Volume 2, Number 2, February 2014
ISSN: 2309-0901
http://cardioprogress.ru

International Heart and Vascular Disease Journal

Journal of the Cardioprogress Foundation

New USA recommendations for cardiovascular prevention

Echocardiographic prediction of preservation of left ventricular function after surgical correction for severe aortic regurgitation

Genetic polymorphism of endothelial nitric oxide synthase in coronary artery disease

WORLD HEART FEDERATION®

World Congress of Cardiology

Scientific Sessions 2014
4-7 May 2014 | Melbourne, Australia

25x25: At the heart of global health

GLOBAL PLATFORM

For cardiovascular disease specialists and public health professionals to share knowledge and network with their peers

WORLD LEADING EXPERTS

Presenting 150 sessions on cardiology, policy and public health

LATEST SCIENTIFIC FINDINGS

Featured in over 1,000 new abstracts on prevention, diagnosis and treatment of cardiovascular disease

INTERNATIONAL CONGRESS WITH A SPOTLIGHT ON REGIONAL ISSUES

Highlighting local successes in rheumatic heart disease and tobacco cessation

BEST-PRACTICE SHARING

Across different resource settings with a highlight on how international learning can be adapted to national circumstances

UNITING EFFORTS TO REDUCE PREMATURE CVD DEATHS 25% BY 2025

Through mobilizing the CVD community and working with the WHO

www.worldcardiocongress.org

Heart Foundation

The Cardiac Society of Australia and New Zealand

MELBOURNE
VICTORIA AUSTRALIA

25 by 25

International Heart and Vascular Disease Journal
Journal of the Cardioprogress Foundation

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

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

Contact details:
Cardioprogress Foundation and Editorial Office:
Room 213, Building 2, Prospect Gostinichny 6, Moscow 127106, Russia
Editorial Office tel.: (+7) 965 236 1600
Official website: www.cardioprogress.ru

Editorial correspondence should be sent to:
Mehman Mamedov, Deputy Editor,
editor.ihvdj@gmail.com
Articles for publication should be sent to:
Anna Arteyeva, Associate Editor,
submissions.ihvdj@gmail.com

Printed in Russia

International Heart and Vascular Disease Journal

Journal of the Cardioprogress Foundation

Volume 2, Number 2, February 2014

Contents

Editor's Welcome

Dear Colleagues,

The idea of creating an international journal in English and Russian languages has proved to be popular. The editors have received many positive reviews from Russian and foreign colleagues, who are interested in publishing articles in the journal.

The second issue includes seven articles from different countries and focuses on the following aspects of cardiovascular disease: the value of endothelial nitric oxide synthase gene polymorphism in the development of coronary artery disease; the relationship between physical activity and cardiovascular risk; assessment of cardiovascular risk in the population of a large cities in Ukraine; an expert's opinion on new US cardiovascular prevention guidelines; echocardiographic predictors of preservation of left ventricular function after surgery; and a clinical case of infectious myocarditis.

The leading article presents results from a stroke register that evaluated therapy received by patients, and its impact on their long-term prognosis.

We hope that the contents of this second issue will be useful for readers and 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 2, February 2014
Journal of the Cardioprogress Foundation

LEADING ARTICLE

Lyubertsy mortality study of patients after cerebral stroke or transient ischemic attack (LIS-2): design and evaluation of drug therapy

Boytsov S.A., Martsevich S.Yu.*, Ginzburg M.L., Kutishenko N.P., Drozdova L.Yu., Akimova A.V., Suvorov A.Yu., Loukianov M.M., Dmitrieva N.A., Lerman O.V., Zhuravskaya N.Yu., Daniels E.V., Fokina A.V., Yudaev V.N., Smirnov V.P., Kalinina A.M., Kotov S.V., Stahovskaya L.V.

This article is reprinted with permission from Rational Pharmacotherapy in Cardiology. First published in Rational Pharmacotherapy in Cardiology, 2013;9(2):114–122

Authors:

Sergey A. Boytsov – PhD, MD, Professor, Director of the National Research Centre for Preventive Medicine (NRCPM), Head of Department of Clinical Cardiology and Molecular Genetics of the same Center; Petroverigsky per. 10, Moscow, 101990 Russia

Sergey Yu. Martsevich – PhD, MD, Professor, Head of Department of Preventive Pharmacotherapy, NRCPM; Petroverigsky per. 10, Moscow, 101990 Russia

Moisei L. Ginzburg – PhD, MD, Head of Cardiology Department, Lyubertsy District Hospital № 2; Oktyabr'skiy prospect 338, Moscow Region, Lyubertsy, 140006 Russia

Natalia P. Kutishenko – PhD, MD, Head of Laboratory of Pharmaco-Epidemiological Research, Department of Preventive Pharmacotherapy, NRCPM; Petroverigsky per. 10, Moscow, 101990 Russia

Lyubov Yu. Drozdova – PhD, MD, Senior Researcher, Department of Preventive Pharmacotherapy, NRCPM

Anna V. Akimova – MD, Junior Researcher of the same Department; Petroverigsky per. 10, Moscow, 101990 Russia

