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Prevalence of ideal cardiovascular health in an adult Finnish population: the national FINRISK 2007 study

Atherosclerosis across 4000 years of human history: the HORUS study of four ancient populations

Report on the III International Forum of Cardiology and Internal Medicine, 24–26 March 2014, Moscow

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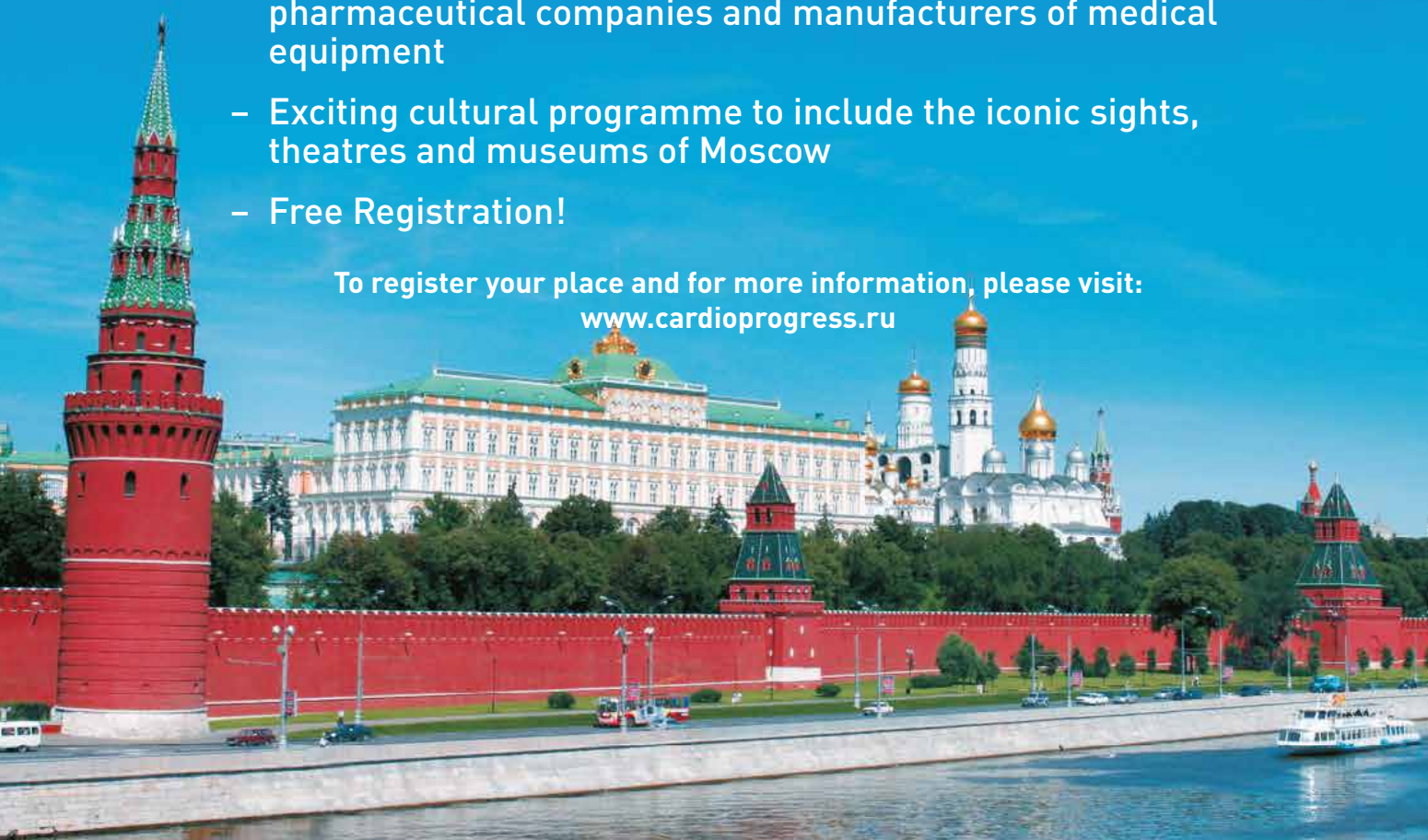

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Editor's Welcome

Dear Colleagues,

I am pleased to say that the popularity of our Journal is growing, with an increase in the number of articles submitted from a broad geography.

Published in this issue are articles that reflect the complexity of problems we face. These include:

– Reduction of muscle symptoms in statin therapy by means of CoQ10

– Capabilities of computed tomography angiography in evaluating coronary bypass grafts

– Decrease in arterial stiffness by means of drug therapy in patients with hypertension and obesity

– Expediency of Factor Five Leiden screening to assess the risk of venous thromboembolism

– Study of mummified bodies by computed tomography to detect signs of atherosclerosis in ancient populations

– Estimation of the prevalence of ideal cardiovascular health among a Finnish population

A report from the III International Forum of Cardiology and Internal Medicine, held in Moscow between 24–26 March 2014, is presented in a separate article prepared by the Forum organizers.

We hope that the content of this third issue is interesting to our readers and we welcome your comments, suggestions, and articles.

Yours sincerely,
Rafael G. Oganov
President, Cardioprogress Foundation
Editor-in-Chief

International Heart
and Vascular Disease Journal • Volume 2, Number 3, June 2014
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LEADING ARTICLE

Prevalence of ideal cardiovascular health in an adult Finnish population: the national FINRISK 2007 study

Peltonen M.*, Laatikainen T., Borodulin K., Wikström K., Jousilahti P., Jula A., Männistö S., Salomaa V., Vartiainen E., Puska P.

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Summary

Aim

Despite major reductions in cardiovascular disease (CVD) mortality rates during the past decades in Finland, the risk factor pattern of the population leaves much room for improvement. The aim of this study was to assess the prevalence of ideal cardiovascular (CV) health in Finnish men and women aged 25–74 years.

Material and methods

Cross-sectional population-based health examination survey was conducted in 2007 in Finland. Age and sex stratified random sample was drawn from the national population register. The total number of individuals in the analyses was 2,128 men and 2,613 women. Ideal CV health metrics were defined according to the recent guidelines of

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the American Heart Association (AHA), considering behavioural factors (smoking, physical activity, diet, obesity), biological and physiological risk factors (blood pressure, total cholesterol, blood glucose).

Results

The prevalence of ideal CV health was the lowest for the physical activity, diet and blood pressure among the total of seven factors considered. Taken together, the prevalence of having 5 or more health metrics as ideal out of the 7 was just 8.8 % (95% CI: 7.7–10.0) in women and 3.0 % (95% CI: 2.3–3.8) in men. In contrast, the proportions of men and women with less than 3 of the metrics as ideal were 50.4 % (95% CI: 48.5–52.3) in women and 69.0 % (95% CI: 67.0–71.9) in men. Age was negatively associated with the number of ideal CV health factors.

Conclusion

The prevalence of ideal CVD related health behaviour and health factors is low in the Finnish adult population.

Keywords

Cardiovascular health, risk factors, health behaviour, health survey, Finland

Introduction

CVD is the leading cause of death in Finland and globally. In many Western countries the age specific rates are declining, but the disease rates are increasing in most developing countries [1]. The main traditional risk factors for CVD are hypertension, hypercholesterolemia and smoking [2]. Levels of blood pressure and total cholesterol can be modified by health behaviour including diet and physical activity [2–4].

In Finland, a marked decrease in CVD mortality has been observed since late 1960s. In working-aged men, the coronary heart disease (CHD) rates have declined by 80% [5]. This decrease has been parallel with a decrease in smoking prevalence and decline in blood pressure and total cholesterol levels [5]. Majority of the decline in CHD mortality can be explained by changes in risk factors, and a smaller part is explained by advancements in treatment and care [5].

Despite the favourable trend in both CVD mortality and risk factors, there is still much room for improvement in CV health in Finland. The prevalence of smoking in Finland is 19% in men and 13% in women in the age group of 15–64 years [6], and the average levels of serum total cholesterol are above the current recommendations [5]. In international comparison, blood pressure levels are still relatively high in Finland [7].

Recently, the *AHA* developed a set of 7 metrics to measure ideal CV health [8]. The proposed concept of ideal CV health puts more focus on health behaviours and risk factors leading to morbidity and mortality, instead of the disease itself. These measurable metrics will be used to monitor the *AHA*'s Strategic Impact Goal 2020, which aims to improve CV health and reduce deaths from CVD and stroke.

The aim of this study was to assess the prevalence of ideal CV health in a population-based study of adults in Finland.

Material and methods

A cross-sectional population-based survey, the National FINRISK Study, was carried out in 2007 in Finland among men and women aged 25–74 years to monitor national risk factor levels. The study was conducted in five geographical areas: the cities of Helsinki and Vantaa (the metropolitan area), the areas of Turku and Loimaa, and the provinces of Northern Savo, North Karelia, and Oulu. A random sample of people aged 25–74 years was drawn from the national population register stratified so that in each geographical area, 200 people of each sex and 10-year age group were chosen. The total sample size was thus 10,000 people, and the eligible study sample was 9,957 people after exclusion of those who died or moved out of the geographical area between the time of the sample selection and scheduled health examination date.

The overall participation rate in the study was 68% (N=6,733). Of these, 475 individuals who filled in the questionnaire but did not participate in the health examination of the study were excluded. The study sample was further restricted to those who participated in a substudy with fasting glucose measurement (N=5,024). In addition, 283 individuals with a history of CVD already at the time of the health examination were excluded. Thus, the analyses were done with data on 2,128 men and 2,613 women.

The survey was conducted according to the standardized protocol based on the *World Health Organisation* Multinational Monitoring of trends and determinants in CVD (WHO MONICA) Project protocol [9] and the later recommendations by the European Health Risk Monitoring Project [10]. The study protocol was approved by the Ethics Committee of the *Hospital District of Helsinki and Uusimaa*. All participants gave their written informed consent.

Study teams in each of the geographical regions, with five trained nurses in each, carried out the survey. The nurses were specially trained in survey methodology. Survey included a self-administered questionnaire and a health examination, where anthropometric measurements, blood pressure measurements and blood sampling were carried out. The questionnaire, together with the invitation letter to the health examination, was sent by mail to all the selected individuals. Physical measurements and blood sampling were carried out in local health centres or other study sites by specially trained nurses. Laboratory measurements were carried out centrally at the Disease Risk Unit at the *National Institute for Health and Welfare*, Helsinki. The testing laboratory of the Disease Risk Unit (No. T077) is accredited by the *Finnish Accreditation Service*, FINAS, and it fulfils the requirements of the standard SFS-EN ISO/IEC 17025:2005.

Ideal CV health was defined according to the recent guidelines of the *AHA* [8]. A set of 7 metrics to measure ideal CV health was developed, including health behavioural factors (smoking, physical activity, diet, obesity) and risk factors (blood pressure, total cholesterol, blood glucose). For physical activity and diet, adaptations to the original definition were made due to the lack of suitable data.

Blood pressure measurement

The nurses measuring blood pressure were circulated between the study areas to eliminate the possible observer bias in the between-areas comparisons. A standard mercury sphygmomanometer with a cuff bladder 14 cm wide and 40 cm long was used. The fifth phase of the Korotkoff sound was used as the diastolic blood pressure and the values were recorded to the nearest even numbers**.** Blood pressure was measured three times and the mean of the last two measurements was used in the present analyses.

Participants with systolic blood pressure <120 mmHg and diastolic blood pressure <80 mmHg without blood pressure lowering medication were categorized as having ideal CV health metric. Those participants with systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 were categorized as having poor CV health. All other participants were categorized in the intermediate category.

Blood sampling

Fasting venous blood samples were drawn from each participant to measure serum total cholesterol by an enzymatic method (Abbott Diagnostics Europe, Wiesbaden, Germany) using Abbott Architect c8000 clinical chemistry analyser. Cholesterol levels <5.18 mmol/l were defined as ideal cholesterol metric; ≥5.18 mmol/l up to 6.18 mmol/l as intermediate; and 6.19 mmol/l or more as poor.

Plasma glucose was determined with a hexokinase method (Abbott Laboratories, Abbott Park, IL). Plasma glucose levels <5.6 mmol/l without glucose lowering medication were defined as ideal; ≥5.6 mmol/l up to 7.0 mmol/l or <5.6 mmol/l with glucose lowering medication as intermediate; and ≥7.0 mmol/l as poor regarding CV health.

Obesity

Weight and height were measured with participants wearing light clothing and no shoes. Height was measured to the nearest 0.1cm, and weight to the nearest 100 grams. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2).

BMI <25 kg/m^2 was defined as ideal; 25–29.9 kg/m^2 as intermediate; and 30 kg/m^2 or more as poor metric for CV health.

Physical activity

Physical activity was assessed in leisure time and during commuting using short self-administered questionnaires. Leisure time physical activity was divided into four categories, reflecting weekly amount and intensity of physical activity. The categories do not follow the current recommendations of physical activity for health, but are able to separate the inactive persons from moderately and vigorously active persons. The two-way commuting trip was assessed in minutes spent walking, biking or otherwise exercising and was further dichotomized into low-commuting physical activity (0–29 min daily) and high-commuting physical activity (more than 30 min daily).

Based on data on both leisure time and commuting physical activity, an index was derived so that those who were physically active both at leisure-time and commuting were classified as having ideal; those who were not active either at leisure-time or commuting were classified as having poor; and all others

(i.e. those being active either at leisure-time or commuting, but not both) were classified as having intermediate physical activity level regarding CV health.

Diet

Information on diet was collected with a self-administered food-frequency questionnaire. Four components were used to define healthy diet: eating either fruits or vegetables daily, eating fish two times or more per week, drinking low fat milk, and using vegetable oils in cooking at home.

From these data, a dietary index was derived so that those having healthy consumption of all the four components (fruits and vegetables, fish, milk and fat used for cooking) were classified as having ideal diet regarding CV health. Those who did not fulfil the healthy criteria for any of these diet components were defined as having poor diet. All the others (i.e. those fulfilling at least one but not all criteria) were defined as having an intermediate diet.

Smoking

Smoking was assessed by structured questions in the self-administered questionnaire. Based on their responses, the participants were classified into three categories: never smokers (ideal); ex-smokers (intermediate); and smokers (poor).

Statistical analyses

Mean values, standard deviations, and percentages were used to describe the characteristics of the study population. Prevalences of individual health metrics were calculated separately for men and women. Total number of ideal CV health factors was estimated by sex and age. Differences between groups were evaluated with t-tests for continuous variables and chi-squared and logistic regression models for dichotomous variables. All *P*-values are two-sided, and *P*-values less than 0.05 were considered statistically significant. The Stata statistical package, version 12.1, was used.

Results

Characteristics of the study population are shown in Table 1. The mean age was 52 years (range 25–74) and mean BMI 27 kg/m^2. Men had higher blood pressure, triglycerides and glucose levels, and lower high density lipoprotein (HDL) cholesterol levels as compared to women.

All the individual health metrics except physical activity indicated lower CV health in men as compared to women (Table 2). One third of the participants had poor physical activity level, whereas just 15% were classified as having physical activity metric as ideal. Most of the participants achieved intermediate level for the metric on diet. In women, 66% were never-smokers as compared to 46% in men. More than 20% of both men and women were classified as obese (BMI ⩾30 kg/m^2) and therefore as having poor health in this metric.

For the CV risk factors, 32% of men and 45% of women were categorized as having poor health metric based on their blood pressure levels (Table 2). Total cholesterol levels were defined as ideal in 48% of women and 46% of men. Glucose levels were more favourable in women compared to men.

Taken together the 7 individual health metrics, the distribution of number of ideal CV health factors is shown in Figure 1. The prevalence of having 5 or more health factors as ideal out of the 7 was just 8.8% (95% CI: 7.7–10.0) in women and 3.0% (95% CI: 2.3–3.8) in men. In contrast, the proportions of men and women with less than 3 of the metrics as ideal were 50.4% (95% CI: 48.5–52.3) in women and 69.0% (95% CI: 67.0–71.9) in men.

Table 1. **Characteristics of the study population**

	Women		Men		
	mean	**SD**	**mean**	**SD**	***P*-value**
N	2,613		2,128		
Age, years	51.5	13.6	52.4	13.3	0.019
Body weight, kg	71.3	14.2	84.5	13.8	<0.001
Body mass index, kg/m^2	26.9	5.4	27.3	4.0	0.011
Systolic blood pressure, mmHg	131.2	20.3	136.4	18.3	<0.001
Diastolic blood pressure, mmHg	77.0	10.4	81.5	11.4	<0.001
Total serum cholesterol, mmol/l	5.31	0.98	5.30	0.99	0.636
HDL cholesterol, mmol/l	1.57	0.37	1.31	0.33	<0.001
Triglycerides, mmol/l	1.25	0.78	1.61	1.02	<0.001
Fasting plasma glucose, mmol/l	5.73	0.78	6.13	1.09	<0.001

Table 2. **Individual metrics for ideal cardiovascular health**

		Women	Men	*P*-value
		Prevalence, %	Prevalence, %	
Health behavior:				
Smoking	Ideal*	66.3	45.9	<0.001
	Intermediate	19.1	32.7	
	Poor	14.6	21.4	
Physical activity	Ideal	13.8	15.5	0.276
	Intermediate	48.8	48.1	
	Poor	37.4	36.4	
Diet	Ideal	12.6	24.1	<0.001
	Intermediate	73.5	65.3	
	Poor	13.9	10.6	
Body mass index	Ideal	42.3	29.0	<0.001
	Intermediate	34.1	50.4	
	Poor	23.5	20.6	
Health factor:				
Total cholesterol	Ideal	47.5	45.9	0.049
	Intermediate	33.5	36.7	
	Poor	19.0	17.4	
Blood pressure	Ideal	26.7	12.2	<0.001
	Intermediate	41.2	42.4	
	Poor	32.2	45.4	
Glucose	Ideal	50.2	24.8	<0.001
	Intermediate	46.3	66.2	
	Poor	3.5	9.1	

* For definitions of ideal, intermediate and poor health metrics, see Methods.

