalence of drugs). It is possible to use a trade name in the text, but not more than once per standard page (1800 symbols including spaces).

7.4.4. You must provide titles and subtitles in the sections: Methods, Results and Discussion. Each reference, image or table should be numbered and specified in order of appearance in the text.

7.4.5. All units of measurement should be provided according to the International System of Units (SI) system. No abbreviations, except standard abbreviations of chemical and mathematical terms, are acceptable.

7.4.6. Each image, chart, table, photo, and reference must be indicated in order of appearance in the text.

7.4.7. References in the text must be numbered in Arabic figures, and provided in square brackets.

7.5. Statistics

7.5.1. All submitted materials may be revised to ensure relevance and accuracy of statistical methods and statistical interpretation of results. The Methods section should contain a subsection with detailed description of statistical methods, including those used for generalization of data; and of methods used for testing hypotheses (if those are available). Significance value for testing hypotheses must be provided. Please indicate which statistical software was used to process results and its version if you use more complex statistical methods (besides a t-test, a chi-square, simple linear regression, etc.).

7.6. Acknowledgements

7.6.1. The Acknowledgements section or Appendix should not exceed 100 words.

7.7. References

7.7.1. Please use separate sheets and double spacing for the list of references. Give each source a consecutive number starting on a new line. The list of references should be structured in order of citation. Use Index Medicus to search for abbreviations of the names of journals.

7.7.2. All documents referred to in the text, should be included in the list of references.

7.7.3. The list of references should not include any dissertations, theses published more than two years ago, or information that is impossible to check (local conference materials, etc.). If material is taken from a thesis, please, mention that in brackets — (thesis).

7.7.4. It is desirable to refer to periodicals with a high impact factor, if possible.

7.7.5. In order to increase the citing of authors, transliteration of sources in Russian are made in the International Heart and Vascular Disease Journal using official coding. Names of authors and journals are transliterated by means of coding, and semantic transliteration (translation) is used for the titles of articles. If a source has an original transliteration, the latter is used. The Editors will be grateful if authors provide the transliterated

variant of the list of references. You can use online services: <http://translit.ru> for making transliteration.

7.7.6. Authors are responsible for the accuracy of information provided in the list of references.

7.7.7. The list of references should conform to the format recommended by the American National Information Standards Organization (NISO), accepted by the National Library of Medicine (NLM) for its databases (Library's MEDLINE/Pub Med database) and updated in 2009. Authors should use the official site of the NLM: <http://www.nlm.nih.gov/citingmedicine> to find recommended formats for the various types of references. Examples of references provided in accordance with the NLM recommendations are given below:

Periodicals

Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001; 285(18):2370-5.

Sources in Russian with transliteration:

Baevskiy RM, Ivanov GG, Chireykin LV, et al. Analiz variabel'nosti serdechnogo ritma pri ispol'zovanii razlichnyh jelektrokardiograficheskikh sistem (metodicheskie rekomendacii) [Analysis of heart rate variability using different ECG systems (guidelines)]. *Vestnik aritmologii*. 2002;24:65-86. Russian.

Please provide initials after the last names of authors. Last names of foreign authors are given in the original transcription. Names of periodicals can be abbreviated. Usually such abbreviations are accepted by the Editors of those periodicals. These can be found on the Publisher's site or in the list of abbreviations of Index Medicus.

Punctuation in the list of references should be considered. A comma should not be put between the name of the journal and the year of its release. After the year of release a semicolon is put without a space, then a colon follows the volume number, and finally page numbers are given. There are no indications like "volume", "№", «pages». Russian periodicals often have no indication of volume or numbering of pages within a year. In this case the number of an issue should be specified in brackets.

If the total number of authors exceeds four people, please provide the names of the first three authors and put "et al." afterwards. If there are not more than 4 authors, the full list of authors should be provided.

Chapters in a book

Swanton RH, Banerjee S. Cardiac Failure. In: Swanton RH, Banerjee S., editors. *Swanton's Cardiology: A concise guide to clinical practice*. 6th ed. Oxford: Blackwell Publishing; 2008. p. 255-309.

Sources in Russian with transliteration:

Belenkov YuN. Kardiomiopatii [Cardiomyopathies]. In: Chazov EI, Belenkov YuN., editors. *Racional'naja farmakoterapija serdechno-sosudistykh zabolevanij: Rukovodstvo dlja praktikujushhih vrachej* [Rationale for drug therapy of cardiovascular diseases: A guide for medical practitioners]. Moscow: Litterra; 2006. p. 431-452. Russian.

Reference to a book chapter should be arranged in the following order: authors of the corresponding chapter; name of the chapter; «In:»; editors (title authors) of the book; name of the book; number of issue, publisher; city of publishing; year of publishing; pages of the corresponding chapter. Punctuation should be considered. There are no quotation marks.

Books

Sources in Russian with transliteration:

Shlyakhto EV, Konradi AO, Tsyrlin VA. Vegetativnaja nervnaja sistema i arterial'naja gipertenzija [The autonomic nervous system and hypertension]. St. Petersburg (Russia): Meditsinskoe izdatelstvo; 2008. Russian.