Alexander Yu. Suvorov – Junior Researcher of the same Department; Petroverigsky per. 10, Moscow, 101990 Russia

Mikhail M. Lukyanov – PhD, MD, Leading Researcher of Department of Clinical Cardiology and Molecular Genetics, NRCPM; Petroverigsky per. 10, Moscow, 101990 Russia

* Corresponding author. Tel: +7 495 621 2049. E-mail: smartsevich@gnicpm.ru

Nadezhda A. Dmitrieva – PhD, MD, Researcher, Department of Preventive Pharmacotherapy, NRCPM
Olga V. Lerman – PhD, MD, Senior Researcher of the same Department; Petroverigsky per. 10, Moscow, 101990 Russia
Natalia Yu. Zhuravskaya – MD, Ph.D. candidate of the same Department; Petroverigsky per. 10, Moscow, 101990 Russia
Elena V. Daniels – MD, Doctor of Cardiology Department, Lyubertsy District Hospital № 2; Oktyabr'skiy prospect 338, Moscow Region, Lyubertsy, 140006 Russia
Anna V. Fokina – MD, Doctor of the same Department; Oktyabr'skiy prospect 338, Moscow Region, Lyubertsy, 140006 Russia
Victor N. Yudaev – PhD, MD, Head of Public Health Department of Lyubertsy District of Moscow area; Zvukovaya ul. 4, Lyubertsy, Moscow Region, 4140000 Russia
Vladimir P. Smirnov – PhD, MD, Head of Lyubertsy District Hospital № 2; Oktyabr'skiy prospect 338, Moscow Region, Lyubertsy, 140006 Russia
Anna M. Kalinina – PhD, MD, Professor, Head of Department of Primary Prevention of Chronic Non-Communicable Diseases in the Healthcare System, NRCPM; Petroverigsky per. 10, Moscow, 101990 Russia
Sergey V. Kotov – PhD, MD, Professor, Head of Chair of Neurology of Postgraduate Education Faculty, Moscow Regional Scientific-Research Clinical Institute named after MF Vladimirsky, Head of Neurology Unit of the same Institute, Chief-Neurologist of the Moscow Region; Schepkina ul. 61/2, Moscow, 129110 Russia
Ludmila V. Stakhovskaya – PhD, MD, Professor of Chair of Basic and Clinical Neurology and Neurosurgery, Russian National Research Medical University named after NI Pirogov; Ostrovitianova ul. 1, Moscow, 1117997 Russia

Aim
Research of social, demographic and anamnestic characteristics of patients that have survived cerebral stroke as well as the medical treatment received by the patients before the reference stroke in the hospital and at discharge within the framework of the stroke register entitled as LIS-2 (Lubertsy study of mortality in patients who have survived stroke).

Material and methods
All the patients (637 people) admitted to the Lyubertsy District Hospital № 2 due to stroke from January 2009 to December 2010 were enrolled into the study.

Results
36% were men and 64% were women with mean age of 70.99±9.6 years old. 554 (87.0%) patients had history of hypertension and 155 (24.3%) a history of atrial fibrillation. 147 (23.1%) patients had previous stroke. Hospital mortality was 21.8% (139 patients died with mean age of 72.7±9.6 years old). At discharge, 374 (75%) patients were prescribed ACE inhibitors, 421 (85%) antiplatelet agents, 4 (1%) warfarin. Statin treatment was recommended to 3 (1%) patients.

Conclusion
We revealed low frequency of prescription of drugs with proven effects on prognosis in patients with risk factors before the reference stroke and in patients discharged from the hospital after stroke.

Key words
Stroke, risk factors prevalence, medical treatment, register

Cerebral stroke is the leading cause of mortality in a majority of developed countries [1]. Patients who survive an acute period of stroke are at high risk of recurrent strokes and have a poor life prognosis [2,3]. However, evidence-based data clearly testify that some concrete medical preparations can significantly improve this prognosis [4].

Cerebral stroke risk factors in general coincide with other cardiovascular disease risk factors, firstly with those of coronary artery disease (CAD). Stroke pathogenesis, especially of its most prevalent type – ischemic stroke (cerebral infarction) due to atherothrombosis, is similar to that one of myocardial infarction (MI) [5,6].

This apparently determines similarity of approaches to the primary and secondary stroke and CAD prevention. It is not surprising that the principal drug groups that have demonstrated their effectiveness in secondary stroke prevention to a great extent coincide with medications used for the secondary CAD prevention. First of all these drugs are antiplatelet, antihypertensive and hypolipidemic agents.

Different clinical guidelines present the basic principles for primary and secondary stroke prevention; among them the guidelines promulgated conjointly by the American Heart Association and American Stroke Association are of special interest [7,8]. It is well known that real clinical practice does not always follow modern clinical guidelines. For example, the large-scale international epidemiological study PURE (Prospective Urban and Rural Epidemiological) study revealed that a majority of patients surviving stroke do not receive therapy that could really extend their life [9]. Respectively, life prognosis of patients in conditions of real clinical practice can significantly differ from the one registered in large-scale controlled trials.