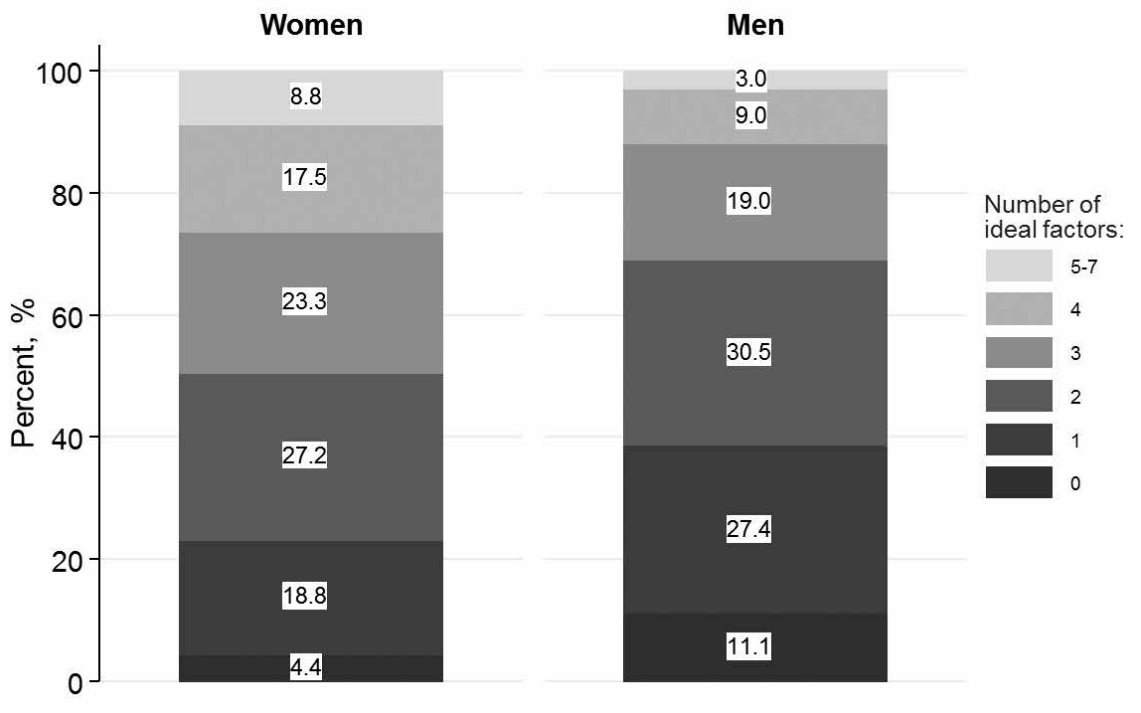

Figure 1. Distribution of the number of ideal cardiovascular health factors by sex

As expected, age was inversely associated with the number of ideal CV health metrics (Figure 2). Still, already in the youngest age group 25–34 years, the proportions with 5 or more ideal metrics were as low as 23.9% (95% CI: 19.6–28.5) in women and 8.6% (95% CI: 5.5–12.8) in men.

Discussion

This study shows that the prevalence of ideal CV health is very low among adult men and women in Finland. The results demonstrate that in spite of major progress in Finland during the past decades, there is still considerable room for improvement and potential for reducing CVD burden at population level. It is noteworthy that the prevalence of ideal CV health is low already in the younger age groups. Low prevalence of ideal CV health has been observed also in other countries. Based on the *AHA* definition of ideal CV health, the prevalence was found to be extremely low in a community-based study of middle-aged individuals in the United States [11]. In Canada, based on the so called CANHEART health index, less than 10% of Canadian

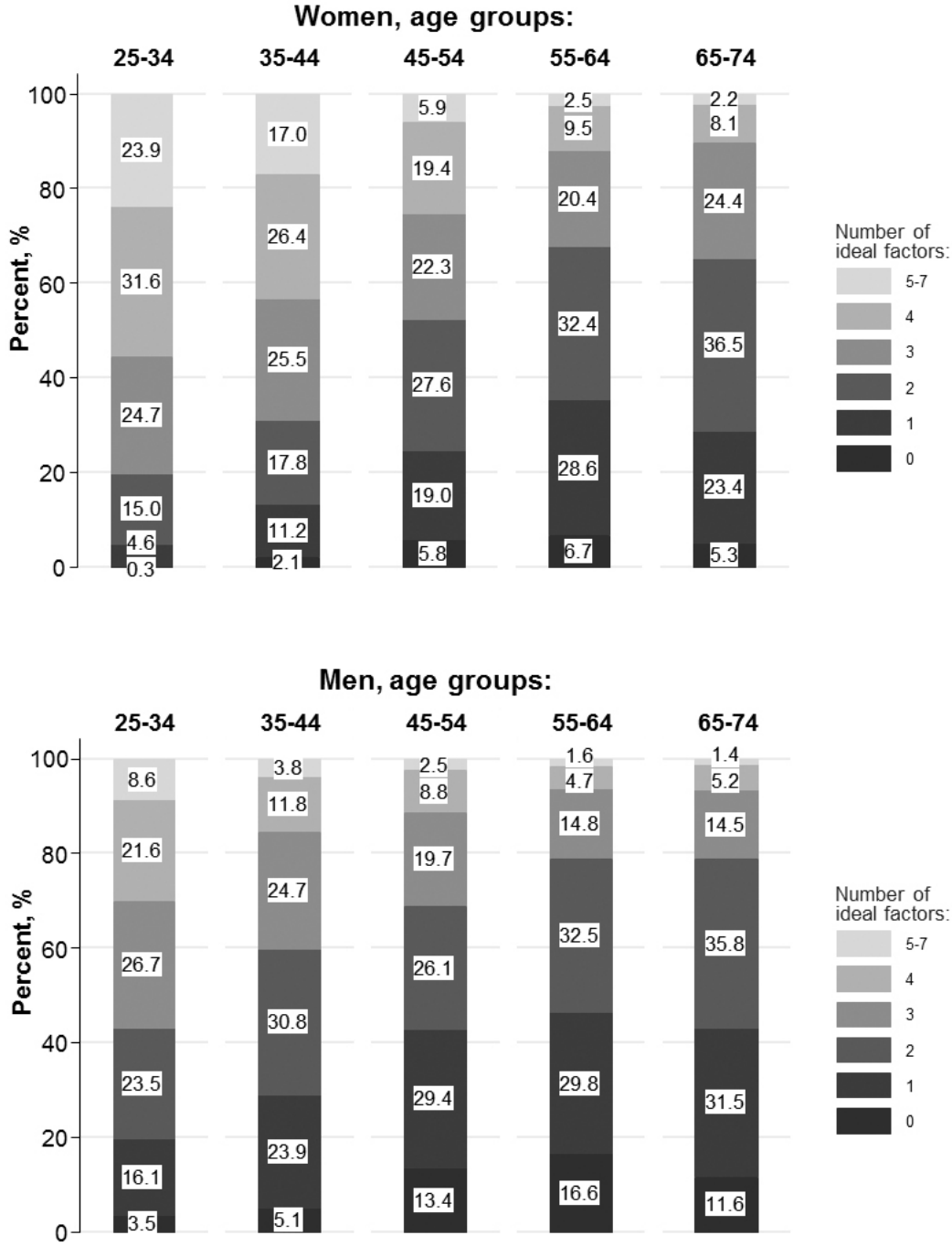

Figure 2. Distribution of the number of ideal cardiovascular health factors by sex and age

adults were in ideal CV health [12]. These results are in good agreement with results from our study.

Ideal CV health is an instrument to assess the needs and potential for CVD prevention and CV health promotion in the population. It can also be used as a tool to monitor progress at the population level. Although this instrument is primarily a tool for CV health, the risk factors, especially the behavioural ones, are also strongly related to many other non-communicable diseases (NCDs). Thus, this instrument suits well for a more general monitoring of progress in NCD prevention and promotion of public health. The metrics in the instrument are the central targets and indicators in the new *WHO* Global Action Plan for the Non-communicable Diseases 2013–2020 [13].

The concept of ideal CV health considers both the traditional risk factors for CVD, as well as health behaviours related to these. Therefore, the instrument can be used as a motivational tool in preventive work. Further, the instrument emphasises the population risk, i.e. the public health needs, and the need to change the population levels or distributions of these factors. This calls for comprehensive interventions, including government policies, health promotion and intersectoral decisions, as described e.g. in the *WHO* Global Action Plan for the Non communicable Diseases 2013–2020 [13].

The number of ideal CV health metrics has been shown to be a strong predictor of both total and CVD specific mortality in the United States [14, 15]. A similar observation was recently reported from China [16]. Several earlier studies have utilised the concept of low risk factor profile and demonstrated its association with future onset of disease [17,18]. Thus, prospective studies using the concept of ideal CV health enable estimation of the potential for improvement in CVD burden in a population by looking at actual mortality and CVD morbidity rates.

There are some limitations, which need to be considered. Available data on physical activity and diet did not allow exactly the same definition as in the *AHA* metrics; adapted definitions, which take into account some aspects of healthy diet and physical activity, were used instead. The validity of these metrics to measure national recommendations and guidelines should be evaluated. Second, the non-participation rates in population surveys are considerable, especially in the younger age groups. It is difficult to point out exactly the effect of non-participation on our estimates of prevalence of ideal CV health. Historically, non-participation in population-based surveys in Finland has been associated with lower CV health [19]. Thus, it is possible that our estimates of ideal CV health, while indicating a very low prevalence, are still too optimistic. Third, our estimates of ideal CV health were derived from the population without a history of CVD. Therefore, taken the population as a whole, the burden of CV risk factors and behaviours is even larger as those with a history of CVD cannot be regarded as having ideal CV health.

In the present study, we have used a cross-sectional population-based study to evaluate the prevalence of ideal CV health. In the future, this metric or adapted metric could be used to monitor changes in the population by looking at changes in ideal CV health and its components (both health factors and behaviours) over time. This type of monitoring could especially be beneficial for younger age groups where disease rates and total risk are still reasonably low.

Development of validated, culturally adapted indicators to be used in the definition of ideal CV health would increase the value of this tool. This could involve inclusion of other relevant health related behaviours in the definition. Evaluation of ideal CV health in subgroups of the population, e.g. in different socioeconomic groups, could be used to identify more targeted health promotion activities.

Conclusion

Despite major reductions in CVD rates during the past decades in Finland, the risk factor pattern of the population leaves much room for improvement. Strategies to increase healthy lifestyles at population level should be developed and implemented.

Conflict of interest: None declared

References

1. WHO. Global status report on noncommunicable diseases 2010. Geneva: World Health Organization; 2011. 176 p.
2. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J. 2012 Jul;33(13):1635–1701.
3. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2013 Nov 12. [Epub ahead of print].
4. Hsu S, Ton VK, Dominique Ashen M, et al. A clinician's guide to the ABCs of cardiovascular disease prevention: the Johns

Hopkins Ciccarone Center for the Prevention of Heart Disease and American College of Cardiology Cardiosource Approach to the Million Hearts Initiative. Clin Cardiol. 2013 Jul;36(7):383–393.

5. Vartiainen E, Laatikainen T, Peltonen M, et al. Thirty-five-year trends in cardiovascular risk factors in Finland. Int J Epidemiol. Apr 2010;39(2):504–518.
6. Helldán A, Helakorpi S, Virtanen S, Uutela A. Suomalaisen aikuisväestön terveyskäyttäytyminen ja terveys, kevät 2012. Health behaviour and health among the Finnish adult population, spring 2012. Terveyden ja hyvinvoinnin laitos (THL), Raportti 15/2013. Helsinki: National Institute for Health and Welfare (THL); 2013. 193 p.
7. Wolf-Maier K, Cooper RS, Banegas JR, et al. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. JAMA. 2003 May 14;289(18):2363–2369.
8. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation. 2010 Feb 2;121(4):586–613.
9. The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. J Clin Epidemiol. 1988;41(2):105–114.
10. Tolonen H, Kuulasmaa K, Laatikainen T, Wolf H. European Health Risk Monitoring Project. Recommendation for indicators, international collaboration, protocol and manual of operations for chronic disease risk factor surveys. Helsinki (Finland): National Public Health Institute; 2002.
11. Bambs C, Kip KE, Dinga A, et al. Low prevalence of «ideal cardiovascular health» in a community-based population: the heart strategies concentrating on risk evaluation (Heart SCORE) study. Circulation. 2011 Mar 1;123(8):850–857.
12. Maclagan LC, Park J, Sanmartin C, et al. The CANHEART health index: a tool for monitoring the cardiovascular health of the Canadian population. CMAJ. 2014 Feb 18;186(3):180–187.
13. WHO. Global action plan for the prevention and control of noncommunicable diseases 2013-2020. Geneva: World Health Organization; 2013.
14. Ford ES, Greenlund KJ, Hong Y. Ideal cardiovascular health and mortality from all causes and diseases of the circulatory system among adults in the United States. Circulation. 2012 Feb 28;125(8):987–995.
15. Dong C, Rundek T, Wright CB, et al. Ideal cardiovascular health predicts lower risks of myocardial infarction, stroke, and vascular death across whites, blacks, and hispanics: the northern Manhattan study. Circulation. 2012 Jun 19;125(24):2975–2984.
16. Liu Y, Chi HJ, Cui LF, et al. The ideal cardiovascular health metrics associated inversely with mortality from all causes and from cardiovascular diseases among adults in a Northern Chinese industrial city. PLoS One. 2014 Feb 24;9(2):e89161.
17. Strandberg A, Strandberg TE, Salomaa VV, et al. A follow-up study found that cardiovascular risk in middle age predicted mortality and quality of life in old age. J Clin Epidemiol. 2004 Apr;57(4):415–421.
18. Akesson A, Weismayer C, Newby PK, Wolk A. Combined effect of low-risk dietary and lifestyle behaviors in primary prevention of myocardial infarction in women. Arch Intern Med. 2007 Oct 22;167(19):2122–2127.
19. Jousilahti P, Salomaa V, Kuulasmaa K, et al. Total and cause specific mortality among participants and non-participants of population based health surveys: a comprehensive follow up of 54 372 Finnish men and women. J Epidemiol Community Health. 2005 Apr;59(4):310–315.

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REVIEW ARTICLE

Factor Five Leiden:
the case for global screening

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Abstract
In 1994 Dr. Bertina et al. discovered Factor Five Leiden, the most common cause of the thrombophilias, occurring in 5% of the Caucasian population. Since then, hundreds of thousands of individuals have experienced venous thromboembolic events and many have died as a consequence of this mutation. Currently global screening for this mutation has not been advocated. A review of the Factor Five Leiden pathophysiology, prevalence, and impact on a variety of common conditions such as oral contraception, pregnancy, and surgery helps establish the case for global screening. In this era of patient-centric medicine, the contention is that patients deserve the right to know their Factor Five Leiden status in order to make informed decisions about not only birth control choices, but also management during high-risk circumstances. This editorial is meant to be thought provoking and hypothesis generating. Should we or should we not screen the public for this common and life-threatening disorder?

Keywords
Factor Five Leiden, thrombophilias, oral contraception, pulmonary embolism, deep vein thrombosis, venous thromboembolic disease

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«Even one preventable death from heart disease and stroke is too many», asserted Tom Frieden, MD, MPH, and Director of the *Centers for Disease Control and Prevention* in a motivational plea to prevent an estimated 200,000 deaths in people under the age of seventy-five [1]. No one would dare dispute the Director's proclamation; it would be heartless to do so. Diminishing mortality and morbidity is the prime agenda for physicians. This is the lens through which I will present a history of Factor Five Leiden and propose a simple strategy to save many thousands of lives.

