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

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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 angiopulmonary 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, undoubtfully, 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)

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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 actively 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); 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 (phase II). 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.

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

Table 1. Summary of cohort population in 6 centers

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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: $\chi^2$, 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.
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 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,
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-
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, 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 (%)

<table>
<thead>
<tr>
<th>Cities</th>
<th>Men, n</th>
<th>Women, n</th>
<th>High risk</th>
<th>Very high risk</th>
<th>High risk</th>
<th>Very high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baku</td>
<td>21</td>
<td>8</td>
<td>8</td>
<td>41</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Ganja</td>
<td>30*</td>
<td>16</td>
<td>16</td>
<td>56</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Sheki</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>18</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Lenkoran</td>
<td>16</td>
<td>12</td>
<td>12</td>
<td>14</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Derbent</td>
<td>7**</td>
<td>3*</td>
<td>15*</td>
<td>12*</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Marneuli</td>
<td>28*</td>
<td>13</td>
<td>31*</td>
<td>29*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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 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)

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

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

* p <0.05 — significance of differences between 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
Efficacy of a Cardiovascular Behavioral Intervention Program and Full Body CT Scanning on Changes in Coronary Artery Calcium, Thoracic and Epicardial Fat

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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 RENEW™ lifestyle intervention program or standard of care. The RENEW™ 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-

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Efficacy of a Cardiovascular Behavioral Intervention Program and Full Body CT...  

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 subclinical 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 performance), 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 cm$^3$) 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>
<thead>
<tr>
<th>Variable</th>
<th>Included (n=73)</th>
<th>Not Included (n=194)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>46.6±6.5</td>
<td>45.3±6.6</td>
<td>0.1654</td>
</tr>
<tr>
<td>Female Gender (%)</td>
<td>17 (23.3)</td>
<td>48 (24.9)</td>
<td>0.7558</td>
</tr>
<tr>
<td>Prior CHD (%)</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>0.5245</td>
</tr>
<tr>
<td>Prior Diabetes (%)</td>
<td>3 (4.1)</td>
<td>10 (5.2)</td>
<td>0.6427</td>
</tr>
<tr>
<td>Cholesterol Lowering Therapy (%)</td>
<td>13 (17.8)</td>
<td>19 (9.8)</td>
<td>0.1115</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>178.8±30.7</td>
<td>188.5±36.8</td>
<td>0.0524</td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dL)</td>
<td>44.2±12.8</td>
<td>50.7±16.7</td>
<td>0.0015</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>88.5±16.6</td>
<td>90.9±21.1</td>
<td>0.3442</td>
</tr>
<tr>
<td>Waist (inches)</td>
<td>39.0±5.7</td>
<td>37.9±4.9</td>
<td>0.1090</td>
</tr>
<tr>
<td>Weight (lbs)</td>
<td>201.7±38.1</td>
<td>194.3±36.4</td>
<td>0.1530</td>
</tr>
<tr>
<td>Pulse (Beats/Sec)</td>
<td>61.3±11.5</td>
<td>63.9±10.3</td>
<td>0.0852</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>78.2±9.0</td>
<td>80.0±12.5</td>
<td>0.2087</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>117.7±12.3</td>
<td>118.6±11.2</td>
<td>0.6031</td>
</tr>
<tr>
<td>CAC Present (score&gt;0) (n,%)</td>
<td>31 (42.5)</td>
<td>52 (26.8)</td>
<td>0.0115</td>
</tr>
<tr>
<td>CAC Volume</td>
<td>41.6±9.15</td>
<td>27.1±104.1</td>
<td>0.2963</td>
</tr>
<tr>
<td>Natural Log Transformed CAC Volume¹</td>
<td>1.7±2.1</td>
<td>1.0±1.8</td>
<td>0.0048</td>
</tr>
<tr>
<td>CAC Score</td>
<td>39.9±99.8</td>
<td>25.7±109.7</td>
<td>0.3362</td>
</tr>
<tr>
<td>Natural Log Transformed CAC Score²</td>
<td>1.5±2.0</td>
<td>0.8±1.7</td>
<td>0.0145</td>
</tr>
</tbody>
</table>

¹Two Sided Fisher’s Exact Test. ²Natural 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
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