All these impose a necessity of evaluation of real stroke patients' care situation, determination of their life prognosis in conditions of such treatment as well as main factors affecting it. Development of a register, providing evaluation of received treatment quality and patients survival rate during more or less long time period, is known to be the best way of overcoming this problem.

There were a number of cerebral stroke registers established in our country, however, almost all of them were organized in accordance with a similar protocol and were aimed at evaluation of stroke morbidity, its risk factors and in-hospital mortality [10–14]. Efforts to estimate long-term outcomes of a treatment were non-systemized and did not meet the requirements of modern research in survival rate evaluation [13]. Estimation of risk factors influencing mortality rate was not performed within a framework of the above mentioned registers.

The main objective of our cerebral stroke register, called LIS-2 (study of mortality among patients survived cerebral stroke in Lyubertsy district), was the assessment of actual therapy received by the patients and its influence on long-term disease outcomes. This article presents the design of the study, characteristics of the patients enrolled into it, and the treatment prescribed before the reference stroke during hospitalization and after discharge.

Materials and methods

The LIS-2 study is a register of patients admitted to the Lyubertsy District Hospital № 2 (LDH № 2) for cerebral stroke or transient ischemic attack (TIA) in 2009-2011.

All the consecutive patients admitted to the LDH № 2 for stroke (ischemic or hemorrhagic) or TIA from 01.01.2009 to 31.12.2011 were enrolled into the register. Those in whom diagnosis of stroke or TIA at admission was not confirmed were not included.

Stroke was diagnosed on the grounds of typical clinical features and specific neurological signs. Such methods of the brain visualization as computer tomography (CT) and magnetic resonance imaging (MRI) were carried out in singular cases in 2009–2010 due to technical capability of the hospital. The patients were examined in accordance with the current health economic standards of medical care. A stroke, a patient was admitted for, was regarded as the reference stroke. Data received at case history analysis concerning patient's history and status at hospitalization, treatment tactics and medications prescribed at discharge from hospital were entered onto a special standardized chart and then in an electronic database.

Prospective part of the study designated for discharged patients consists of several stages. At the first stage telephone contact with a patient or his relatives is obtained. In cases of lethal outcome after discharge from hospital, the cause of death is determined as precisely as possible. At the second stage patients are invited for the control examination, laboratory assays (blood count, lipid profile analysis, electrocardiogram (ECG)) and completion of questionnaires. If a patient can not attend a doctor by himself, a general practitioner visits him at home, registers ECG and lipid profile indices by a rapid test method using the CardioCheck analyzer; all received data are

filled in the standardized chart and the electronic database.

This article presents analyzed data from medical records of the patients admitted to hospital from 01.01.2009 to 31.12.2010.

Results

A total of 637 patients [230 (36.0%) men and 407 (64.0%) women] were admitted to the LDH № 2 for stroke or TIA from 01.01.2009 to 31.12.2010. Ischemic stroke was diagnosed in 558 (87.6%) patients, TIA in 55 (8.6%) and hemorrhagic stroke in 24 (3.8%) patients.

Mean age was 71.0±9.6 years old, youngest age was 25 and oldest 99 years (Figure 1). It is important to note that primarily patients above 60 years old were hospitalized due to stroke in 2009-2010. 567 (89.0%) patients were retirees and 207 (32.5%) were disabled.

We analyzed history of cardiovascular disease (CVD) and their risk factors in our patients (Table 1). According to medical records data 84 (13.2%) patients were smoking; 70 (11.0%) abused alcohol; and 63 (9.9%) were previously diagnosed with hyperlipidemia, with the total cholesterol level during hospitalization higher than 4,5 mmol/L in 329 (52.9%) patients. 120 (18.8%) patients had obesity; 142 (22.3%) were overweight; the weight of 100 (15.7%) patients was normal; and, in 275 (43%) cases, anthropometric indices were not completely indicated. 554 (87%) patients had a history of arterial hypertension; 155 (24.3%) a history of atrial fibrillation (AF), with 117 patients (75.4% of all the AF patients) having permanent AF, 27 (17.4%) paroxysmal AF, 2 (1.3%) persistent AF, and 9 (5.8%) paroxysm of unknown duration. 80 (12.6%) had previous MI; 4 (0.5%) patients had undergone percutaneous coronary intervention with stent placement, with a similar number of patients having had coronary artery bypass surgery. 137 (21.5%) patients had diabetes mellitus type 2. The reference stroke was a recurrent one in 147 (23.1%) patients. 13 (2.0%) patients had a history of TIA.

In-hospital mortality was 21.8% [n=139; mean age 72.7±9.6 years old; 43 (30.9%) men and 96 (69.1%) women], 498 (78.2%) patients were discharged for out-patient follow-up.

129 (92.8%) patients of all the deceased were retired persons, 47 (33.8%) were disabled. 109 (78.4%) deceased persons had hypertension, 50 (36.0%) had AF, 16 (11.5%) had previous MI, and 32 (23.0%) had diabetes (Table 2). The reference stroke was the recurrent one in 35 (25.2%) deceased patients.