Homeostasis is essential in countless aspects of human biology and physiology, but perhaps its failure is most obvious in the thrombophilias, disorders leading to excess and inappropriate clotting. Although several genetic mutations have been identified as etiologies of the thrombophilias, the most prevalent is Factor Five Leiden, a mutation described by Professor Bertina *et al*. in 1994 [2]. Factor five is one of our vitamin K-dependent hepatic-derived clotting factors. In the setting of vascular injury, thrombin activates factor five on the surface of endothelial cells so it may participate in forming a robust and ostensibly protective clot [3]. Activated factor five binds negatively charged phospholipids on the surface of platelets to then function as a receptor site for activated factors nine and ten [4]. Homeostasis always demands mechanisms to control the volume of biologic processes; in this case, there needs to be an off-switch so that the budding clot does not grow out of control. Protein C is this switch. Also a vitamin K-dependent plasma protein, Protein C undergoes activation to degrade factor five, damp its efficacy, and limit progression of the nascent thrombus. A number of disorders can result in activated protein C (APC) resistance. Autoantibodies against protein C, anti-phospholipid antibodies, and functional protein S deficiency are a few culprits [4]. These disorders are rare, however, accounting for very few cases of venous thrombosis. Yet, we know that APC resistance is present in 40% of patients with venous thrombosis, but only 7% of the general population [3]. In 1994 Professor Bertina described the prime cause of resistance to Activated Protein C (APC), a mutation in factor five. Being discovered in Leiden, the mutation was appropriately dubbed Factor Five Leiden. We now know this mutation's identity; R506Q, a substitution of glutamine for arginine at position 506, and DNA testing can easily and accurately identify it [5,6]. We also know its prevalence. The mutation occurs in a heterozygous form in 5% of the Caucasian population, while the homozygous prevalence is 1/1,600 [7]. Clearly the Factor Five Leiden mutation prevalence is extraordinarily high, but that does not necessarily translate into morbidity and mortality. To understand the consequences of the mutation we require more information. Before addressing this question though, I will bring the disorder to light by painting the image of a real patient — me.

In 2007, at the age of forty-seven, I, a preventive cardiologist but formerly an interventional cardiologist, became a victim of my genes. After a particularly difficult weekend of planting trees in the sweltering sun I entered my house and announced to my wife (also a physician) that I had developed severe left-sided, localized chest pain. My ribs were tender to palpation and so I assumed I had either fractured them or strained an intercostal muscle. That night I slept very little, finding it difficult to escape the pain. The following morning I went to the gym to perform my daily exercise routine, an hour on the elliptical and thirty minutes of resistance training. Feeling subpar, I simply walked on the treadmill. My workout partner, a Harvard-trained interventional cardiologist, and I discussed the differential diagnosis. Musculoskeletal pain topped the list; the pain was too severe, localized, and reproducible with palpation for us to feel I had experienced a pulmonary embolism. In fact, we even concluded there was no reason for me to have experienced a clot; I was devoid of predisposing risks. I went to work as usual, suffered through the day, and returned home for another failed attempt to sleep. At four AM, unable to continue my relentless tossing and turning, I went to my office to do paperwork. I had developed weakness and shortness of breath and could no longer evade the inevitable conclusion that this might in fact be a pulmonary embolism (PE). At seven AM I contacted a radiologist colleague to arrange a lunchtime chest CT angiogram. Wisely he had me cancel my patients so I could expeditiously come to his centre for the study. The scan was easy; the results were not. My colleague and friend rested his hand on my shoulder and declared, «It's a miracle you're alive.» Disbelieving and embarrassed, I responded, «Come on. Just tell me I have something wrong and I'm not just being a baby.» My fear of humiliation had definitely clouded my senses. The scan was correct. I had a large clot burden bilaterally involving central and peripheral pulmonary arteries. I had also infarcted my left lower lung (Figures 1–5). During the requisite lower extremity venous ultrasound (which did detect a large right proximal deep vein thrombosis (DVT)) I began to shower more emboli, desaturated and dropped my blood pressure, and was therefore

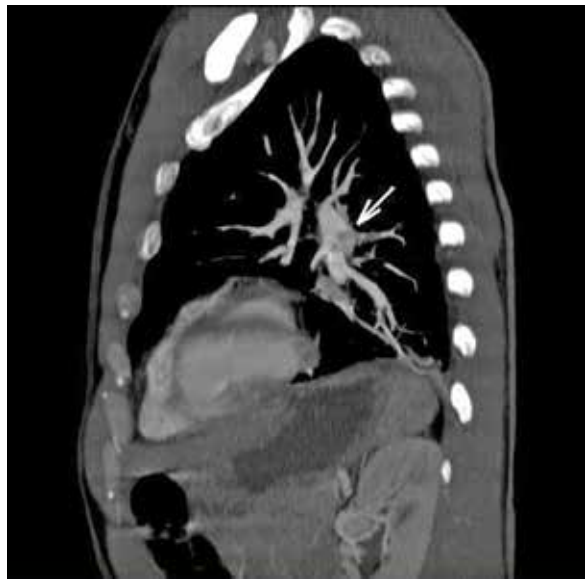

Figure 1. Computed tomographic (CT) sagittal slice: large thrombus in the proximal left pulmonary artery (arrow)

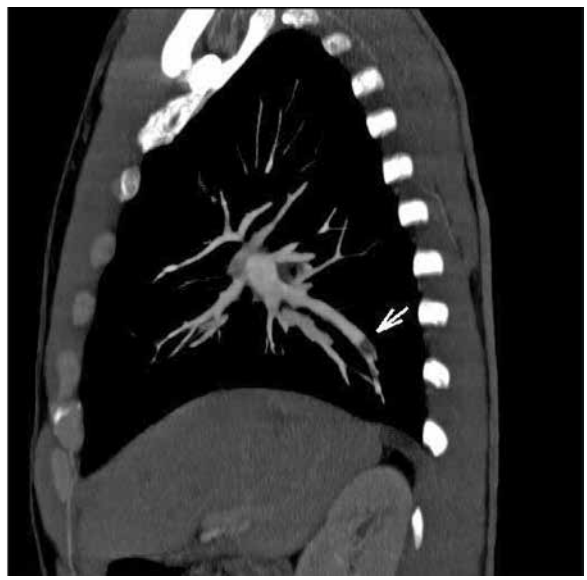

Figure 2. Computed tomographic (CT) sagittal slice: thrombus in the pulmonary artery to the right lower lobe (arrow)

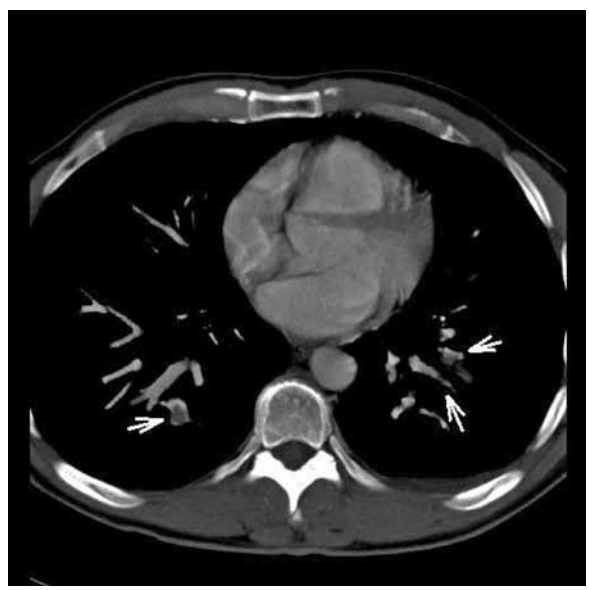

Figure 3. Computed tomographic (CT) axial slice: bilateral lower lobe pulmonary arterial thrombi (arrows)

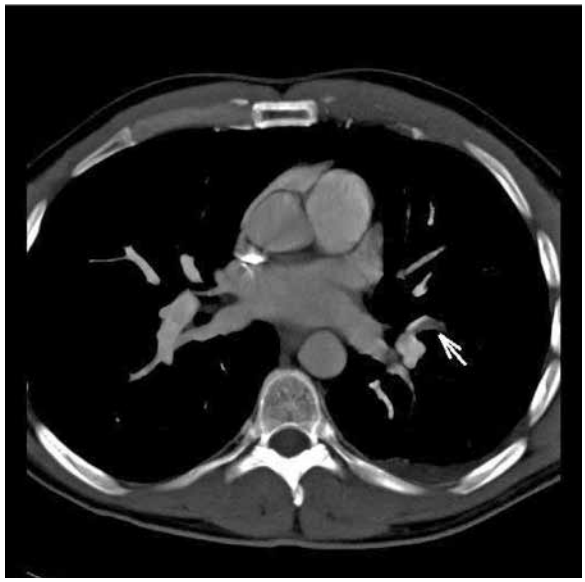

Figure 4. Computed tomographic (CT) axial slice: thrombus in a branch of the pulmonary artery to the left lower lobe (arrow)

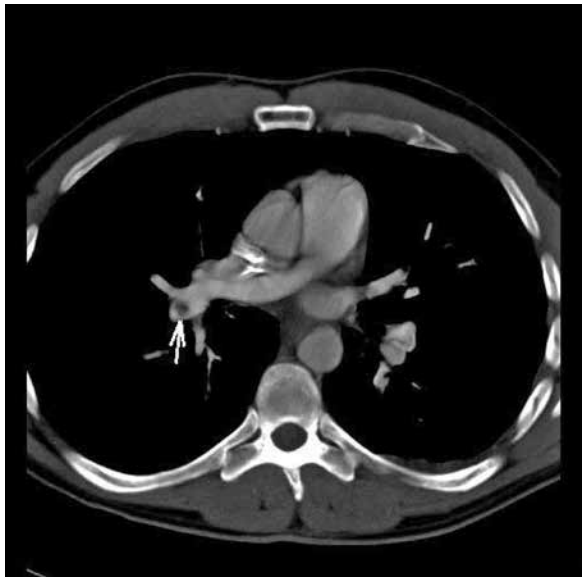

Figure 5. Computed tomographic (CT) axial slice: thrombus in the proximal right pulmonary artery (arrow)

whisked to the lab for an inferior vena cava (IVC) filter followed by nine days in the intensive care unit (ICU). I survived the event but am now left with residual issues as a consequence of my delay in diagnosis and treatment. Had I suspected a PE, I would surely have been treated early and avoided the impact of such a large burden of clot.

Virchow's triad — hypercoagulability, venous stasis, and venous injury — are the three elements that predispose to thrombogenesis. At the time, I believed I had none of the three. My workup however revealed my being heterozygous for the Factor Five Leiden mutation. I was in fact hypercoagulable, which combined with significant volume depletion from planting trees in the hot Florida sun had put me at risk for venous thromboembolic disorders (VTE). Again, had I known my genetic state I would have averted a great deal of damage. I survived the PE, but each year many thousands do not. In fact, the majority of PEs are discovered postmortem, not the way most physicians like to make their diagnoses [7]. Retrospective reviews have shown that although most patients' charts documented evidence of their impending fate, the PEs remained undiagnosed until after death. Fatal PEs are also far more frequent than most imagine; some estimates claim PE to be the third leading cause of death in the US, accounting for 650,000 deaths per year [8]. Venous thromboembolism with or without death is also far more common than most physicians believe. It occurs in 1 per 1,000 people annually and its inci-

dence increases significantly with age [4]. Thus, VTE represents a significant threat, one that merits preventive strategies if possible. Let's return specifically to Factor Five Leiden in order to understand its part in the genesis of both VTE and PE.

Rosendaal *et al*. evaluated 471 consecutive patients under the age of 70 with their first documented DVT and compared them with 474 healthy adults [9]. They found a seven-fold increased relative risk for heterozygous Factor Five Leiden patients and an eighty-fold increased relative risk for homozygous patients. As the risk of venous thrombosis increases with age, the absolute risk is highest in the elderly. The authors estimated a 2% per year risk of venous thrombotic disease in homozygous individuals over the age of 50. This translates into a near certainty of an event during every homozygous patient's lifetime. Although heterozygous individuals experience a lower lifetime risk of clotting, they too are at much greater risk than the general population.

Simioni *et al*. also evaluated patients with their first episode of venous thrombosis to determine how both prothrombin and Factor Five Leiden mutations influenced future thrombotic events [10]. Not surprisingly they found a significantly increased risk of second events among carriers of either mutation. A relative risk of 2.4 was revealed, translating into a ten-year risk for future venous thromboembolism of 55%.

Recalling Virchow's triad we know that certain events increase our risk for VTE: surgery, immobilization, pregnancy, and oral contraception (OC) being some of the most common culprits. On top of the background of mutations that increase thrombosis — Factor Five Leiden being by far the most common — adding a second component of Virchow's triad greatly increases the risk of VTE. Thus, looking at specific and common circumstances that predispose us to venous thrombosis can elucidate the impact that Factor Five Leiden has on DVT and PE. Understanding Factor Five Leiden's magnitude of influence will enable us to establish appropriate approaches to diminish untoward events. As pregnancy and OC have been best studied they will be discussed.

Pregnancy brings with it hypercoagulability [11]. In fact, pregnant women are five times as likely to experience VTE as non-pregnant comparably-aged women [12]. Obvious physical changes such as an enlarging uterus will cause lower extremity venous stasis and compression of the venous system. There are other changes that have a major impact as well. Coagulation is increased through higher levels of factors two, seven, and ten [13]. Fibrin levels soar [14]. Protein S decreases, and the fibrinolytic system is down-regulated. These changes all conspire to increase venous clotting. Add to this an additional thrombophilia, the Factor Five Leiden mutation, and the risk of pregnancy-associated VTE increases an additional three-to-seven fold [11]. In addition to the mother's risk of VTE, there is also a significant risk to the unborn child. Fetal growth retardation, stillbirth, and placenta abruptio are all increased in women who bare at least one allele for the Factor Five Leiden mutation [15]. In the Kupferminc study, over 50% of women with the aforementioned complications of pregnancy bore a genetic mutation predisposing to thrombosis, about half of them possessing the Factor Five mutation. Pregnancy-associated complications tend to recur and therefore it has been suggested that women with such complications undergo testing for thrombophilias. Perhaps it would make more sense to test women prior to their initial event.

OC is another area of great concern for women with thrombophilias. The risk of VTE increases four-fold in normal women using OC [7]. Factor Five Leiden increases a woman's risk of VTE seven-fold. The combination of OC and Factor Five Leiden demonstrates an unfavourable synergy, increasing the risk 36 fold. It is important to note that the women we are now discussing are in the prime of their lives, working, raising children, and building a future. Their deaths from VTE disease can have dramatic repercussions impacting many others' lives. Even in 1995, just a year after Factor Five Leiden's discovery, Bridey *et al*. called for global screening in their Thrombosis and Haemostasis editorial [16]. So based upon this as well as aforementioned facts, the logical question arises, «Should we globally screen people for Factor Five Leiden?»

Here are the arguments opposing screening: the numbers needed to treat are too high. Although we would identify people at risk, how would their management change? Women with Factor Five Leiden might unnecessarily lose the opportunity to utilize OC, the «easiest» form of birth control. It is too costly to genetically screen our entire population. Knowledge of an abnormal result might adversely impact insurance.

In response to each of these arguments I would bring us back to Dr. Freiden's proclamation, «Even one preventable death from heart disease and stroke is too many». In medicine we are trained to save lives and the optimal way to do so is undeniably through prevention. In our newfound era of patient-centric medicine, nothing is more inviolable than candour in the doctor-patient relationship. It is disingenuous for practitioners to know the risk inherent in harbour-

ing a Factor Five Leiden mutation and yet withhold such information from our patients. Shouldn't every woman choosing her method of birth control be made aware of the VTE risk OC conveys, as well as the vastly enhanced risk Factor Five Leiden introduces? At the risk of being sentimental, how would any of us feel if our wives or daughters or granddaughters perished from an otherwise avoidable PE as a consequence of OC in the setting of undetected Factor Five Leiden? Truly the only valid argument against global screening is economic. There is no risk to this test, only benefit. Money alone must not be the deciding vote in any medical decision-making. In earnest, I cannot conceive of a solid and defensible reason not to screen everyone for Factor Five Leiden. After all, knowledge is always king.

Conflict of interest: None declared

References

1. Freiden T. MD, MPH's Blog [Internet]. 2013 Sep 4. Available from: http://blogs.cdc.gov/cdcdirector
2. Bertina RM, Koeleman BP, Koster T, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature. 1994 May;369(6475):64–7. DOI:10.1038/369064a0.
3. Svensson PJ, Dahlback B. Resistance to activated protein c as a basis for venous thrombosis. NEJM. 1994;330:517–522.
4. Dahlback, B J. Physiologic Anticoagulation J Clin Invest. 1994 Sep;94(3):923–927.
5. Consensus Statement on factor five Leiden testing. 2007 May 5. Available from: http://www.acmg.net/resources/policies/pol-009.asp
6. Kujovich JL. Factor five Leiden thrombophilia. Gene Tests [Internet]. 2007 Feb 12. Available from: http://www.geneclinics.org/profiles/factor-five-leiden/details.html Accessed December 9
7. Vandenbroucke J P, et al. Factor Five Leiden: should we screen oral contraceptive users and women? BMJ. 1996,313:1127–30.
8. Feied CF, Handler JA. Pulmonary Embolism. Emedicine/WebMD. 2008. Available from: http://emedicine.com/emerg/topic490.ht Accessed December 4 2008
9. Rosendaal FR, Koster T, Vandenbroucke JP, Reitsma PH. High risk of thrombosis in patients homozygous for Factor Five Leiden (activated protein C resistance) Blood. 1995 Mar 15;85(6):1504–08.
10. Simioni P, Prandoni P, Lensing AW, et al. Risk for subsequent venous thromboembolic complications in carriers of the prothrombin or the factor V gene mutation with a first episode of deep-vein thrombosis. Blood. 2000 Nov 15;96(10):3329–33.
11. Toglia RM, Weg JG. Venous Thromboembolism during pregnancy. NEJM. 1996 July 11;108–14.
12. National Institute of Health Consensus Development Conference. Prevention of venous thrombosis and pulmonary embolism. JAMA. 1986;256:744–9.
13. Woodhams BJ, Candotti G, Shaw R, et al. Changes in coagulation and fibrinolysis during pregnancy: evidence of activation of coagulation preceding spontaneous abortion. Thromb Res. 1989;55:99–107.
14. Gerbasi FR, Bottoms S, Farag A, et al. Increased intravascular coagulation associated with pregnancy. Obstet Gynecol. 1990;75:385–9.
15. Kupferminc MJ, Eldor A, Steinman N, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy. N Engl J Med. 1999 Jan 7;340(1):9–13.
16. Bridey F, Wolff M, Laissy JP, et al. Fatal cerebral venous sinus thrombosis associated with the factor V Leiden mutation and the use of oral contraceptives. Thromb Haemost. 1995;74(5):1382.