### Table 2. Baseline Characteristics by Groups

<table>
<thead>
<tr>
<th></th>
<th>Intervention n=38</th>
<th>Control n=35</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender [Female %]</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Gender [Female %]</td>
<td>12</td>
<td>31.6</td>
<td>5</td>
</tr>
<tr>
<td>Prior Diabetes¹</td>
<td>1</td>
<td>2.6</td>
<td>2</td>
</tr>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>47.4</td>
<td>6.7</td>
<td>45.8</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>179.2</td>
<td>25.8</td>
<td>178.3</td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dL)</td>
<td>45.1</td>
<td>11.4</td>
<td>43.2</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>140.9</td>
<td>79.7</td>
<td>131.4</td>
</tr>
<tr>
<td>LDL Cholesterol (mg/dL)</td>
<td>108.5</td>
<td>28.9</td>
<td>111.0</td>
</tr>
<tr>
<td>Non-HDL Cholesterol (mg/dL)</td>
<td>131.0</td>
<td>34.6</td>
<td>129.4</td>
</tr>
<tr>
<td>Total Cholesterol/HDL</td>
<td>4.2</td>
<td>1.2</td>
<td>4.4</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>88.5</td>
<td>17.5</td>
<td>88.5</td>
</tr>
<tr>
<td>Waist (inches)</td>
<td>38.3</td>
<td>5.8</td>
<td>39.8</td>
</tr>
<tr>
<td>Weight [lbs]</td>
<td>195.3</td>
<td>36.0</td>
<td>208.7</td>
</tr>
<tr>
<td>Pulse [Beats/Sec]</td>
<td>62.3</td>
<td>10.7</td>
<td>60.3</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>77.3</td>
<td>7.8</td>
<td>79.2</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>117.2</td>
<td>13.6</td>
<td>118.3</td>
</tr>
<tr>
<td>CAC Volume</td>
<td>28.7</td>
<td>61.2</td>
<td>55.6</td>
</tr>
<tr>
<td>Natural Log Transformed CAC Volume²</td>
<td>1.4</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Coronary Calcium Score</td>
<td>25.2</td>
<td>65.1</td>
<td>55.9</td>
</tr>
<tr>
<td>Natural Log Transformed CAC Score²</td>
<td>1.2</td>
<td>1.9</td>
<td>1.8</td>
</tr>
</tbody>
</table>

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

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.
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 cm$^3$ vs. 122.5 cm$^3$ for epicardial fat and 183.3 cm$^3$ vs. 214.9 cm$^3$ 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 cm$^3$ lower (p=0.0807) and thoracic fat volume 34.5 cm$^3$ 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

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

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

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.

**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.
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 hardness (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 ENRICHD 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 4. Difference of Epicardial and Thoracic Fat Change Between Control and Intervention Groups

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Control (n=19)</th>
<th>Intervention (n=23)</th>
<th>Parameter (Slope)</th>
<th>p-value</th>
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<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epicardial Volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>122.5 (53.1–191.9)</td>
<td>107.8 (–1.2–214.4)</td>
<td>–14.7</td>
<td>0.32</td>
</tr>
<tr>
<td>Adjusted</td>
<td>111.7 (92.2–131.2)</td>
<td>111.4 (95.3–127.6)</td>
<td>–0.4</td>
<td>0.98</td>
</tr>
<tr>
<td>Thoracic Fat Volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>214.9 (–74.2–355.6)</td>
<td>183.3 (–20.0–386.4)</td>
<td>–31.6</td>
<td>0.27</td>
</tr>
<tr>
<td>Adjusted</td>
<td>190.8 (151.2–230.4)</td>
<td>194.6 (164.0–229.3)</td>
<td>5.8</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Changes from baseline to follow-up</strong></td>
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<td></td>
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</tr>
<tr>
<td>Epicardial Volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>12.1 (–43.0–67.2)</td>
<td>–5.6 (–53.6–42.4)</td>
<td>–17.7</td>
<td>0.035</td>
</tr>
<tr>
<td>Adjusted</td>
<td>10.6 (–4.5–25.2)</td>
<td>–6.9 (–19.2–5.3)</td>
<td>–17.5</td>
<td>0.081</td>
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<td>Thoracic Fat Volume</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>–4.5 (–109.6–100.6)</td>
<td>–23.0 (–123.0–77.0)</td>
<td>–18.5</td>
<td>0.26</td>
</tr>
<tr>
<td>Adjusted</td>
<td>4.6 (–20.2–28.6)</td>
<td>–29.9 (–49.5–9.3)</td>
<td>–34.5</td>
<td>0.044</td>
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</tbody>
</table>

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.
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.