Estimation of medical treatment received by the patients before the reference stroke, in hospital and therapy prescribed at discharge

Estimation of the treatment before the reference stroke revealed that 265 (41.6%) patients received antihypertensive therapy as follows: angiotensin-converting-enzyme (ACE) inhibitors in 195 (74%) patients, ß-blockers in 68 (25.7%), and calcium channel blockers in 53 (8.3%) patients. 43 (6.8%) patients were prescribed antiplatelet agents, 4 (0.6%) patients (or 2.6% of 155 patients with AF history) warfarin. 6 (0.9%) patients used anti-cholesterol drugs.

The most frequently prescribed drugs in hospital were: cinnarizine in 444 (69.7%) patients, gamma-

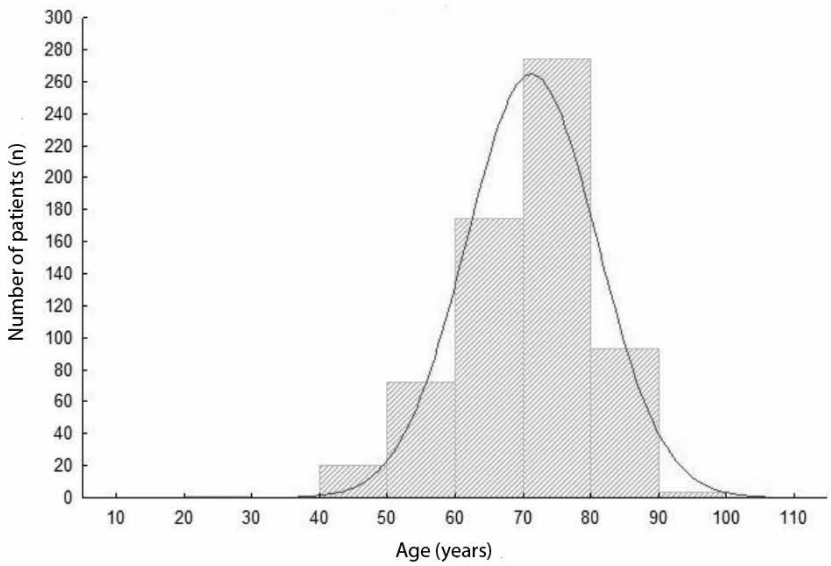

Figure 1. **Age distribution of patients enrolled in the LIS-2 register (n=637)**

aminobutyric acid (Aminalon) in 438 (68.8%), ACE inhibitors in 432 (67.8%), acetyl salicylic acid in 392 (61.5%), and papaverine in 347 (54.5%) patients. 4 (0.6%) patients received warfarin. Statins were not administrated at all.

We also analysed recommendations for discharged patients (n=498). ACE inhibitors were recommended to 374 (75.1%) patients and calcium channel blockers as an antihypertensive drug to 10 (2.0%) patients. The most frequently prescribed diuretic was indapamide (n=125; 25.1%). Antiplatelet agents (acetyl salicylic acid) were prescribed to 421 (84.5%) patients, warfarin to 4 (1%) patients. 3 (0.6%) patients were recommended statins. Such medications as vinpocetine and piracetam were prescribed more often (n=346; 69.6% and n=300; 60.2%, respectively).

Discussion

The LIS-2 register is a limited register, key factor of which is the diagnosis of stroke or TIA in patients admitted to the neurology unit of a municipal hospital. This register has a number of limitations due to difficulties in diagnosis verification, because such methods as CT or MRI were used in singular cases; besides, patients with stroke or TIA predominantly admitted to the hospital were of elderly age (above 60 years old). Due to difficulties in diagnosis verification, and taking into account similar approach to primary and secondary stroke and TIA prevention, we included in the register both patients with diagnosis of TIA and stroke.

A lot of publications and discussions are devoted to the problem of implementation of evidence-based recommendations in clinical practice [15–17]. Primarily the problem is of current interest in terms of secondary stroke prevention, what has been demonstrated in a number of trials including the above mentioned international epidemiological PURE study [9].

The reasons for this are various and include clinical inertness, presence of controversial data, incompatibility of clinical guidelines made for different nosologies [17–18]. Perhaps, in case of stroke, one such reason is absence of evident clinical effect of drugs that proved their positive effect on a patients' life prognosis.

Numerous stroke registers organized in Russia almost did not concern the problem of prescribing medications with proven effect. The first results of the LIS-2 study have demonstrated rather low frequency of the prescription of the main drug groups with proven positive influence on patients' life prognosis. It should be noted that the frequency of using different groups of drugs varied significantly: so, while antiplatelet agents and ACE inhibitors / angiotensin receptor blockers were recommended to the majority of patients at their discharge from hospital (84.5 and 75.1%, respectively), such medicines as statins and anticoagulants were in fact prescribed almost to no one. It should be mentioned that according to re-

Table 1. **Clinical and anamnestic characteristics of the patients** (n=637)