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Evaluation of coronary artery bypass grafts with 64 slice CT, our initial experience

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Abstract

Aim

Purpose of our study is to assess the effectiveness of 64-slice cardiac computed tomography (CT) angiography, in detecting stenosis or occlusion of coronary bypass grafts in our patient population.

Material and methods

33 patients who have coronary bypass grafts and have applied to our radiology department for CT coronary angiography investigation between December 2008 and March 2010 were included in our study. All patients had cardiac CT investigation. 18 patients had both catheter coronary angiography (CCA) and cardiac CT. Cardiac CT angiography reports and images, CCA investigations, clinical follow-up and other results of the patients were evaluated retrospectively.

Results

94 grafts of 33 patients were included in our study. There were 32 left internal mammary arteries (LIMA), 1 radial artery, and 61 saphenous vein grafts. There were 50 grafts of 18 patients who also underwent CCA. 2 of these 50 grafts were not included in statistical analysis, because they could not been visualized in CCA due to lack of the catheterization. Totally, 48 grafts were included in statistical analysis. In comparison with CCA, the sensitivity of cardiac CT angiography in the detection of 50% or higher bypass graft stenosis or occlusion was 95.4%; specificity, 92.3%; accuracy, 93.7%; positive predictive value, 91.3%, and negative predictive value, 96%.

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Conclusion

64 slice cardiac CT investigation is a non-invasive imaging technique with high negative predictive value for evaluation of coronary bypass grafts.

Key words

Coronary artery bypass, coronary angiography, multidetector computed tomography, coronary disease, imaging

Introduction

As a result of the high prevalence of coronary artery disease in the Western World, coronary artery revascularization has become one of the most frequent medical procedures [1]. With the increasing success of these procedures, long term follow-up of these patients become a need [1].

Invasive CCA is accepted as diagnostic standard for this purpose [2]. But invasive procedure has some risks (death, myocardial infarction, cerebrovascular accident, arrhythmia, dissection etc.) and higher hospitalization costs [2].

Multidetector CT coronary angiography is a non-invasive imaging technique that can perform as outpatient procedure [2].

With the use of 64 slice CT in 2005, imaging with higher temporal and special resolution became possible [2]. While a temporal resolution is 105–250 milliseconds (ms) with 16 slice CT, it is 83–165 ms with 64 slice CT, and a special resolution increases from 0.5 x 0.5 x 0.6 millimetres (mm) to 0.4 x 0.4 × 0.4 mm [2].

In 2006 double source 64 slice CT, in 2007–256 slice CT, and in 2008–320 slice CT came into clinical use [3]. With this progress, it became possible to imagine the heart in one or two heart beats.

Purpose of our study is to assess the effectiveness of 64 slice cardiac CT angiography, in detection of stenosis or occlusion at coronary bypass grafts in our patient population.

Material and methods

33 patients who had coronary bypass grafts and evaluated with cardiac CT investigation between December 2008 and March 2010 in our radiology department were included in our study. 18 of 33 patients had both CCA and cardiac CT. Others had follow-up results after cardiac CT. Cardiac CT angiography reports and images, CCA investigations, clinical follow-up and other results of the patients were evaluated retrospectively. Patient informed consent, institutional academic board approval and ethical committee approval were obtained.

All patients were asked to come to the examination with 6 hours of hunger for solid diet and 12 hours of caffeine free diet. Scan area were chosen craniocaudally from thoracic inlet to basis of the heart. Region of interest was placed at the beginning of descending aorta for the bolus-tracking technique. When heart rate was higher than 75 beats per minute (bpm) and there was no contraindication for beta-blockers, patients were given 5 mg/ml of Beloc (Metoprolol tartrate, Astra Zeneca-Eczacıbaşı Health Products Co., Istanbul, Turkey) intravenously. Metoprolol was diluted with saline solution (0.9% NaCl) to 10 cc and infused slowly. Most patients were under medication after their bypass surgery. It was not necessary to administer a beta-blocker for 50% patients. None of the patients needed more than 15 mg metoprolol (three times injection).

All cardiac CT angiography investigations were performed with 64 slice CT device (Philips Brilliance 64; Philips Medical Systems, Holland). Transaxial slices were reconstructed at increments of 0.45 mm, an effective slice thickness of 0.9 mm, an image matrix of 512 × 512 pixels and a field of view of 220 mm. Collimation was 64 × 0.625 mm and gantry rotation time was 0.4 seconds. Scan filter (kernel) was Xres Standard (XCB) and pitch was 0.2. When patient had stent in bypass grafts or native coronaries, the filter was changed to Xres Detailed Stent (XCD). Tube output was 120 kilovolts (kV) at 800 milliampere-seconds (mAs). These values were increased to 900–1000 mAs and 140 kV if patient was obese. 90 to 120 ml of non-ionic iodinated contrast media and following 40 ml saline solution were injected to patients. Saline solution was containing 20 per cent of non-ionic contrast media. Ultravist-370 (Iopromide, Bayer Schering Pharma AG., Leverkusen, Germany) or Iomeron 400 (Iomeprol, Bracco S.p.A. —Gürel İlaç Tic. A.S., Istanbul, Turkey) were used as contrast media. The contrast media injection speed was 6 ml per second. Radiation dose of the CT investigation was the same as in the available literature for 64 slice CT devices.

All scans were reconstructed by using retrospective gating. Different reformat images (80%, 75%, 45%, 35%, etc.) were prepared and evaluated. All standard and reformat images were evaluated in Philips Extended Brilliance TM work station (V3.5.0.2254, Philips Electronics N.V.2004) by two independent radiologists who are experienced in cardiac CT. Arterial and venous grafts were evaluated for occlusion, stenosis or patency, and a report was prepared. When there was no contrast passage, graft was evaluated as occluded. When the narrowing in graft diameter (according to normal diameter of graft before or straight after the narrowing) was 50% or more, graft was evaluated as stenotic. If lumen was normal or the narrowing was less than 50%, graft was evaluated as patent. If there was discordance between reports of two radiologists, the graft was evaluated again by both radiologists, and decision was made by consensus. In statistical analysis, occlusions and stenoses (50% and more) were evaluated together in one group.

94 grafts of 33 patients were included in our study. There were 50 grafts from 18 patients who also underwent CCA. 2 of those 50 grafts were not included in statistical analysis, because they could not been visualized in CCA due to lack of catheterization. Totally, 48 grafts were included in statistical analysis. Cardiac CT results were compared with CCA results. Cardiac CT findings of 44 grafts from 15 patients who did not have CCA correlation were discussed and mentioned separately in the text. According to the clinical evaluation, laboratory and follow-up results, CCA was not needed for this patient group according to cardiologist in charge.

Statistical analysis was performed by SPSS version 15.0 (SPSS Inc. Chicago, Illinois, USA) software for Windows. Sensitivity, specificity, accuracy, positive predictive value and negative predictive value were calculated for cardiac CT angiography. Also McNemar, Kappa and Spearman rank correlation coefficient tests were performed. *P* value <0.05 was considered statistically significant. The correlation coefficient values were interpreted as follows: 0.00-0.20, poor agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, good agreement; and 0.81–1.00, excellent agreement.

Results

There were no serious complications in any patients during cardiac CT angiography.

Demographic characteristics of patients were summarized in Table 1.

Table 1. **Demographic characteristics of patients in our study**

Patient Characteristics	Value
Age (year)	
Mean	62
Range	(42–76)
Gender	
Female	6
Male	27
Period between CCA — cardiac CT	
Maximum	10 months
Minimum	1 day
Mean*	44 days
Period between bypass surgery and cardiac CT	
Longest period	21 years
Shortest period	10 months
Mean	6 years**

* If 2 patients who had waiting period longer than one month between CCA and cardiac CT investigation were ignored, a mean period between two investigations decreased to 14 days.
** Mean time period between surgery and cardiac CT was 5.96 years and it was shown as 6 years.

There were 33 arterial (32 LIMA, 1 radial artery) grafts and 61 venous (all saphenous vein) grafts. Distribution of grafts according to graft type and distal anastomosis side were summarized in Table 2.

Table 2. **Distribution of grafts according to graft type and distal anastomosis side**

Vessel that distal anastomosis was performed	Saphenous vein graft	Arterial graft (LIMA, RA)
LAD	1	31
Diagonal artery	14	1
LCX	5	— -
Obtuse Marginal artery	20	1*
RCA*	20	— -
Acute marginal artery	1	— -
TOTAL	61	33

* Radial artery (RA) graft was shown.
** One of the grafts that distal anastomosis was made on RCA was connected to innominate artery at proximal anastomosis due to diffuse and severe atherosclerotic chances on ascendant aorta.

Occlusion of 8 LIMA grafts (25%), severe stenosis (50% and more narrowing) of 2 LIMA grafts, and patency of 22 LIMA grafts (69%) were detected at cardiac CT investigation. One LIMA graft which had 50% stenosis in cardiac CT was described as patent in CCA. One LIMA graft which was patent in cardiac CT was not added to statistical analysis due to lack of catheterization and visualization in CCA. Occlusion of 16 saphaneus vein grafts, severe stenosis (50% and more narrowing) of 6 venous grafts and patency of 39 venous grafts were detected at cardiac CT investigation. One venous graft which was stenotic in cardiac CT was evaluated as patent in CCA. 70% stenosis was described in CCA on another venous graft which had

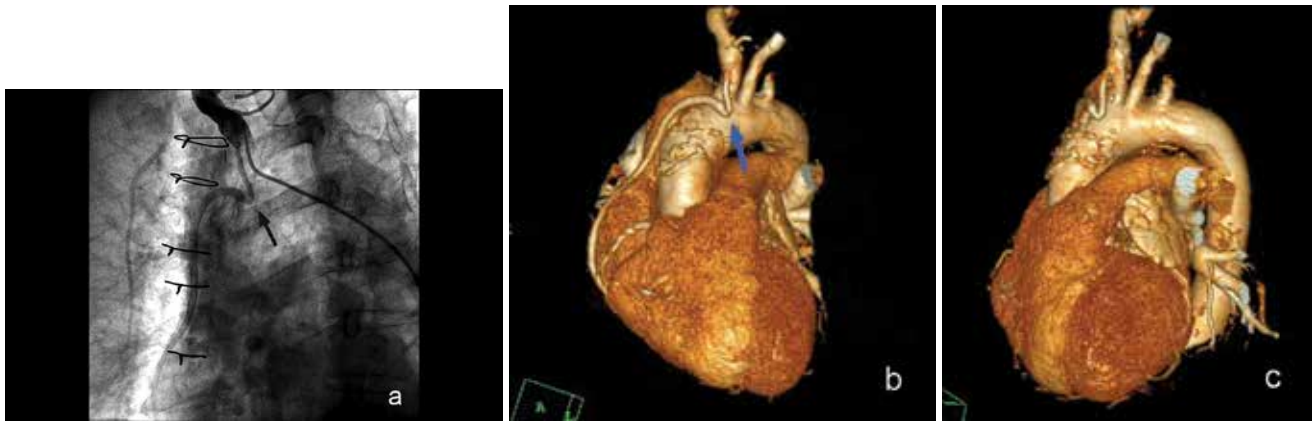

Figure 1. a, b, c. CCA image (a) and first volume rendering (VR) image (b) show stenosis more than 50% on brachiocephalic artery-RCA saphaneus venous graft (SVG). But in another angle on second VR image (c) the stenosis does not seem to be more than 50%

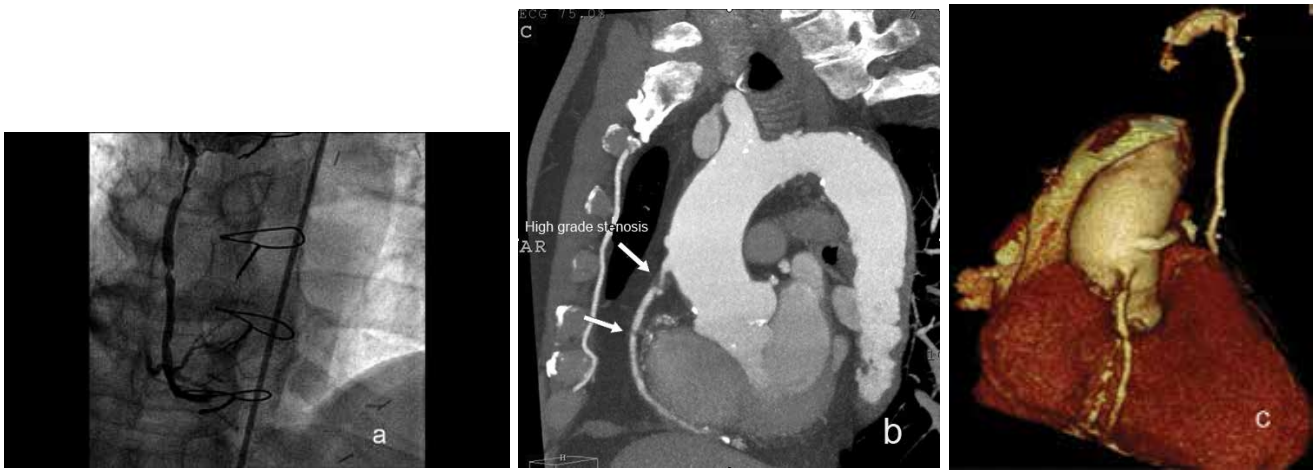

Figure 2. a, b, c. CCA (a), maximum intensity projection (MIP) (b) and VR (c) images show high grade stenosis on aorta-RCA-SVG

less than 50% stenosis and assumed as patent in cardiac CT (Figure 1). One radial artery graft was patent in both investigations.

In CCA correlation group (48 grafts of 18 patients), 21 of 22 grafts (95.4%) which were occluded or stenotic in CCA were found occluded or stenotic in cardiac CT too (Figure 2) (Table 3). 24 of 26 grafts (92.3%) which were patent in CCA were also found patent in cardiac CT. 2 grafts which were stenotic in cardiac CT were evaluated as patent in CCA.

Table 3. **Comparison of cardiac CT and CCA**

			CCA		Total
			occluded	patent	occluded
CT	occluded	count	21	2	23
		% within CT	91.3%	8.7%	100.0%
	patent	count	1	24	25
		% within CT	4.0%	96.0%	100.0%
Total		count	22	26	48
		% within CT	45.8%	54.2%	100.0%

2 grafts (1 LIMA, 1 saphenous) which were patent in Cardiac CT were not included in statistical analysis due to lack of catheterization in CCA.

In whole patient group, totally 32 of 92 grafts were occluded and 60 were patent in cardiac CT. There were 44 grafts of 15 patients in clinical follow-up group. 35 of these 44 grafts were patent in cardiac CT. Occlusion or severe stenosis were detected with cardiac CT on 9 grafts of 15 patients in clinical follow-up group. Patients were evaluated in follow-up period according to LIMA graft patency, at least one patent graft existence, chest pain presence, response to maximum medical treatment, ECG changes, and myocardial scintigraphy results. In spite of occlusion found in some grafts with cardiac CT, clinical follow-up decision for these grafts was made by a cardiologist according to the *American Heart Association* (AHA) and *American College of Cardiology* (ACC) guidelines and results of data mentioned above. The longest follow-up period was 10 months and the shortest — 2 months.