<table>
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<td>(p=0.97)</td>
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</table>

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.

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

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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

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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 no 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 segmental 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).
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 hypokinesis, 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 death.

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); moderately 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
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 S, Q, I phenomenon [deep waves S, and Q], 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 SIQIII 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 patients 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 S, Q, I 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).

Table 2. Prevalence of ECG criteria in PE patients

<table>
<thead>
<tr>
<th>Groups of patients</th>
<th>ECG characteristic</th>
<th>S, Q, I, %</th>
<th>Negative, T in V1-V3, leads, %</th>
<th>RBBB, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>The risk of PE-associated death according to the ESC criteria (2014)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk n=31</td>
<td></td>
<td>61.3</td>
<td>48</td>
<td>19.4</td>
</tr>
<tr>
<td>Moderately high n=37</td>
<td></td>
<td>54.1</td>
<td>45.9</td>
<td>24.3</td>
</tr>
<tr>
<td>Moderately low risk n=52</td>
<td></td>
<td>46.2</td>
<td>48.1</td>
<td>31.5</td>
</tr>
<tr>
<td>Low risk n=251</td>
<td></td>
<td>3.2</td>
<td>23.9</td>
<td>21.9</td>
</tr>
<tr>
<td>Considering total absence of circulation in segmental arteries</td>
<td></td>
<td>46.9</td>
<td>48.3</td>
<td>27.3</td>
</tr>
<tr>
<td>Massive n=143</td>
<td></td>
<td>4.4</td>
<td>21.9</td>
<td>22.9</td>
</tr>
<tr>
<td>Non-massive n=228</td>
<td></td>
<td>0.14</td>
<td>0.98</td>
<td>0.33</td>
</tr>
<tr>
<td>p1</td>
<td></td>
<td>0.11</td>
<td>0.8</td>
<td>0.71</td>
</tr>
<tr>
<td>p2</td>
<td></td>
<td>0.93</td>
<td>0.98</td>
<td>0.58</td>
</tr>
<tr>
<td>p3</td>
<td></td>
<td>0.49</td>
<td>0.6</td>
<td>0.79</td>
</tr>
<tr>
<td>p4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comment: 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.
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 average 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 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.

Figure 3. Distribution of symptoms in PE patients with high, moderately high, and moderately low risk of death and massive PE.
culation in less than 10 segmental arteries) lesions of pulmonary arterial tree: 3857.4±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, collapsoid 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


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

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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.

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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, cytokines, 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 Frivald 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 registered 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.
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 prothrombotic cytokines, such as, tumor necrosis factor (TNFα), 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 TNFα, 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
Relationship between the degree of epicardial fat volume and severity of coronary atherosclerosis

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 ≥ 6 mm 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

<table>
<thead>
<tr>
<th>Predictors</th>
<th>OR</th>
<th>95%CI</th>
<th>χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>6.52</td>
<td>2.61–15.9</td>
<td>10.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>tEAT</td>
<td>4.41</td>
<td>2.02–9.43</td>
<td>22.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leptin</td>
<td>3.50</td>
<td>1.46–8.37</td>
<td>11.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resistin</td>
<td>3.13</td>
<td>1.32–7.42</td>
<td>10.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WC</td>
<td>1.72</td>
<td>0.76–3.74</td>
<td>5.63</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

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.

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.

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**

Treatment of Hypertension

Wilbert S. Aronow*

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 ≥ 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 ≥ 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,
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 >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 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–neprolysin 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]. Chlorothalidone was better than lisinopril, amloidope, and doxazosin in reducing cardiovascular disease and renal outcomes in nondiabetics 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 methylodopa, 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 naive 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].

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

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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-DAYE, 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.

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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 form 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-DAY, STOP PAD, TREAT, TRIUMPH, in registers and in practical studies ARTEMIS, GWTG-HF, POICE, sub-analyses of recently presented large projects CANTOS, CANVAS, COMPASS, CVD-REAL 2, FOURIER.

The patients who underwent the myocardial 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 underwent 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 x 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 PHARMCLIO 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 receive 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 0.70; 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 undergone myocardial infarction, with LV EF ≤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 manifestations 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**


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
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(version 2017)

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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.


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

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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).

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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.

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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.

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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).

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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.).

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

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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.

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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**

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

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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.

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

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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±m; M±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.

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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):

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- 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.

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