Clinical and anamnestic risk factors	Yes	No	Not known
Smoking, n (%) / Курение, n (%)	84 (13.2)	496 (77.9)	57 (8.9)
Alcohol abuse, n (%)	70 (11.0)	510 (80.1)	57 (8.9)
Hypertension, n (%)	554 (87.0)	41 (6.4)	42 (6.6)
Diabetes mellitus, n (%)	137 (21.5)	489 (76.8)	11 (1.7)
Atrial fibrillation, n (%)	155 (24.3)	460 (6.3)	22 (3.5)
Previous stroke, n (%)	147 (23.1)	80 (12.6)	78 (12.2)
Previous transient ischemic attack, n (%)	13 (2)	410 (64.4)	214 (33.6)
Previous myocardial infarction, n (%)	80 (12.6%)	499 (78.3%)	58 (9.1%)

Table 2. **Comparative analysis of survived and deceased in-hospital patients**

Parameter	The deceased during hospitalization (n=139)	The discharged (n=498)	*P*
Mean age, years / Средний возраст, лет	72.7±9.6	70.5±9.6	0.02
Stroke risk factors			
Smoking, n (%)	10 (7.2)	74 (14.9)	0.02
Alcohol abuse, n (%)	12 (8.6)	58 (11.6)	0.32
Hypertension, n (%)	109 (78.4)	445 (89.4)	0.0007
Atrial fibrillation, n (%)	50 (36.0)	105 (21.1)	0.0003
Diabetes mellitus, n (%)	32 (23.0)	105 (21.1)	0.06
History of CVD			
Previous stroke, n (%)	35 (25.2)	112 (22.5)	0.51
Previous myocardial infarction, n (%)	16 (11.5)	64 (12.9)	0.23

cent guidelines, statins are indicated for all patients surviving ischemic stroke and indirect anticoagulants (if not contraindicated) for all patients with AF, who made according to LIS-2 data about 24.3%.

We only estimated drugs prescription in hospital and at discharge according to nothing else but medical documentation data. In the following actual medical treatment of the survived patients is to be assessed with the help of special questionnaires at repeated visits, which will provide significantly more objective estimation of the treatment quality.

There is one more problem of implementation of evidence-based recommendations in clinical practice. It is known that randomized controlled trials (RCT), on which recent clinical guidelines are based, are carried out on accurately selected groups of patients. Such patients not always conform to typical patients with variety of concomitant diseases and often extremely older (these patients are oftentimes excluded from studies). So, it is disputable if drugs that have proven their positive effect in an RCT would similarly act in real practice. Modern registers technically allow estimation of a drug's influence on disease outcomes, as it was demonstrated in the similar by its design LIS study that included patients survived acute MI [19–21]. We hope that the LIS-2 study will also let estimate effect of some drugs on long-term outcomes of the disease.

Conclusion

The register of patients with cerebral stroke was created in Lyubertsy district (Moscow Region). Data from the register show that drug therapy used in secondary prevention of cerebral stroke does not conform well to current clinical guidelines. Monitoring of a disease's long-term outcomes in the register will identify the key factors that determine long-term prognosis for life and in particular the role of drug therapy.

References

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics – 2013 update: a report from the American Heart Association. Circulation. 2013;127(1):e6–e245.
2. Hankey GJ. Long-term outcome after ischaemic stroke/transient ischaemic attack. Cerebrovasc Dis. 2003;16 Suppl 1:14–9.
3. Mohan KM, Wolfe CD, Rudd AG, et al. Risk and cumulative risk of stroke recurrence: a systematic review and meta-analysis. Stroke. 2011;42(5):1489–94.
4. Baker WL, Marrs JC, Davis LE, et al. Key Articles and Guidelines in the Acute Management and Secondary Prevention of Ischemic Stroke. Pharmacotherapy. 2013 Feb 11. [Epub ahead of print].
5. Moustafa RR, Baron JC. Pathophysiology of ischaemic stroke: insights from imaging, and implications for therapy and drug discovery. Br J Pharmacol 2008;153 Suppl 1:S44–54.
6. Frizzell JP. Acute stroke: pathophysiology, diagnosis, and treatment. AACN Clin Issues. 2005;16(4):421–40.
7. Goldstein LB, Bushnell CD, Adams RJ, et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42(2):517–84.
8. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42(1):227–76.
9. Yusuf S, Islam S, Chow CK, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. Lancet. 2011;378 (9798):1231–43.
10. Spirin NN, Korneeva NN. Dannyye gospitalnogo registra insulta v Kostrome [Hospital stroke registry data in Kostroma]. Fundamentalnyye issledovaniya. 2012;4(1):123–8. Russian.
11. Khutieva LS, Efremov VV. Kliniko-epidemiologicheskaya kharakteristika i faktory riska mozgovykh insultov v respublike Ingushetiya [Clinical-epidemiological characteristic and stroke risk factors in the Republic of Ingushetia]. Novye Novyye tekhnologii. 2012;1:234–9. Russian.
12. Lebedev IA, Anishchenko LI, Akinina SA, et al. Kliniko-epidemiologicheskiye osobennosti mozgovogo insulta v Khanty-Mansiyskom avtonomnom okruge (po dannym populyatsionnogo registra) [Clinical-epidemiological particularities of cerebral stroke in the Khanty-Mansijsk Autonomous District (in accordance to a population register)]. Vestnik Rossiyskoy voyenno-meditsinskoy akademii. 2011;3:103–7. Russian.
13. Kotova EYu, Mashin VV. Epidemiologiya i osnovnyye faktory riska razvitiya insulta v g. Ulyanovske (po dannym registra insulta) [Epidemiology and the main risk factors of stroke in Ulyanovsk (in accordance to a stroke register)]. Ul'yanovskiy mediko-biologicheskiy zhurnal. 2011;2:10–7. Russian.
14. Bidenko MA, Shprah VV, Martynenko EA. Struktura, iskhody i faktory riska mozgovykh insultov po dannym gospitalnogo registra v g. Irkutske [Structure, outcomes and risk factors of cerebral stroke in accordance to in-hospital register data in Irkutsk]. Sibirskiy meditsinskiy zhurnal. 2008;79(4):61–4. Russian.
15. Martsevich SYu, Voronina VP, Drozdova LYu. Zdorovye i obrazovaniye vracha: dve sostavlyayushchiye uspekha [Doctor's health and education: two components of success]. RFK. 2010;6(1):73–6. Russian.
16. Khelia TG, Martsevich SYu, Selivanova GB, et al. Izucheniye znaniya sovremennykh printsipov ratsionalnoy farmakoterapii serdechno-sosudistykh zabolevaniy po dannym oprosa