Statistical results

48 grafts of 18 patients who had CCA were evaluated statistically. In comparison with CCA, the sensitivity of cardiac CT angiography in the detection of 50% or higher bypass graft stenosis or occlusion was 95.4%;

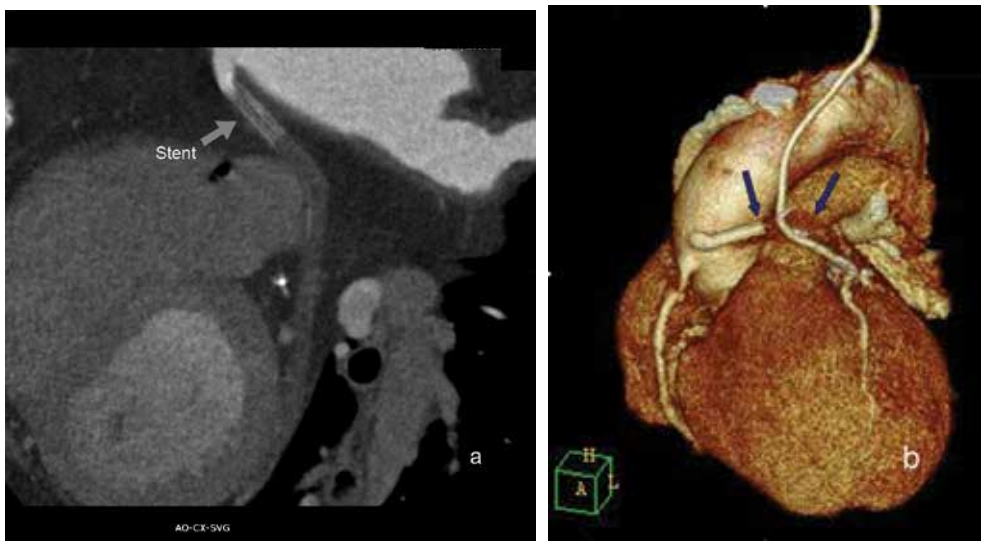

Figure 3. a, b. Occluded SVG is shown on MIP (a) and VR (b) images. Also there is occluded stent on proximal side of the graft

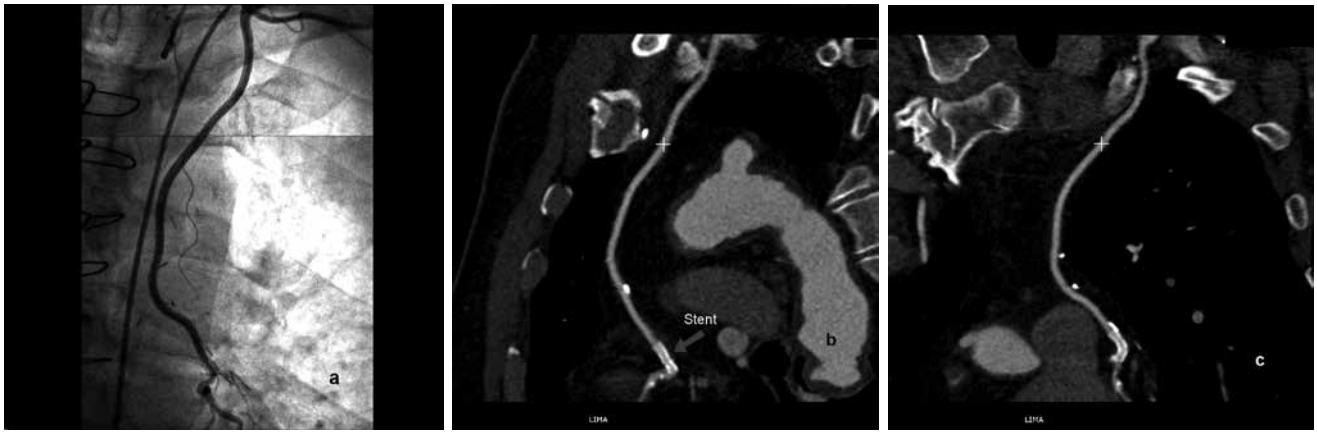

Figure 4. a, b, c. Patent LIMA graft is shown on CCA image (a). MIP images (b and c) show patent LIMA graft and also stent at distal anastomosis

the specificity, 92.3%; the accuracy, 93.7%; the positive predictive value, 91.3%, and the negative predictive value, 96%. There was no difference between two investigation methods statistically (P>0.05). Kappa (κ) value was 0.87 and r value was 0.0875 for these two investigation methods which was evaluated as excellent agreement and perfect match.

Discussion

Selective CCA is a gold standard for coronary bypass graft evaluation. But it is an invasive method and has a risk for serious major complications [2]. On the other hand, recent progress on multidetector CT technology showed that cardiac CT is a minimal invasive alternative method for evaluating coronary bypass grafts compare to CCA. In 2006 Ropers *et al*. [4] and in 2007 Feuchtner *et al*. [2] reported that none of the grafts were excluded from their study due to bad image quality. They used 64 slice CT in their studies. Like these two studies, no patients were excluded from our study due to bad image quality.

In a study, conducted by Feuchtner *et al*., 70 grafts of 41 patients were evaluated, the sensitivity of 64 slice CT in the detection of 50% or higher bypass graft stenosis or occlusion was found 85%, and specificity was 95% [2]. Like this study, we evaluated 50% or higher bypass graft stenosis and occlusions together in the same group. The number of our patients (33 patients) was less than the one in the Feuchtner *et al*. study but the number of grafts evaluated (92 grafts) was higher. Feuchtner *et al*. had CCA correlation for all grafts in his study. Sensitivity was 95.4% and specificity was 92.3% in our study. Our sensitivity was higher than the one in the Feuchtner *et al*. study. On the other hand, Ropers *et al*. evaluated 138 grafts in his study and found that sensitivity of 64 slice CT in the detection of 50% or higher bypass graft stenosis or occlusion was 100%, and specificity was 94%. Sensitivity and specificity of our study were between the values of these two studies. Patients with stents in grafts or native coronaries were excluded from the Ropers *et al*. study. In addition to this, in this study much more aggressive beta-blocker treat-

ment (oral and intravenous) compare to our study was given to the patients before the cardiac CT investigation to keep heart rate under 60 bpm. We did not exclude patients with stents in their grafts from our study (Figures 3 and 4). In our study, when the heart rate was 70 bpm or below, we performed cardiac CT investigation without beta- blocker administration. We think, low sensitivity and specificity values of our study compared to Ropers's study can be explained by these differences.

In the Feuctner *et al*. study, there were maximum two weeks between cardiac CT and CCA investigations. In our study, a mean interval between two investigations was 44 days. There were two patients who had long period (300 days and 252 days) between two investigations. First patient (300 days interval) had one graft, and the graft was occluded in both investigations. Other patient had two grafts which were defined as patent in both investigations. Because of these reasons, we thought there was no bias despite the long interval between investigations. If we ignore these two patients, the mean interval decreases to 14 days.

In 2006, Pache *et al*. [5] reported that 2 venous grafts and one arterial graft were missed at CCA investigation. Similarly, 1 saphaneus, and 1 LIMA graft could not be visualized and 1 patent right coronary artery (RCA) saphaneus graft was misdiagnosed as root of occluded RCA — saphenous graft with CCA in our study.

Indications for reoperation of patients with coronary bypass grafts were explained in *ACC/AHA* guidelines [6]. Presence of a functioning LIMA graft, anastomosed to left anterior descending coronary artery (LAD), with recurrent ischemia on other areas of the heart, potential loss of this graft may results in reoperation [6]. In our study, 44 grafts of 15 patients who did not have CCA investigation, were evaluated with only cardiac CT results. 2 of 14 LIMA grafts without CCA correlation were occluded and one was stenotic in cardiac CT. All of these three patients had additional patent grafts. At least one patent graft was present in each patient in clinic follow-up group. Because of these reasons, we thought that the follow-up decision was made by a cardiologist according to *ACC/AHA* criteria.

In 2009, Mannacio *et al*. [7] used 64 slice CT in their study to evaluate 73 grafts in 25 patients. CCA investigation was not performed for correlation of cardiac CT results in this study. They used clinical progress, cardiac specific biomarkers, homodynamic finding for evaluating early graft dysfunction. In 2009, Bassri *et al*. [8] used 16 slice CT in their study to evaluate 366 grafts and did not performed CCA correlation. Like these two studies, we did not have CCA correlation for the follow-up group.

Major limitation of our study was evaluation of 15 patients (44 grafts) only with cardiac CT results and lack of CCA correlation. But, as we mentioned above, some recent studies which were done with 64 slice CT did not have CCA correlation due to high sensitivity and specificity of 64 slice CT.

Another limitation of our study was to be a retrospective study. Because of this, standard examination quality could not be obtained.

In our study, the total number of grafts, especially with CCA correlation, was low. In literature, there are wide series like Meyer *et al*. [9] in which 406 grafts of 138 patients were evaluated.

CT technology has progressed really fast recently. In 2006 dual source 64 slice CT, in 2007–256 slice CT, and in 2008–320 slice CT were available in clinical use [3].

Dewey *et al*. used 320 slice CT in their study [10] and evaluated 30 patients. Their sensitivity was 100%, and specificity was 94%. In this study, a mean effective radiation dose of cardiac CT with 320 slice CT was 4.2 millisievert (mSv). On the other hand, it was 8.5 mSv for CCA. It was reported in the study that 87% of the patients would choose CT over CCA if investigation of their coronaries was needed again in the future.

Considering the recent progress on CT technology that mentioned above, we think that it would not be wrong to say, cardiac CT will be performed for all diagnostic investigations in the future, instead of CCA.

Conclusion

Cardiac CT investigation with 64 slice CT is a non-invasive method with high negative predictive value for imaging of grafts after coronary bypass operation. In our study, it has been established that in patient group in our university hospital, 64 slice cardiac CT has high specificity and sensitivity in detecting bypass graft patency, which is similar to the available literature.

As a result, we think this method is a powerful alternative to catheter angiography which is still accepted as gold standard for evaluation of bypass grafts.

Conflict of interest: None declared

References

1. Budoff M, Shinbane J. Cardiac CT imaging — Diagnosis of cardiovascular disease. 1st ed. London: Springer-Verlag; 2006. p. 55–57, 135–178.
2. Feuchtner GM, Schachner T, Bonatti J, et al. Diagnostic performance of 64-slice computed tomography in evaluation of coronary artery bypass grafts. AJR. 2007;189:574–580.

3. Karabulut N. Çok kesitli bilgisayarlı tomografi koroner anjiyografi: Genel ilkeler, teknik ve klinik uygulamalar [Multislice computerized tomography coronary angiography: general principles, technique and clinical applications]. Anadolu Kardiyol Derg. 2008;8 Suppl 1:29–37.
4. Ropers D, Pohle FK, Kuettner A, et al. Diagnostic accuracy of non-invasive coronary angiography in patients after bypass surgery using 64-slice spiral computed tomography with 330-ms gantry rotation. Circulation. 2006;114;2334–2341.
5. 5. Pache G, Saueressig U, Frydrychowicz A, et al. Initial experience with 64-slice cardiac CT: non-invasive visualization of coronary artery bypass grafts. Eur Heart J. 2006;27:976–980.
6. 6. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery. A Report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). J Am Coll Cardiol. 2004 Sep 1;e284–285.
7. 7. Mannacio VA, Imbriaco M, Iesu S, et al. 64-Slice Multidetector Computed Tomographic Evaluation of Arterial Conduit Patency after Off-Pump Coronary Artery Bypass Grafting. Tex Heart Inst J. 2009;36(5):409–15.
8. 8. Bassri H, Salari F, Noohi F, et al. Evaluation of early coronary graft patency after coronary artery bypass graft surgery using multislice computed tomography angiography. BMC Cardiovasc Disord. 2009;9:53. DOI:10.1186/1471–2261–9–53.
9. 9. Meyer TS, Martinoff S, Hadamitzky M, et al. Improved non-invasive assessment of coronary artery bypass grafts with 64-slice computed tomographic angiography in an unselected patient population. J Am Coll Cardiol. 2007;49:946–950.
10. 10. Dewey M, Zimmermann E, Deissenrieder F, et al. Non-invasive Coronary Angiography by 320-Row Computed Tomography With Lower Radiation Exposure and Maintained Diagnostic Accuracy. Circulation. 2009;120:867–875.

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Aortic stiffness and the possibility of its drug correction in patients with hypertension and obesity

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Abstract
Numerous studies confirm the importance of assessing aortic stiffness in determining the risk of cardiovascular events in patients with hypertension and obesity, and the need for medications for its medical correction. Most of the antihypertensive drugs have, in varying degrees, a direct or indirect effect on arterial stiffness. That is why the use of combination therapy may be more effective. Lipid-lowering and antidiabetic therapy has an additional effect on vessel stiffness in these patients. However, data on the effect of diet and weight-reducing drugs on the condition of large vessels are few and require clarification.

Keywords
Hypertension, obesity, aortic stiffness, central blood pressure, pulse wave velocity

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Numerous epidemiological and clinical studies have shown that aortic stiffness is an important factor in evaluating the prognosis of cardiovascular disease in patients with hypertension and obesity. According to studies, pulse wave velocity (PWV), central pressure, as well as parameters of the reflected waves are independent predictors of cardiovascular (CV) events in different groups of patients. An interesting study, conducted by Guerin *et al.*, involved 150 patients, aged 52 ± 16 years, with severe chronic kidney disease (CKD). All patients had two measurements of their carotid-femoral PWV and were prescribed antihypertensive therapy with angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers (CCBs) and / or beta-blockers. During follow-up (51±38 months), 59 patients died, 40 of them from cardiovascular disease (CVD). Analysis of the results showed that, despite comparable BP reduction, in the group of deceased patients there was an increase in PWV. Thus, the value of PWV was an independent death risk factor from CVD [1].

The CAFE (Conduit Artery Function Evaluation) study included 2,199 patients aged 40–79 years with hypertension and at least three additional risk factors for CV events (smoking, hypercholesterolemia, microalbuminuria, diabetes, etc.). Mean body mass index (BMI) of participants was 29±4.6 kg/m². During follow-up (average 4.5 years), all patients had central pulse wave analysed, and PWV was determined. To identify predictors of CV events, several variants of multifactorial regression analysis were performed: PWV, central BP, and the characteristics of the reflected waves were assessed separately or in conjunction with age and main risk factors, the data of all enrolled patients or patients without a history of CVD were analysed. In all models, central pulse pressure, as well as peripheral, proved to be a significant predictor of CV events in this category of patients. Increase of central pulse pressure by 10 mmHg raises the risk of CV events, on average, by 1.2 times [2].

Data from the CAFE study were confirmed in the Strong Heart Study, involving 3,520 participants. Mean age was 58±14 years; mean BMI — 31.5±6.8 kg/m². According to multifactorial regression analysis, central pulse pressure was an independent predictor of CV events and was exceeded by the significance of peripheral pulse pressure in individuals older than 62 years. It was also noted that an increase in central pulse pressure by more than 50 mmHg was associated with a high risk of CV events, regardless of a participant's sex and age [3].

In a study conducted by Wang, data from 1,272 patients aged 30–79 years were analysed. During follow-up (10.8±1.7 years), 130 people died, including 37 from CVD. According to multifactorial regression analysis, central systolic BP was the most significant predictor of aortic stiffness. The increase in central systolic BP by 10 mmHg raised the risk of CV events by 1.3 times [4].

Data on the prognostic significance of the reflected wave parameters are contradictory. In some studies, involving small groups of patients, it has been shwon that augmentation index (AIx) is an independent predictor of CV events, not yielding, and according to some data, even exceeding the prognostic value of central pulse pressure [5–6]. However, in large multicenter trials these data were not confirmed.

Thus, most researchers point out the importance of assessing aortic stiffness in determining the risk of CV events, and the need for medications for its medical correction. Pharmacological agents capable of reducing arterial stiffness include antihypertensive, lipid-lowering, antidiabetic, and also weight loss medications. The drug effect on aortic stiffness can be direct, caused by direct influence of a drug on the arterial wall, and indirect, associated with a decrease in BP, peripheral vasodilatation, changing in the parameters of the reflected wave, and a decrease in heart rate. It is assumed that the most pronounced direct effect on aortic stiffness is from ACE inhibitors and angiotensin receptor blockers (ARBs), and, to a lesser degree, CCBs and aldosterone antagonists. Drugs that have an indirect effect include CCBs, diuretics and, to a lesser extent, ACE inhibitors and ARBs. Currently, special attention is paid to the influence of ACE inhibitors and ARBs on the remodeling of the aortic wall. Studies show that long-term administration of drugs in this group is accompanied by an improvement of elastic properties in large arteries, regardless of the hypotensive effect. In a study, conducted by Tropeano *et al.* (Diabetes Artery Perindopril Hypertension Normalization Excess sTiffness — DAPHNET), 57 patients with hypertension and type II diabetes aged 56–70 years were recruited. Within 6 months after the normalization of the peripheral BP, patients received 4 or 8 mg dose of perindopril. All patients underwent applanation tonometry, ultrasound of the carotid arteries. During the therapy, both groups showed a decrease of central BP, improvement in the elastic properties of the carotid artery and, in particular, reduction of intima-media thickness, which was more pronounced in patients treated with 8 mg of perindopril. Thus, a direct dose-dependent effect of the drug on the stiffness of large arteries was demonstrated [7].

In a study, conducted by Mackenzie, 59 patients were involved with isolated systolic hypertension aged 62–74 years. Patients were taking perindopril over 10 weeks. All patients underwent applanation tonometry, and PWV was determined. In the background of a significant reduction in peripheral and central BP, no changes in PWV were identified. The study authors suggest that the lack of dynamics in carotid-femoral PWV is associated with a short period of treatment [8].

Tomiyama *et al*. conducted a study involving 134 patients with stage I–II hypertension. All patients were treated with candesartan for 2–3 years. In the background of prolonged use of the drug there was a significant decrease in PWV, on average by 2.0±0.18 m/s [9].