Websites

Websites should be provided in the list of references, but not in the text. References to websites should be made only when original text is not available. References should be provided in the following way:

WHO. Severe Acute Respiratory Syndrome (SARS) [Internet]. [place unknown: publisher unknown]; [updated 2010 June 1; cited 2010 June 10]. Available from: <http://www.who.int/csr/sars/>.

7.8. Diagrams, charts, and drawings

7.8.1. Diagrams, charts, and drawings should be submitted electronically in the following formats: «MS Excel», «Adobe Illustrator», «Corel Draw» or «MS PowerPoint». Diagrams, charts, and drawings must be allocated on separate pages, numbered in order of citation, and have names and notes if necessary. They must not repeat the content of tables. Please indicate the names and units of measurement for graph axes. Provide the legend for each graph (denote lines and filling). If

you compare diagrams, provide significance of differences. Do not use 3-D models for histograms. If appropriate, please identify places in the text where you wish graphics, drawings and graphs to be inserted.

7.8.2. Photographs must be submitted electronically with a minimum resolution of 300 dots per inch (dpi). Microphotos must be cropped so that only main content is left. Arrows should be used to show main features. All symbols, arrows and legends on gray-scale illustrations should be in contrast with the background.

7.8.3. Size of legends on images and photos should be big enough to be legible after compression for publication. The optimal size is 12 points.

7.8.4. All abbreviations should be defined either after the first citation in a legend, or in alphabetic order at the end of each legend. All symbols (arrows, circles, etc.) must be explained.

7.8.5. If data was published earlier, it is desirable to provide written permission from the publisher for the use of this data.

7.9. Tables

7.9.1. Tables should be typed with double spacing, have numbers in order of citation in the text, and names. Tables should be compact and demonstrative. Names of columns and rows must reflect the content. Data presented in tables should not be repeated in the text or images. Please clearly specify units of measurement of variables and form of data presentation ($M \pm m$; $M \pm SD$; Me ; Mo ; percentiles etc.). All figures, sums and percentages must be thoroughly checked and correspond to those in the text. Explanatory footnotes should be provided below the table if necessary.

7.9.2. Abbreviations should be listed in a footnote under the table in alphabetic order. Symbols of footnotes should be given in the following order: *, †, ‡, §, ||, ¶, #, **, † † etc.

7.9.3. If a table(s) was published earlier, it is desirable to provide written permission from the publisher for use of this table(s).

8. Rules for the Review of Manuscripts

8.1. Reviewing of articles is carried out by members of the editorial board as well as invited reviewers - leading experts in the relevant field of medicine in Russia and other countries. The decision on the choice of a reviewer for the examination of the article is made by the editor-in-chief, deputy editor-in-chief,

scientific editor, editorial director. The review period is 4 weeks, but at the request of the reviewer it can be extended.

8.2. Each reviewer has the right to refuse to review if there is a clear conflict of interest, reflecting on the perception and interpretation of the manuscript materials. Based on the results of the review of the manuscript, the reviewer gives recommendations on the future of the article (each decision of the reviewer is justified):

- The article is recommended for publication in this form;
- The article is recommended for publication after correcting the deficiencies noted by the reviewer;
- The article needs additional review by another specialist;
- The article can not be published in the journal.

8.3. If the review contains recommendations for correcting and finalizing the article, the editorial board of the journal sends the author a text of the review with a proposal to take them into account when preparing a new version of the article, or to argue them (partially or completely) with arguments. The finalization of the article should not take more than 2 months from the moment of sending an electronic message to the authors about the need to make changes. The article refined by the author is sent again for review.

8.4. In the event of the authors' refusal to modify the materials, they must, in writing or verbally, notify the editorial office of their refusal to publish the article. If the authors do not return the revised version after 3 months from the date of sending the review, even if there is no information from the authors refusing to modify the article, the editorial board removes it from the register. In such situations, the authors are notified of the removal of the manuscript from the registration in connection with the expiration of the time allotted for revision.

8.5. If the author and reviewers have unresolved contradictions regarding the manuscript, the editorial board is entitled to send the manuscript for additional review. In conflict situations, the decision is made by the editor-in-chief at a meeting of the editorial board.

8.6. The decision to refuse publication of the manuscript is taken at a meeting of the editorial board in accordance with the recommendations of reviewers. An article not recommended by a decision of the editorial board for publication is not accepted for reconsideration. The notice of refusal of publication is sent to the author by e-mail.

8.7. After the editorial board accepts the decision to admit the article for publication, the editorial office informs the author about it and specifies the terms of publication.

8.8. The presence of a positive review is not a sufficient basis for the publication of the article. The fi-

nal decision on publication is made by the editorial board. In conflict situations, the decision is made by the editor-in-chief.

8.9. The original of the reviews is kept in the editorial office of the journal for 3 years.

FOUNDATION FOR THE ADVANCEMENT OF CARDIOLOGY

“CARDIOPROGRESS”

knowledge, observation, action



The main functions of the Cardioprogress Foundation are:

- Research
- Education
- Science
- Publishing
- International collaboration
- Advertising and information

Official website: www.cardioproggress.ru

Tel: 007 965 236 1600

Email: inf.cardio@gmail.com

Moscow, Russia