vrachey pervichnogo zvena zdravookhraneniya goroda Moskvy [Assessment of awareness about contemporary principles of rational medical treatment for cardiovascular diseases in accordance to inquiry of primary care doctors in Moscow]. Kardiovaskulyarnaya terapiya i profilaktika. 2012;11(5):61–6. Russian.

17. Julian DG. Translation of clinical trials into clinical practice. J Intern Med. 2004 Mar;255(3):309–16.
18. Fletcher RH, Fletcher SW. Clinical epidemiology: the essentials. 5th ed. Philadelphia, Pa.; London: Lippincott Williams & Wilkins; 2013.
19. Martsevich SYu, Ginzburg ML, Kutishenko NP, et al. Issledovaniye LIS (Lyuberetskoye issledovaniye smertnosti bolnykh, perenesshikh ostryy infarkt miokarda): portret zabolevshego [The LIS research (study of mortality among patients survived acute myocardial infarction in Lyubertsy district): a portrait of a diseased]. Kardiovaskulyarnaya terapiya i profilaktika. 2011;10(6):89–93. Russian.
20. Martsevich SYu, Ginzburg ML, Kutishenko NP, et al. Issledovaniye LIS (Lyuberetskoye issledovaniye smertnosti bolnykh, perenesshikh ostryy infarkt miokarda). Otsenka lekarstvennoy terapii. Chast 1. Kak lechatsya bolnyye pered infarktom miokarda, i kak eto vliyayet na smertnost v statsionare [The LIS research (study of mortality among patients survived acute myocardial infarction in Lyubertsy district). Drug therapy evaluation. Part 1. How patients are treated before myocardial infarction and how this impacts on in-hospital mortality]. RFK. 2012;8(5):681–684. Russian.
21. Martsevich SYu, Ginzburg ML, Kutishenko NP, et al. Issledovaniye LIS (Lyuberetskoye issledovaniye smertnosti bolnykh, perenesshikh ostryy infarkt miokarda). Otsenka lekarstvennoy terapii. Chast 2. Vliyaniye predshestvuyushchey lekarstvennoy terapii na otdalennyy prognoz zhizni bolnykh) [The LIS research (study of mortality among patients survived acute myocardial infarction in Lyubertsy district). Estimation of medical treatment. Part 2. Influence of previous medical treatment on patients long-term life prognosis]. RFK. 2012;8(6): 738–745. Russian.

International Heart
and Vascular Disease Journal • Volume 2, Number 2, February 2014
Journal of the Cardioprogress Foundation

EXPERT OPINION

New USA recommendation
for cardiovascular prevention

Ceska R.*

Author:

Richard Ceska, MD, PhD, FACP, FEFIM
President of the Czech Society of Internal Medicine
Chair of the **International Atherosclerosis Society** (IAS) Regional Federation for Europe

In November 2013, immediately before the *American Heart Association* (AHA) Meeting in Dallas, joint recommendations of *AHA* and *American College of Cardiology* (ACC) were presented. The *National Institute of Health* (NHLBI) also took a crucial part in preparation of the new guidelines. The new recommendations excited the public's interest even before the *AHA* meeting, were controversially and extensively discussed in the press (including newspapers such as the *New York Times*), and became the main topic of the meeting.

New recommendations for cardiovascular prevention are actually a composite of four documents:

• Recommendations for the treatment of obesity and overweight (this is the first time that obesity and overweight are perceived as a disease requiring treatment and are directly incorporated into cardiovascular prevention).

• Recommendations for a healthy lifestyle, including both diet and increasing physical activity. Well-known dietary recommendations are now entrenched primarily to reduce the sodium content in the diet (at 1.5g/day) but I would argue that more attention is paid to physical activity even though 40 minutes of aerobic activity (fast walking – highly recommended) 3–4 times a week would be sufficient to reduce the cardiovascular risk for the majority of the population.

• Recommendations for the treatment of cholesterol (also including non-high density lipoprotein (HDL) cholesterol) are closely linked to the risk calculator (see below). Perhaps the most revolutionary innovation is a practical retreat omission target of treatment algorithm.