There are not many studies evaluating the effect of aldosterone antagonists on aortic stiffness. Thus, Kithas & Supiano describe the results of their study, which involved 45 hypertensive patients from a relatively older age group (mean age 69 years). All patients underwent ambulatory blood pressure monitoring (ABPM), applanation tonometry, and PWV was measured. During 6-month therapy of spironolactone there was a significant decrease of PWV, an average of 1 m/s. The authors suggest that the decrease in PWV was due to the suppression of the arterial wall remodeling processes activated by aldosterone, and to an increase in the aorta elasticity [10].

Among the drugs that have indirect (mediated) effects on aortic stiffness, a special place is occupied by CCBs. Due to peripheral vasodilation, drugs in this group increase the propagation time of the reflected wave from the reflection points to the ascending aorta, reduce the amplitude of the reflected wave, and ultimately, reduce central systolic and pulse pressure. In a study, conducted by Palombo C., Malshi E., Morizzo C., 41 patients, aged 50–64 years, with stage I–II hypertension were involved. During the observation period (6 months), all patients underwent ultrasound examination of the carotid arteries, analyses of central pulse wave and local arterial stiffness. In the background of the therapy with long-acting CCB there was found a significant decrease in peripheral and central BP and AIx by reducing the amplitude of the reflected wave. At the same time the indicators of local stiffness of the carotid artery did not change [11]. Several other studies have shown that when compared with ACE inhibitors or ARBs, CCBs have a less pronounced effect on PWV, whereas peripheral and central BP reduces in all groups equally [9].

Data on the effect of thiazide diuretics on aortic stiffness are limited and conflicting. Most of the studies comparing the efficacy of antihypertensive drugs of different classes, mentioned lack of influence of diuretics on central BP, parameters of the reflected wave, and PWV. However, in a trial, conducted by Dart *et al.* (ANB2-Second Australian National Blood Pressure Trial), it was shown that prolonged use of hydrochlorothiazide in 199 hypertensive patients aged 65–84 years was accompanied by a significant reduction in central BP, comparable with the effect of ACE inhibitor — enalapril [12].

Recently, particular attention has been paid to the effectiveness of combination therapy, consisting of antihypertensive drugs of different classes.

Asmar *et al*. (REASON — Preterax in regression of Arterial Stiffness in a controlled double-blind study) evaluated the effect of combination in low doses of perindopril and indapamide on peripheral and central BP, parameters of the reflected wave and PWV in comparison with atenolol. The study included 354 patients with hypertension aged 18–84 years. During the observation period (12 months), all patients received applanation tonometry, central pulse wave analysis, and PWV was determined. In the background of the combined therapy, statistically significant reduction was shown in central systolic and pulse pressure, AIx, and PWV. In the atenolol group, there was a significant decrease of PWV, more pronounced than in the perindopril / indapamide group, however, central BP changed insignificantly, with the AIx slightly increased. The study authors suggest that the positive effect of perindopril / indapamide on central BP and PWV was due to a combination of direct and indirect effects of drugs on aortic stiffness. Insignificant effect of atenolol on central BP and parameters of the reflected waves, according to the authors, was due to the slowing of the heart rate, lengthening the period of exile and, as a consequence, an increase in central systolic and pulse pressure [13].

Williams *et al*. (CAFE) evaluated the effect of amlodipine and perindopril combination on peripheral and central PB, parameters of the reflected wave and PWV in patients with hypertension, compared with atenolol and thiazide diuretic combination. In the background of the prolonged combination therapy there was a significant decrease in peripheral BP in both groups. In the amlodipine / perindopril group there was revealed a more pronounced reduction of the central BP, as well as reflected wave characteristics such as pressure augmentation and AIx. Carotid-femoral PWV in both groups decreased slightly, on average by 0.5 m/s. According to the authors, the lack of central BP reduction in the atenolol group is not

only due to slowing of the heart rate, but also to peripheral vasoconstriction, which led to shortening of the distance from the reflection points to the ascending aorta, increase in the amplitude of the reflected wave, and central systolic blood pressure [2].

Similar results were obtained in a study, conducted by Boutouyrier *et al*. (EXPLOR), which involved 393 patients with hypertension aged 47–67 years. In the background of the combined amlodipine / valsartan therapy for 6 months, a significant reduction of central BP and AIx was shown, whereas in the amlodipine / atenolol group the central systolic BP decreased slightly, and the AIx increased. PWV significantly decreased in both groups, on average by 0.97 m/s. The study authors suggest that this atenolol effect is associated not only with the heart rate and the influence on peripheral vessels, but also with the lack of direct effect of the drug on aortic stiffness, in contrast to the combination of an ACE inhibitor and CCB [14].

Many authors believe that the main reason for the lack of beta-blockers influence on central BP is a decrease in heart rate, but according to some studies, a significant decrease in heart rate caused by drugs of other classes is not always accompanied by increase in AIx and central systolic BP. Topouchian *et al*. evaluated the effect of verapamil, trandolapril and their combination on the large arteries stiffness in 69 patients with hypertension aged 29 to 76 years. During the 7 month follow-up, all patients in the dynamics were carried out applanation tonometry, ultrasound of the carotid arteries, and carotid-femoral PWV was determined. Despite the decrease in heart rate, in all groups there was revealed a significant decrease in central systolic and pulse pressure, PWV (an average of 2 m/s), as well as improvement of the carotid artery elastic properties, which was more pronounced in the background of the combined therapy [15].

In a study, conducted by Matzui *et al*. (Japan-Combined Treatment with Olmesartan and a Calcium Channel Blocker Versus Olmesartan and Diuretics Randomized Efficacy — J-CORE) there was compared the effect of long-acting CCB and thiazide diuretic in combination with ARB on central BP and PWV in 207 hypertensive patients. Selected by researchers CCB had a negative chronotropic action due to suppression of the sympathetic nervous system activity. In the background of the combined CCB and ARB therapy for 6 months it was showed a significant reduction in central systolic and pulse pressure, AIx and PWV. The combination of ARB and thiazide diuretic was less effective. According to the authors, the reduction of the central BP, to a greater extent, depended not on heart rate, but on peripheral vasodilation [16].

Recently there have been several comparative studies of beta-blockers, with special attention given to the medicine with vasodilating properties. Mahmud *et al*. evaluated the effect of nebivolol and atenolol on central BP, parameters of the reflected wave and PWV in 40 hypertensive patients aged 48–50 years. In both groups there was a significant decrease in peripheral BP and heart rate, but only in the nebivolol group there was a reduction in AIx, which led to a significant reduction in central pulse pressure. PWV decreased in both groups equally, on average by 2 m/s [17].

Similar results were obtained by Shah *et al*. (Carvedilol Reduces Aortic Wave Reflection and Improves Left Ventricular / Vascular Coupling: A Comparison with Atenolol — CENTRAL), where 41 patients with stage I–II hypertension were involved. The study assessed effect of carvedilol and atenolol on central BP and reflected wave parameters. Despite a comparable decrease in peripheral BP and heart rate, in the carvedilol group a significant decrease in AIx and augmentation pressure was revealed, whereas in the background of receiving atenolol these indices increased [18].

Thus, numerous studies suggest that antihypertensive drugs of various classes have different effects on aortic stiffness characteristics such as central BP and PWV.

Recently, there have been studies on the effect of lipid-lowering and anti-diabetic drugs on aortic stiffness. It is assumed that combined antihypertensive and metabolic therapy leads to a more pronounced positive impact on arterial stiffness in patients with hypertension and obesity through previously unexplored mechanisms.

Manisty *et al*. analyzed data from 283 patients with hypertension who participated in the substudy ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial — Lipid Lowering Arm). 142 patients were receiving, in addition to combined antihypertensive therapy, atorvastatin in a daily dose of 10 mg for 6 months, 141 patients received placebo. All patients underwent applanation tonometry with the central pulse wave analysis. In the background of the atorvastatin therapy there was revealed a significant decrease in carotid AIx, compared with placebo. Substantial, but insignificant decrease was noted in the central systolic BP in patients taking a combination of amlodipine/perindopril and atorvastatin. Positive effect of atorvastatin on the reflected wave parameters, according to the

authors, is due to the drug impact on the endothelium and release of NO, as well as its anti-inflammatory properties [19].

The CHICAGO (Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone) study involved 462 patients with type II diabetes, and normal and high BP. The average age of the participants was 60±8.1 years, mean BMI — 32±5.1 kg/m². All patients had ultrasound of the carotid arteries at baseline, after 24, 48 and 72 weeks of hypoglycemic therapy. In the background of the prolonged pioglitazone therapy there was shown an improvement in elastic properties of the carotid arteries, particularly a small decrease in intima-media thickness. The study authors suggest that the positive effect of the drug on arterial stiffness is associated not only with its main, but also with its additional anti-atherogenic and anti-inflammatory effect [20].

Data on the effect of diet and drugs that reduce weight on arterial stiffness are few. For example, in the SAVE study (Slow the Adverse Effects of Vascular Aging) there were included 339 patients with abdominal obesity between ages 20 to 45 years and BMI of 25 to 39.9 kg/m². All patients at baseline and after 6 months of non-pharmacological correction (diet) had carotid-femoral PWV determined. With the reduction in weight there was observed a significant decrease in PWV, accompanied by normalization of carbohydrate metabolism that, according to the authors, was due to the reduction of quantity of metabolically active adipose tissue, reduction in sympathetic influence on the blood vessels, and decrease in heart rate [21].

Similar results were obtained by Cooper *et al.*, where 344 patients with overweight and obesity between ages 20 to 45 years were involved. With the reduction in weight during 12 months there was a significant decrease in PWV. According to the authors, mechanisms of the effect of obesity on aortic stiffness require further study, and may be linked to the influence of pro-inflammatory cytokines produced by excess adipose tissue [22].

Thus, currently there are two main variants of the impact on the large arteries stiffness in patients with hypertension and obesity: direct (independent of BP level) and indirect (associated with BP, heart rate, condition of peripheral vessels). Long-term use of ACE inhibitors and ARBs is accompanied by improvement in the aorta elasticity. CCBs and diuretics have the most pronounced indirect effect on arterial stiffness due to peripheral vasodilatation. Most antihypertensive drugs have direct and indirect effects on blood vessels in different degrees; however, combination therapy may be more effective. Beta-blockers, among other drugs, significantly reduce the pulse wave velocity. Certain drugs of this class, such as atenolol, have little effect on the pressure in the aorta. Beta-blockers, which have vasodilating properties, significantly reduce central BP. Lipid-lowering and anti-diabetic drugs have additional influence on aortic stiffness due to metabolic and anti-inflammatory effect. Data on effect of non-pharmacological correction of obesity on the state of the aorta are few and require clarification.

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References

1. Guerin AP, Blacher J, Pannier B, et al. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. Circulation. 2001;103:987–92.
2. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic BP and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation. 2006;113(9):1213–25.
3. Roman MJ, Devereux RB, Kizer JR, et al. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. Hypertension. 2007;50:197–203.
4. Wang KL, Cheng HM, Chuang HM, et al. Central or peripheral systolic or pulse pressure: which one best relates to target organs future mortality? J Hypertens. 2009;27:461–467.
5. Vlachopoulos C, Aznaouridis K, Stefanadis C, et al. Prediction of cardiovascular events and all cause mortality with central haemodynamics: a systematic review and meta-analysis. Eur Heart J. 2010;31:1865–1871.
6. London GM, Blacher J, Pannier B, et al. Arterial wave reflections and survival in end-stage renal failure. Hypertension. 2001;38:434–438.
7. Tropeano AI, Boutouyrie P, Pannier B, et al. Brachial pressure-independent reduction in carotid stiffness after long-term angiotensin-converting enzyme inhibition in diabetic hypertensives. Hypertension. 2006;48:80–6.
8. 8. Mackenzie IS, McEniery CM, Dhakam Z, et al. Comparison of the effects of antihypertensive agents on central blood pressure and arterial stiffness in isolated systolic hypertension. Hypertension. 2009;54:409–13.
9. 9. Tomiyama H, Yoshida M, Yamada J. Arterial-cardiac destiffening following long-term antihypertensive treatment. Am J Hypertens. 2011;24:1080–86.
10. Kithas PH, Supiano MA. Spironolactone and hydrochlorthiazide decrease vascular stiffness and blood pressure in geriatric hypertension. J Am Geriatric Soc. 2010;58:1327–32.

11. Palombo C, Malshi E, Morizzo C. Arterial wave reflection during antihypertensive therapy with barnidipine: a 6-month open label study using an integrated cardiovascular ultrasound approach in patients with newly diagnosed hypertension. Clin Ther. 2009;31(12):2873–85.
12. Dart AM, Cameron JD, Gatzka CD. Similar effects of treatment on central and brachial blood pressures in older hypertensive subjects in the Second Australian National Blood Pressure Trial. Hypertension. 2007;49:1242–47.
13. Asmar RG, London GM, O´Rourke ME, et al. Improvement in blood pressure, arterial stiffness and wave reflections with a very low-dose perindopril/indapamide combination in hypertensive patients: a comparison with atenolol. Hypertension. 2001;38 (4):922–6.
14. Boutouyrier P, Achouba A, Trunet P, et al. Amlodipine-valsartan combination decreases central systolic blood pressure more effectively than the amlodipine-atenolol combination: the EXPLOR study. Hypertension. 2010;55(6):1314–22.
15. Topouchian J, Asmar R, Sayegh F. Changes in arterial structure and function under trandolapril-verapamil combination in hypertension. Stroke. 1999;30(5):1056–1064.
16. Matzui Y, Eguchi K, O'Rourke M. Differential effects between a calcium channel blocker and a diuretic when used in combination with angiotensin II receptor blocker on central aortic pressure in hypertensive patients. Hypertension. 2009;54:716–723.
17. Mahmud A, Feely J. Beta-blockers reduce aortic stiffness in hypertension but nebivolol, not atenolol, reduces wave reflection. Am J Hypertens. 2008;21:663–667.
18. Shah NK, Smith SM, Nichols WW. Carvedilol reduces aortic wave reflection and improves left ventricular/vascular coupling: a comparison with atenolol (CENTRAL study). J Clin Hypertens. 2011;13(12):917–924.
19. Manisty C, Mayet J, Tapp RJ. Atorvastatin treatment is associated with less augmentation of the carotid pressure waveform in hypertension: a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Hypertension. 2009;54(5):1009–13.
20. Mazzone T, Meyer PM, Feinstein SB. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. JAMA. 2006;296:2572–2581.
21. Hughes TM, Althouse AD, Niemczyk NA. Effects of weight loss and insulin reduction on arterial stiffness in the SAVE trial. Cardiovasc Diabetol. 2012;10:111–114.
22. Cooper J, Buchanich J, Youk A, et al. Reductions in arterial stiffness with weight loss in overweight and obese young adults: potential mechanisms. Atherosclerosis. 2012;223(2):485–490.

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Statin myopathy as a clinical problem. Can we help?

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Abstract

Objectives

Statins reduce low density lipoprotein (LDL) cholesterol and prevalence of atherosclerosis. Unfortunately, as statins also have side effects, e.g. dyspepsia, hair loss, insomnia and statin- myopathy, some statins cannot be administered in sufficient doses or administered at all. The aim of this study was to demonstrate the effect of coenzyme Q10 in patients with statin myopathy.

Design/setting

The aim of our study was to show the effect of administration of coenzyme Q10 (CoQ10) by statin myopathy. 28 patients (18 women and 10 men) aged 60.6±10.7 years were observed. Muscle weakness and pain was monitored. Pursuance of muscle pain and weakness were performed prior to administration of CoQ10 and after 3 and 6 months of dosing. Statistical analysis was performed using Friedman test, Annova and Students t-test.

Results and conclusion

Pain decreased on average by 53.8% ($P<0.0001$), muscle weakness by 44.4% ($P<0.0001$). After administration of CoQ10 over 6 months, muscle pain and sensitivity significantly decreased.

Key words

Statin, side effect, statin-myopathy, coenzyme Q10

Acknowledgement

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Introduction

Statins, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, significantly decrease cardiovascular morbidity and mortality. This effect is not only due to their hypolipidemic effects, in particular by lowering total and LDL cholesterol, but also due to pleiotropic effects.

Almost every patient with increased cardiovascular (CV) risk benefits from statin treatment. Side effects may impede its administration. Rare side effects such as gastrointestinal disorders, hair loss, insomnia, etc. do not represent a major clinical problem. The most concerning and the most common adverse reaction to statin administration is muscle damage — myopathy. The prevalence is diverse and ranges from 1–5% [1], according to randomized studies, up to 9-20%, according to, for example, the PRIMO study dealing primarily with statin myopathy [2]. Differences in prevalence may be explained by the dose and the types of statin administered, by concomitant medication, and, in particular, by the study design [3]. Nowadays, genetic polymorphisms predisposing to the emergence of statin myopathies are discussed [4].

Etiopathogenesis of statin myopathy has not been entirely clarified. Statins, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (Figure 1), affect not only the synthesis of cholesterol, but also other metabolic products. Reducing cholesterol levels may contribute to its depletion in the myocyte membrane structure and subsequently to its instability [5]. Another possible mechanism involves influencing metabolic regulations mediated by isoprenoids (farnesyl pyrophosphate and geranylgeranyl pyrophosphate). Reducing their production may result in decreasing production of regulatory proteins, whose absence leads to early apoptosis. Further, a decrease in the synthesis of these intermediate products, results in a decrease in the synthesis of CoQ10.

Coenzyme Q10 (ubiquinone, CoQ10) is a lipophilic, water-insoluble substance, which has an effect on electron transport and energy production (adenosine triphosphate (ATP)) in the mitochondria [6]. CoQ10 has an antioxidant effect on mitochondria and cell membranes, protects membrane lipids from oxidation and thereby stabilizes biological membranes [7]. It also inhibits the oxidation of LDL cholesterol. CoQ10 is partly consumed as food [e.g.: corn, nuts, soy, meat (poultry, pork or beef), fish (sardines, mackerel), broccoli] and partly synthesized in the body. Its levels decline with age [8]. In humans, it is present in a (biologically) active, reduced form (ubichinol). It is found in food in an oxidized or mixed form. Absorption of CoQ10 (ubiquinone) is low. More than 60% of an oral dose of CoQ10 is excreted in faeces. In addition, the absorption of CoQ10 varies greatly, depending not only on food intake, but also on the amount of fats in the diet. The absorption is lower on an empty stomach and increased with food containing fat. CoQ10 is distributed in blood even within the lipoprotein fractions including very low density lipoprotein (VLDL), LDL and high density lipoprotein (HDL). The maximum serum concentration of CoQ10 is stabilised after approximately three to four weeks of daily use. Then, with continued dosing, the concentration plateaus. The major route for CoQ10 elimination is via bile [9].

The aim of our pilot project was to determine whether patients with muscle symptoms benefit from the use of reduced form of coenzyme Q10, while administering statins.

Materials and methods

30 patients with symptomatic myopathy with statin treatment were monitored. Their subjective symptoms were classified as moderate or light. One patient was removed from the monitoring process due to lack of cooperation and a second patient terminated their participation prematurely. Data from 28 patients (18 women and 10 men) aged 60.6±10.7 years with BMI 28.5±2.5 kg/m^2 were statistically processed.

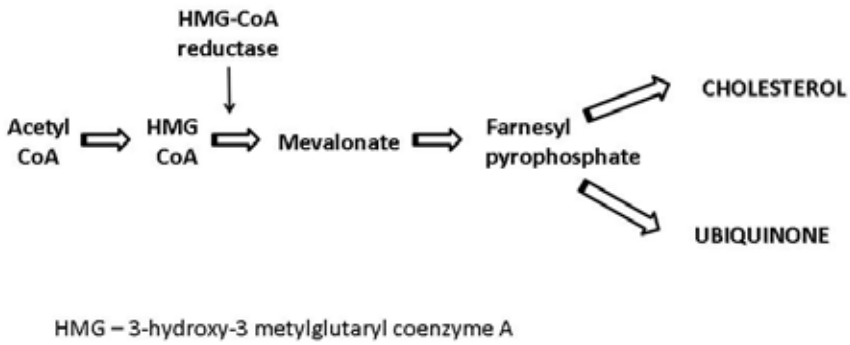

Figure 1. Effect of statin to HMG-CoA reductase

9 patients received atorvastatin at a daily dose (DD) of 5, 10, and 20 mg (6 patients at DD of 20 mg); 7 patients received rosuvastatin at DD of 5, 10, 20, 40 mg; 6 patients received simvastatin at DD of 20 mg; 3 patients received fluvastatin at DD of 80 mg; 2 patients received lovastatin (one 40 mg and the other 10 mg); and one patient received pravastatin at DD of 10 mg. They used the same dose and type of statin throughout duration of the study. On average, patients were treated with a constant daily dose of one type of statin for about 3 years, where the total length of statin treatment was 9±5 years. They were treated with a statin only, not with any other hypolidemic drug (niacin, fibrate etc.). Patients with renal insufficiency, severe hepatopathy, and overt hypothyroidism were not included in the study.

Patients underwent the following protocol: 4 medical ward rounds — 1st ward round (-1 month), 2nd ward round (0 month), 3rd ward round (3rd month) and 4th ward round (6th month). During every visit, a medical history was taken, including a pharmacology. Patients were physically examined, biochemical analysis was performed (liver test, creatinphosphokinase, total, LDL, HDL cholesterol) and sampling to determine the serum concentrations of CoQ10. The lab tests were not performed immediately after weekends. At the same time, patients were presented with a likert scale depicting a range of muscle pain and weakness, where they marked the level of their difficulties on a scale of one to ten.

When comparing the monitored parameters (muscle pain, weakness, lab tests, blood pressure, heart rate, weight) between the ward round № 1 (screening) and the ward round № 2 (initial administration of CoQ10), there was no statistical difference in any of the considered parameters, from which we assumed a stabilised condition of the patients.

Between the ward round № 2 and the ward round № 4, i.e. for the period of six months, patients were given a reduced CQ10 at a dosage of 30 mg twice a day (Q max Active, SVUS Pharma a.s.).

Statistical analysis for quantities of Gaussian distribution was performed by using the Annova test, T-test, and using the Friedman test for quantities of non-Gaussian distribution.

Patients signed an informed consent before entering the study and the study was conducted in accordance with the rules of good clinical practice.

Results

The effect of reduced CQ10 administration on muscle symptoms (pain and weakness) was evaluated using the above described scale before the CoQ10 administration, after 3 months, and after 6 months. After six months of reduced CoQ10 administration, there was a statistically significant decrease in both subjective muscle pain and weakness. Muscle pain decreased on average by 53.8% (P<0.0001), muscle weakness by 44.4% (P<0.0001) (Figures 2 and 3).

Creatine kinase (CK) levels were monitored in all patients. CK levels in individual ward rounds showed no statistically significant differences and showed substantial interindividual variability.

Furthermore, the plasma CoQ10 level was observed in patients during the monitoring process, particularly prior to administration, in the 3rd and 4th rounds. After three months of administration of reduced CoQ10, the average plasma CoQ10 levels increased by 28% (P<0.02). After six months of administration, plasma CoQ10 levels increased on average by 194% (from 0.903 μg/ml to 2.66 μg/ml; P<0.0001) (Table 1).

At the same time, biochemical indicators were monitored as secondary parameters. After administration of reduced CoQ10, there was a statistically sig-

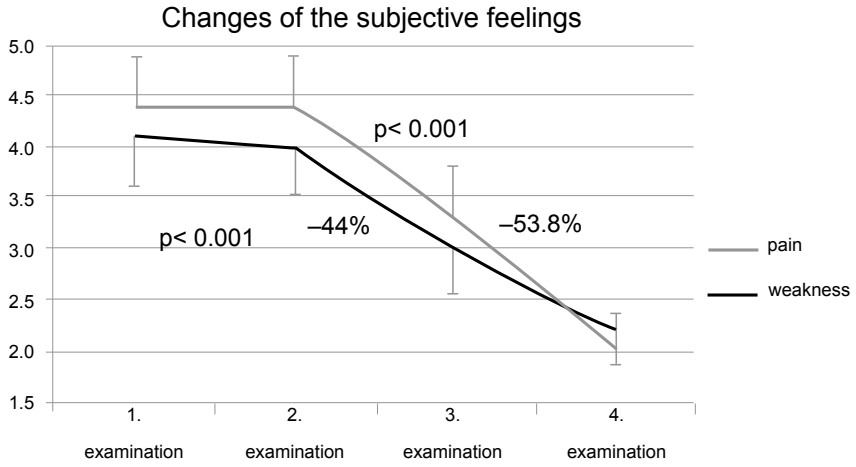

Figure 2. Percentage of subjectively perceived changes

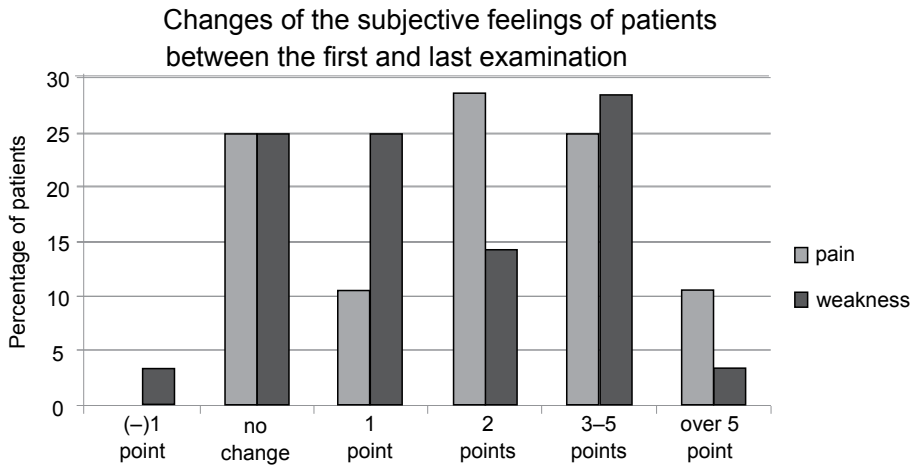

Figure 3. Changes of the subjective feelings in points

nificant increase in levels of apolipoprotein A-I (Apo A-I). From the original average values of 1.55±0.2 g/l on the visit 2, there was an increase to 2.00±0.2 6g/l on the visit 3, which represents an average increase of 29% (P<0.0001). During a six-month administration of reduced CoQ10, there was also a slight but statistically significant (P<0.05) reduction in LDL cholesterol.

Using the Systematic Coronary Risk Evaluation (SCORE) system [10], the CV risk for patients was calculated. After a 6-month administration of CoQ10, there was a statistically significant reduction in CV risk (from 8.5%±5.8% to 4.7±3.1%; P<0.0002).

Table 1. **Table of monitored values**

	Visit 1	Visit 2	Visit 3	Visit 4
pain (point)	4.4 ± 2.6	4.4 ± 2.6	3.3 ± 2.5	2.04 ± 2.0
weakness (point)	4.1 ± 2.3	4.0 ± 2.6	3.0 ± 2.4	2.2 ± 1.8
CK (ukat/l)	3.1± 1.94	2.84 ± 1.47	3.1 ± 1.6	2.95 ± 2.27
coenzyme Q10 (ug/ml)	0.910 ± 0.34	0.903 ± 0.27	1.15 ± 0.27	2.66 ± 0.59
Apo A-I (mmol/l)	1.5 ± 0.4	1.5 ± 0.2	1.9 ± 0.2	2.0 ± 0.3
LDL cholesterol (mmol/l)	3.1 ± 0.8	3.0 ± 0.7	2.9 ± 0.6	2.7 ± 07

Discussion

Due to a huge increase in prescribing statin treatment, there is unfortunately a simultaneous increase in the prevalence of statin myopathy [11]. Several recently published studies have addressed the influence of CoQ10 on statin myopathy, with ambiguous results. We report decreased muscle pain and muscle weakness after a 6-month supplementation of reduced CoQ10.

Young *et al.* [12] published a double-blind placebo-controlled study, where they administered 200 mg of CoQ10/day together with 10–40 mg of simvastatin to 44 patients. Although they observed elevated plasma levels of CoQ10, they did not notice any statistically significant subjective differences between placebo and treatment branches. They administered CoQ10 only for 12 weeks, which might be too short a period of time to display the full effect. In contrast, Caso *et al.* [13] administered 100 mg CoQ10 versus 400 IU of Vitamin E to 32 patients with hypercholesterolemia and statin myopathy. In the branch treated with CoQ10, there was a decrease in muscle pain of 38%, while in the branch treated with Vitamin E no difference was recorded. Lastly, Mabuchi *et al.* [8] administered CoQ10 to patients treated by 10 mg of atorvastin with an elevation in CK, aspartate aminotransferase (AST) and alanine transaminase (ALT). After 16 weeks of dosing, there was no change of the monitored parameters. No effect on muscle myopathy was monitored. However, we know that CK levels do not correlate with patients' reported degree of inconvenience.

In our study, the levels of CoQ10 were measured in serum. According to some studies [14,15], however, plasma levels of CoQ10 do not fully correlate with the intracellular levels in myocytes. As documented by other works, muscle CoQ10 levels decrease after statin treatment. In contrast, Päivä *et al.* [16] disproved this theory in their work. In patients treated with high-dose atorvastatin, the authors did not observe a change of muscle CoQ10 levels in muscle biopsies before and during administration of statin.

Limitations of our study include processing in a group of patients treated with heterogeneous statin medication, the absence of a placebo group and, undoubtedly, the small sample size.

Surprisingly positive results in lipidogram are very suspectly subject to a better compliance of patients to treatment.

Although these results cannot be generalized, they support the previously published data on the potential benefits of supplementation of CoQ10 in patients with statin-induced myopathy. This hypothesis is supported by the pathophysiological mechanisms finding their use in the direct or statin-mediated effects on skeletal muscle cells. Only a large, placebo-controlled clinical trial can answer the question definitively, whether coenzyme Q10 prevents the formation or at least reduces the clinical symptoms of muscle toxicity of statins.

Conflict of interest: None declared

References

1. Armitage J. The safety of statins in clinical practice. Lancet. 2007;370:1781–1790.
2. Bruckert E, Hayem G, Dejager S, et al. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients — the PRIMO study. Cardiovasc Drugs Ther. 2005;19:403–14.
3. Harper CR, Jacobson TA. Evidence-based management of statin myopathy. Curr Atheroscler Rep. 2010;12:322–330.
4. Hubacek JA, Adamkova V, Zidkova K, et al. Statin pharmacokinetics. Vnitr Lek. 2008;54:62–67.
5. Carel FS, Stalenhoef AFH. Effect of ubiquinone (coenzyme Q10) on myopathy in statin users. Curr Opin Lipidol. 2008;19:553–557.
6. Harper CR, Jacobson TA. The broad spectrum of statin myopathy: from myalgia to rhabdomyolysis. Curr Opin Lipidol. 2007;18:401–408.
7. De Pinieux G, Chariot P, Ammi-Saïd M, et al. Lipid-lowering drugs and mitochondrial function: effects of HMG-CoA reductase inhibitors on serum ubiquinone and blood lactate/pyruvate ratio. Br J Clin Pharmacol. 1996;42:333–337.
8. Mabuchi H, Nohara A, Kobayashi J, et al. Effects of CoQ10 supplementation on plasma lipoprotein lipid, CoQ10 and liver and muscle enzyme levels in hypercholesterolemic patients treated with atorvastatin: a randomized double-blind study. Atherosclerosis. 2007;195:e182–189.
9. Young JM, Molyneux SL, Florkowski CM, et al. Pharmacokinetic comparison of a generic coenzyme Q10 solubilizate and a formulation with soybean phytosterols. Phytother Res. 2012;26:1092–1096.
10. Vaverková H, Soška V, Rosolová H, et al. Doporučení pro diagnostiku a léčbu dyslipidemií v dospělosti, vypracované výborem České společnosti pro aterosklerózu [Recommendations for the diagnosis and treatment of dyslipidemia in adulthood, developed by the Board of the Czech Society for Atherosclerosis]. Cor Vasa. 2007;49:K73–K86. Czech.
11. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. JAMA. 2003;289:1681–1690.
12. Young JM, Florkowski CM, Molyneux SL, et al. Effect of coenzyme Q (10) supplementation on simvastatin-induced myalgia. Am J Cardiol. 2007;100:1400–1403.
13. Caso G, Kelly P, McNurlan MA, Lawson WE. Effect of coenzyme q10 on myopathic symptoms in patients treated with statins. Am J Cardiol. 2007;99:1409–1412.
14. Laaksonen R, Jokelainen K, Sahi T, et al. Decreases in serum ubiquinone concentrations do not result in reduced levels in muscle tissue during short-term simvastatin treatment in humans. Clin Pharmacol Ther. 1995;57:62–66.
15. Laaksonen R, Jokelainen K, Laakso J, et al. The effect of simvastatin treatment on natural antioxidants in low-density lipoproteins and high-energy phosphates and ubiquinone in skeletal muscle. Am J Cardiol. 1996;77:851–854.
16. Päivä H, Thelen KM, Van Coster R, et al. High-dose statins and skeletal muscle metabolism in humans: a randomized, controlled trial. Clin Pharmacol Ther. 2005;78:60–68.

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EXPERT OPINION

Atherosclerosis across 4000 years of human history: the HORUS study of four ancient populations

A report based on presentations delivered by Professor **Dr John Harold**, Immediate Past President, American College of Cardiology

Horus Study Group:
Randall C Thompson, Adel H Allam, Guido P Lombardi, L Samuel Wann, M Linda Sutherland, James D Sutherland, Muhammad Al-Tohamy Soliman, Bruno Frohlich, David T Mininberg, Janet M Monge, Clide M Vallodolid, Samantha L Cox, Gomaa Abd el-Maksoud, Ibrahim Badr, Michael I Miyamoto, Abd el-Halim Nur el-din, Jagat Narula, Caleb E Finch, Gregory S Thomas*

Report prepared by:
Natalia S. Kurbatova, MD, medical journalist

Summary
Traditionally, atherosclerosis is considered to be a disease of modern human beings, which is caused by the combined action of many negative factors from today's environment on the body. Nevertheless, as it was shown in an American study of four ancient populations of different geographical locations and lifestyles, the prevalence of atherosclerosis in our ancestors was also quite high.