• The last, but probably the most important and indeed the latest recommendation is "recommendations for the calculation of cardiovascular risk". This recommendation is based on a completely new risk calculator based on the latest results of population studies. In addition to traditional risk factors such as cholesterol, HDL cholesterol, hypertension, diabetes, smoking, age or sex, the riskiness of African-American origin is emphasised. The calculator calculates the risk of a cardiovascular event in the next 10 years. If the risk is 7.5% or higher the patient is "indicated" for treatment.

This criterion of 7.5% was the main source of criticism in the media, which emphasized that more than 30 million Americans may be treated unnecessarily with statins. Even some prominent American physi-

* Corresponding author. Tel: +420 224 962 94. Email: richard.ceska@vfn.cz

cians criticized the risk calculator as overestimating and indicating treatment to more patients than necessary (for example Paul Ridker, who later withdrew his opinion and supported the new recommendations). The authors of guidelines defended their approach in two ways (both of them I find rational).

1. Guidelines in the case of primary prevention and the risk calculated at 7.5% do not represent an imperative to initiate drug therapy with statins. This is the start of a dialogue between a patient and a physician. It also initiates the judgement of the individual at risk especially with regard to family issues (it was repeatedly emphasized at the Meeting as a decisive factor). Is this then the way to more personalised medicine?

2. The authors argue that in a country where a third of the population die from cardiovascular disease (CVD) and 60% will experience a cardiovascular event during their lifetime, is probably not a mistake to treat 30 million people with statins, which have such corroborative data like no other medication.

Secondary prevention, the presence of diabetes mellitus type 2 or 1 and a significant hypercholesterolemia, familial hypercholesterolemia are considered to bear an unquestionable risk.

I followed the Guidelines in printed form, in discussions in professional journals and in newspapers, especially at the *AHA* Meeting. Even the last day of the Meeting Plenary was totally crowded (several thousand participants) which indicates a great interest of doctors who discussed specific cases with guidelines. And it was interesting that even the authors of the guidelines were not dogmatic, they did not insist on a precise recommendation and tried to individualize the procedure. Does this mean that we approach personalised medicine?

New American guidelines on cardiovascular prevention are quite new. We will see how they apply in practice. Even though the American approaches are quite different from the European, we will definitely gain from the new guidelines as well.

For information, see the *European Atherosclerosis Society* (EAS) statement in Appendix 1.

Appendix 1

New guidelines in USA: "2013 *ACC/AHA* Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk". How do they compare with the *EAS/ESC* Guidelines for the management of dyslipidaemia?

The *AHA* and *ACC* recently released three documents dealing with guidelines for the prevention of CVD: document on lifestyle management, on the assessment of cardiovascular risk and on "The treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults". It is welcomed that an updated version on the treatment of cholesterol is now available for the USA. In line with the document released by *EAS* and *ESC* in 2011 for the management of dyslipidaemias the *AHA/ACC* document emphasizes the importance of low density lipoprotein (LDL) cholesterol reduction in cardiovascular prevention, in both the primary and the secondary prevention of CVD. In both the European and in the *AHA/ACC* guidelines the importance of risk stratification is emphasized. In the new US document four groups are identified that could benefit from statin treatment: individuals 1) with clinical atherosclerotic cardiovascular disease (ASCVD), 2) with primary elevations of LDL cholesterol above 4.9 mmol/L (190 mg/dL), 3) with diabetes aged 40-75 with LDL cholesterol 1.8–4.9 mmol/L (70–189 mg/dL) without clinical ASCVD, 4) without clinical ASCVD or diabetes with LDL cholesterol 1.8–4.9 mmol/L and estimated 10-year ASCVD risk ≥7.5%. In the *EAS/ESC* guidelines risk stratification results in four groups of total cardiovascular risk: very high, high, moderate and low risk. Prevention is adapted according to the total cardiovascular risk estimation. In the European guidelines it is recommended to consider drug treatment of LDL cholesterol in the setting of primary prevention when total cardiovascular risk is high, or very high and/or in those with a moderate risk if LDL cholesterol ≥(100 mg/dL) despite lifestyle changes. In the new *ACC/AHA* guidelines statin treatment is recommended for primary prevention in subjects with a risk of ASCVD event of 7.5%, irrespective of LDL cholesterol level, which would correspond to a 2.5% risk for CVD death in 10 years according to the Systematic COronary Risk Evaluation (SCORE) model. **The impact of the *ACC/AHA* strategy should be put into the perspective of a much larger number of subjects in the population that would be eligible for lifelong statin treatment from the age of 40 years onwards**. The potential side effects should be considered, if such a large fraction of the population is put on statin treatment.