Keywords
Atherosclerosis, computed tomography, ancient populations

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When did mankind first face with atherosclerosis in the long history of its development? Whether this disease is caused by lifestyle, organism aging, or any other reason? These and other issues for many years have been interested not only to cardiologists, but to other specialists. On the background of doubling life expectancy in developed countries in the period from 8 to 10 centuries, atherosclerotic lesions of vessels displaced infectious diseases as the leading cause of mortality. In this regard, for a long time in the scientific community there was a view that the onset of atherosclerosis was associated primarily with the influence of environmental factors. Consequently, simulation of pre-industrial and even before agricultural lifestyles allows the modern mankind to avoid if not atherosclerosis, but its clinical manifestations.

In the ancient human societies who lived in very dry, hot or cold climates there was a tradition of mummification of the dead independently of each other. Thus, the various pre-industrial cultures created to modern scientists all conditions for a natural experiment, which was to examine the well-preserved mummies by computed tomography (CT) for the presence of atherosclerotic lesions in the vascular system. Such lesions in the form of calcium salt deposits are a typical feature of mature atherosclerotic plaques and perfectly visible on CT images.

Pronounced signs of atherosclerosis found at autopsy of several Egyptian mummies of 18th dynasty (1550-1292 BC), were mentioned in 1911 by Sir Mark Armand Ruffer, who is the founder of the Egyptian paleopathology. The results of his work published in the Pathology and Bacteriology journal, indicate the presence of foci of calcification in the aorta, which were identified by direct examination of mummies.

Ancient Egyptians knew quite a lot about heart and vascular diseases. The Ebers Papyrus (1555 BC), which is a kind of ancient Egyptian medical encyclopedia, provides, perhaps, the very first in general in the history of cardiology and mankind description of myocardial infarction: «If thou examinst a man for illness in his cardia, and he has pains in his arms, in his breast and on one side of his cardia...it is death threatening him...».

It is believed, however, that particular culture and lifestyle played a special role in the predisposition to the development of atherosclerosis in ancient Egypt. Besides, mummification was distributed mainly among people of high socio-economic status, which also reflected on their life experiences and risk factors.

In this context, a group of US experts led by Professors Randall C. Thompson and Gregory Thomas Gregory S. Thomas conducted a study of four ancient populations that lived in various climatic and geographical areas in the time interval of 4000 years. The results of the HORUS (named after the Egyptian god Horus) study were published in the Lancet in March 2013 [1]. The purpose of the study was to examine the prevalence of atherosclerosis among ancient cultures of different geographical and temporal residence.

Using CT scan of the whole body, experts studied 137 mummies from completely different geographical regions. Only mummies in good condition and presumably belonged to adults were selected for this study. 76 Egyptian mummies (pre-dynastic era, around 3100 BC) were obtained for the study from the *Egyptian Museum of Antiquities* in Cairo, the *Bowers Museum* in California, and the *Nelson-Atkins Museum of Art* (Missouri, USA). Mummies of ancient Peruvians (51 bodies), who lived on the territory of modern South America, gave the *Museo de Sitio Arturo Jiménez Borja – Puruchuco* (Lima, Peru), situated very high in the mountains, which contributes to the conservation of natural bodies. Peruvian tradition of burying their dead in a sitting position in bags also contributed to the preservation of tissues.

5 Unangan mummies (Aleuts, lived on the volcanic Kagamil Island, which is located in the Bering Sea, not far from modern Siberia) were obtained from the *National Museum of Natural History* (Washington, USA). Mummies of the Pueblo Indians (5 mummies) were excavated from caves in predominantly modern Utah (South West of North America) and made available to researchers by the *Museum of Archaeology and Anthropology*, *University of Pennsylvania* (Philadelphia, USA).

Thus, all examined mummies belonged to people of completely different habitat, lifestyle, nutrition, physical activity and social status. Unlike the Egyptians, where the upper class prevailed among the mummified individuals, representatives of other nations belonged to farmers and hunter-gatherers.

In the interpretation of obtained CT images seven highly qualified specialists – 5 cardiologists and 2 radiologists – took part. Their task was to, first, detect most cardiovascular tissue, and secondly, to determine the presence or absence of calcification in the vessel wall and the heart. Diagnosis of atherosclerosis was considered significant when foci of calcification were found in the wall of exactly determined by CT scanning artery. When areas of calcification were on the proposed course of the artery (which itself was absent), the diagnosis of atherosclerosis was seen as possible.

The most studied mummy was the body of Ahmose-Meritamon, an Egyptian princess who lived in Thebes during the 18th Dynasty (1580-1550 BC) and died at the age of 40. Her name translated from the ancient Egyptian means «Child of the Moon, Beloved of Amun». A thorough investigation of her mummy with CT image reconstruction showed widespread atherosclerosis with lesions of the main large arteries, which in the modern world would certainly require surgery.

Results of the HORUS study

In 47 (34%) of 137 examined mummies, the signs of overt or possible atherosclerosis were showed in: 17 (39%) of 44 female mummies and 30 (39%) of 77 male mummies. The disease was found in all 4 investigated populations, and the differences between them were insignificant – the prevalence of atherosclerosis varied from 38% in the Egyptian population to 60% of the Unangan population. As expected, the incidence of atherosclerosis and the severity of its manifestations increased with age.

Because the heart tissues of many mummies (61%) were absent, to estimate the true prevalence of atherosclerotic lesion of the heart and coronary arteries was not possible.

What is the reason for such a high incidence of atherosclerosis among ancient people? Should immediately eliminate tobacco use, as in the ancient world it was not common, and therefore can not serve as a risk factor for cardiovascular disease.

With regard to a lifestyle, the ancient Egyptians and the inhabitants of Peru were farmers who raised domesticated cattle; Pueblo Indians engaged in farming and gathering; Unangan – gathering and hunting, and agriculture was not known to them. Vegetarianism for representatives of all 4 cultures was not typical. Physical activity due to the lack of means of transport was very high (except for the upper class of ancient Egypt).

Food, as well as climatic conditions, for all 4 populations differed greatly. Availability of fish and wildlife was high everywhere, but if cattle served as the main source of protein for ancient Egyptians, the Unangans had almost exclusively fish diet. Thus, the Egyptian diet of those who held in their lifetime a high socioeconomic status consisted mostly from saturated fats, which serves as a risk factor for atherosclerosis. In parallel with this, for all 4 populations a huge consumption of the most diverse plant foods was characteristic.

For all ancient people, included in the study, the use of fire for cooking and heating homes was typical. However, while the ancient Egyptians and Peruvians prepared food outdoors, Pueblo Indians and Unangan preferred closed hearths as they lived underground or in semi-dugouts. And this, in turn, contributed to the constant inhalation of smoke and combustion products that could play some role in the development of atherosclerosis.

Certain meaning in atherogenesis researchers assigned to infections which were an integral aspect of everyday life of ancient people and the leading cause of mortality. The high prevalence of chronic infections and inflammation in the old days could provoke inflammatory aspects of atherosclerosis. This is consistent with a more rapid emergence of atherosclerotic lesions in modern humans suffering from systemic connective tissue diseases. In this regard, the researchers plan in future to conduct DNA analysis and biopsy of tissues from all mummies to assess the immune status and other genetic risk factors for atherosclerosis.

Conclusion

The HORUS study experts revealed the presence of atherosclerosis in different cultures of very wide geographical spread on a large historical period of time: about 4,000 years. Atherosclerosis, including coronary artery disease, has been found even in those ancient populations where this disease was not expected, namely hunters-gatherers, who had a very active life.

The study results allowed experts to conclude that atherosclerotic disease among ancient peoples was quite common, and in the cultures which were different not only geographically and genetically, but also in lifestyle, food, farming, and etc.

The presence of atherosclerosis (quite pronounced in some cases) in living long before the modern human people suggests that the disease may be a natural component of the aging process, not just a characteristic of a particular lifestyle or diet.

Conflict of interest: None declared

References

1. Thompson RC, Allam AH, Lombardi GP, et al. Atherosclerosis across 4000 years of human history: the Horus study of four ancient populations. Lancet. 2013 Apr 6;381(9873):1211-22.

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Report
on the III International Forum of Cardiology and Internal Medicine, 24–26 March 2014, Moscow

The III International Forum of Cardiology and Internal Medicine (the Forum) has now successfully concluded its work. The Forum was held from 24 to 26 March 2014 in Moscow in the new building of the Presidium of the *Russian Academy of Sciences*.

The Forum was supported by the *Ministry of Healthcare of the Russian Federation*, *Department of Healthcare of Moscow*, *Ministry of Healthcare of Moscow Region*, *Russian Society of Cardiology*, *World Heart Federation*, *Russian Academy of Science,* and the *Cardioprogress Foundation*.

Co-Chairmen of the Forum were Rafael G. Oganov, Academician of the *Russian Academy of Sciences* and Evgeny V. Shlyakhto, Academician of the *Russian Academy of Sciences*.

Chairman of the Scientific Committee for the Forum was Yury A. Vasyuk.

This Forum is one of the large-scale scientific activities for professionals working in the field of cardiology and related fields of medicine. The Forum was attended by 1,680 experts from Russia, the CIS countries (Uzbekistan, Kazakhstan, Tajikistan, Belarus, Azerbaijan, Armenia) and the far abroad (Finland, Czech Republic, Romania, Switzerland, UK).

Information partners for the Forum included the following journals: Cardiovascular Therapy and Prevention, Russian Journal of Cardiology, Rational Pharmacotherapy in Cardiology, Cardiology, Poliklinika (Polyclinic), and newspapers: Meditsinskiy vestnik (Medical Bulletin), and Cardiology Today.

All the stages of preparation for the Forum and its programme were covered on the official website for the Forum: www.cardioprogress.ru, as well as on partners' websites: www.roscardio.ru, www.internist.ru, www.medtusovka.ru.

The high scientific and educational level of the Forum's activities was achieved by participation of leading Russian and foreign scientists, clinicians, talented teachers and healthcare policy-makers. During the opening ceremony of the Forum, speeches were given by Professor Alexander O. Nedoshivin, General Secretary of the *Russian Society of Cardiology;* Pekka Puska (Finland), a leading international expert; Sergey A. Boytsov, a main specialist in preventive medicine for the *Ministry of Healthcare of the Russian Federation* and Director of the *National Research Centre for Preventive Medicine of the Ministry of Healthcare of the Russian Federation*; and, Lukas Zlatohlavek (Czech Republic).

- The main scientific topics of the Forum were:
- Improvement of cardiac patients' care
- Emergency and first responder (ambulance) help in cardiovascular diseases
- Clinical examination of cardiac patients
- Prevention of cardiovascular disease at population and individual levels
- New medical technologies in prevention and treatment of cardiac patients
- Problems in rehabilitation of cardiac patients

For the official participation of specialists in the Forum, decrees and orders were issued by the *Ministry of Healthcare of the Russian Federation, Department of Healthcare of Moscow,* and the *Ministry of Healthcare of Moscow Region*.

An information letter and scientific programme for the Forum were advertised in the list of activities by *World Heart Federation*, *European Society of Cardiology,* and the *Russian Society of Cardiology*.

The opening ceremony of the Forum was broadcasted online at www.cardioprogress.ru. Preparation

and work of the Forum was covered by social networks: facebook, twitter, vkontakte.

For the Forum, the scientific programme, book of abstracts (which included about 350 works), exhibition catalogue of domestic and foreign medicines, medical devices, modern information technologies and specialized publications were published.

The scientific programme included participation from Russian scientific societies and associations, including the *Armenian Cardiologists Association*, Tajik Society of Cardiology, *Belorussian Scientific Society of Cardiologists*, and the Azerbaijan Society of Cardiology. The scientific programme included: two plenary sessions with the participation of leading international experts, scientific sessions, satellite symposia, lectures, round table discussions, schools for doctors, clinical debates, and a two-day poster session. The Forum also held a symposium of young scientists with the participation of six speakers, aged up to 35 years old, from Moscow and five other Russian cities and regions. The overall programme of the Forum reflected the latest advances in the diagnosis, prevention and treatment of cardiovascular disease and other internal diseases. In general, the scientific programme aroused great interest amongst a broad medical community.

The Organizing Committee awarded diplomas for contributions to areas relating Cardioprogress Foundation activities, to: Vladimir P. Tyurin, chief physician of the *Department of Healthcare of Moscow;* Yan L. Gabinsky, for the development of cardiac services; Elman Z. Alekperov and U.K. Kamilova, for their contribution to the strengthening of international cooperation and collaboration; L.A. Khaisheva, for her contribution to the implementation of regional cardiac projects; Alan Cole, for his contribution to strengthening of international collaboration between the World Heart Federation and the C*ardioprogress* Foundation; Richard Williams, for contribution to publication of the International Heart and Vascular Disease Journal; and Pekka Puska, for his contribution development of a global strategy for the prevention of cardiovascular disease.

The centrepiece of the Forum exhibition was a stand representing the Cardioprogress Foundation and the Organizing Committee, which was very popular among Forum participants. On the stand, information bulletins, including Cardiology Today newspaper, the second edition of the International Heart and Vascular Disease Journal, scientific literature, and souvenirs were presented. Exhibition of domestic and foreign medicines, medical devices, modern information technologies and specialized publications were closely associated with the scientific programme of the Forum. Forum participants had the opportunity to not only learn about the latest medicines, presented at the stands by leading pharmaceutical companies, but also to get objective information on the clinical efficacy of medicines at symposia, discussions, seminars, and lectures.

It should be emphasized that registration and participation in the Forum was free. All registered participants received a bag with Forum materials. As part of the opening ceremony there was a concert of classical music. Forum delegates enjoyed a free buffet on two occasions, which also presented an opportunity to network with colleagues.

During the Forum, a hall was provided as a place for working and Wi-Fi for free internet access. Delegates received certificates to demonstrate attendance at the Forum. 138 people were involved in the administration and technical support for the Forum.

At the final plenary session, the Co-Chairman of the Forum, Rafael G. Oganov, made a report on its results. A joint meeting of the Forum's Organizing Committee, *Cardioprogress Foundation*, and the *Heart World Federation* was held on 26 March 2014. Rafael G. Oganov delivered a report on the 3-year activity and development prospects of the Cardioprogress Foundation. Alan Cole announced plans and prospects for collaboration between the *Cardioprogress Foundation* and the *World Heart Federation*. Mehman M. Mamedov spoke about interaction of the *Cardioprogress Foundation* with government and other relevant organizations. A report on the activities of the International Heart and Vascular Disease Journal was delivered by Richard Williams. G.Y. Maslennikova highlighted the prospects for the expansion of publishing and educational activities of the Cardioprogress Foundation.

Co-Chairman of the III International Forum of Cardiology and Internal Medicine, Academician,
Rafael G. Oganov
Chairman of the Organizing Committee of the III International Forum of Cardiology and Internal Medicine, Professor,
Mehman N. Mamedov

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and Vascular Disease Journal • Volume 2, Number 3, June 2014
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Guidelines for authors

International Heart and Vascular Disease Journal
Requirements for Submission and Publication

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

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

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

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1. Submission requirements and publishing policy

1.1. A manuscript should be submitted to the following e-mail address: submissions.ihvdj@gmail.com

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

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

2. General recommendations for submission of original scientific works

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

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

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

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

3. Publication of uncontrolled trials results

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

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

4. Ethical aspects

4.1. Trials should be conducted in accordance with principles of "good clinical practice". Participants of a trial should be informed about the purpose and main aims of the trial. They must sign to confirm their written informed consent to participate in the trial. The «Material and methods» section must contain details of the process of obtaining participants informed consent, and notification that an Ethics Committee has approved conducting and reporting the trial. If a trial includes radiological

methods it is desirable to describe these methods and the exposure doses in the «Material and methods» section.

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

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

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5.2. If more than 4 authors are indicated in the author's list, it is desirable to describe the contribution of each author in a covering letter. If the authorship is attributed to a group of authors, all members of the group must meet all criteria for authorship. For economy of space, members of the group may be listed in a separate column at the end of the manuscript. Authors can participate in the submitted manuscript in the following ways: 1) contributing to the concept and research design or analyzing and interpreting data; 2) substantiating the manuscript or checking the intellectual content; 3) providing final approval for the manuscript. Participation solely in collection of data does not justify authorship (such participation should be noted in the Acknowledgements section). Manuscripts should be submitted with a covering letter containing the following information: 1) the manuscript has not been submitted to any other media; 2) the manuscript has not been published previously; 3) all authors have read and approved the manuscript's content; 4) the manuscript contains full disclosure of any conflict of interests; 5) the author/authors confirm responsibility for the reliability of the materials presented in the manuscript. The author responsible for the correspondence should be specified in the covering letter.

6. Conflict of interests/financing

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

7. Manuscript content

7.1. Title page

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

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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).

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Periodicals

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

Sources in Russian with transliteration:

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

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

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no indications like "volume", "№", "pages". Russian periodicals often have no indication of volume or numbering of pages within a year. In this case the number of an issue should be specified in brackets.

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

Chapters in a book

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

Sources in Russian with transliteration:

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

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

Books

Sources in Russian with transliteration:

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

Websites

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

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

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