In the *ACC/AHA* guidelines the use of a new risk estimation model is recommended for estimating the total CVD risk (Pool cohorts' equations) has been developed. From the available documents it cannot be evaluated how this would work in relation to the European SCORE model. When using such models it is essential that the population from which the model is derived should be as similar as possible to the population that is seen by the clinicians. **For the**

Table 1. **Examples of similarities and differences in drug therapy between the EAS/ESC and AHA/ACC guidelines**

	Secondary prevention	Statin intolerance in secondary prevention	Primary prevention LDL>4.9 mmol/L	Primary prevention in diabetes	Primary prevention High risk
EAS/ ESC	Target LDL cholesterol<1.8 mmol/L OR at least 50% reduction. If target cannot be reached with statin, drug combination may be considered	Reduce statin dose, consider combination therapy	Target LDL cholesterol<2.5 mmol/L. If target cannot be reached maximal reduction of LDL cholesterol, using appropriate drug combinations in tolerated doses	Diabetes with other risk factors or organ damage: Target LDL cholesterol≤1.8 mmol/L or at least 50% reduction. Uncomplicated diabetes: Target LDL 2.5 mmol/L	SCORE≥5% risk of fatal CVD: Target 2.5 mmol/L
AHA/ACC	High-intensity statin. If 50% reduction is not reached drug combination may be considered.	Moderate or low dose statin, consider combination therapy.	High-intensity statin therapy, at least 50% reduction of LDL cholesterol, if not 50% reduction consider additional therapy	Diabetes with high risk: High-intensity statin therapy. Diabetes with low risk: Moderate intense statin	Total risk for CVD event >7.5%: Moderate to high intensity statin therapy. Risk 5–7.5%risk of CVD event: moderate intense statin therapy

European population we therefore prefer to continue using the SCORE charts or national charts calibrated on SCORE.

The approach to the treatment of the risk groups is in the *ACC/AHA* guidelines only identified as two options: high intensity or moderate intensity statin treatment (the final choice of strategy is often left to the doctor´s clinical judgment). No treatment goals in mmol/L of LDL cholesterol are suggested, although the option of having treatment goals is accepted. It can certainly be argued that treatment goals are arbitrary and often based on extrapolations from available data, but also on an evaluation of a larger pool of knowledge and science in the field. Treatment goals are widely used in different clinical settings, such as for the treatment of hypertension or type 2 diabetes. Targets are in daily practice most important in working with patient to doctor communications and optimizing compliance**. Furthermore risk reduction in general should be individualized for each patient, and this can be more appropriate if targets are defined. The simplistic approach of limiting the current knowledge on cardiovascular prevention only to criteria used in randomized controlled trials may limit the exploitation of the potential that is available for CVD prevention when a wider scientific basis is taken into account.**

In monitoring statin therapy the *ACC/AHA* guidelines suggest that an expected 50% reduction of LDL cholesterol on intense statin treatment should be used as an adherence control; in high risk patients this may also be a reason to increase dose or consider additional therapy. This is left to the doctors' clinical judgment. **Also in the *EAS/ESC* guidelines a 50% reduction from baseline level target is suggested as an optional target in those at very high total risk if the LDL cholesterol target of <1.8 mmol/L (70 mg/dL) cannot be reached.**

When comparing these guidelines it should be considered that the *EAS/ESC* guidelines had a broader approach on dyslipidaemia in general, while the *ACC/AHA* guidelines have is focused on statin treatment in cardiovascular prevention. Therefore, in the *EAS/ESC* guidelines, special groups such as familial hypercholesterolemia, stroke patients, combined hyperlipidaemia and diabetes are discussed more in detail. The *EAS/ESC* guidelines also include a more in depth discussion and options on other drug treatments than statins.

The European guidelines have worked well in Europe, they have been widely accepted and adopted, and based on the discussion above we recommend the *EAS/ESC* guidelines as best fitted for Europe. There are differences in approaches to cholesterol lowering between the guidelines, which however should not obscure the common ground in emphasizing the importance of LDL cholesterol lowering in cardiovascular prevention and a very similar view on which high risk groups that should be the target for drug treatment. Examples of similarities and differences in drug therapy between the two guidelines are given in table 1.

References

1. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2013 Nov 12. [Epub ahead of print].

International Heart
and Vascular Disease Journal • Volume 2, Number 2, February 2014 **ORIGINAL ARTICLES**
Journal of the Cardioprogress Foundation

Cardiovascular risk
in an urban population in Ukraine

Mitchenko E.I.*, Mamedov M.N., Kolesnik T.V., Deev A.D.

Authors:
Elena I. Mitchenko, MD, Professor, Strazhesko Institute of Cardiology, Kiev, Ukraine
Mehman N. Mamedov, MD, Professor, National Research Centre for Preventive Medicine, Moscow, Russia
Tatjana V. Kolesnik, MD, Professor, Dnepropetrovsk State Medical Academy, Dnepropetrovsk, Ukraine
Alexander D. Deev, PhD, National Research Centre for Preventive Medicine, Moscow, Russia

On behalf of the Working Group of the Ukraine-Russia study of 20 risk factors in Dnepropetrovsk**

Abstract

Aim

To conduct a large-scale study of cardiovascular risk in an urban population in Ukraine following current recommendations of the European Society of Cardiology (ESC).

Materials and Methods

The study protocol included identification and assessment of 20 cardiovascular risk factors in an urban population of Dnepropetrovsk (Ukraine), involving 1,000 respondents (468 men and 532 women) living in five districts of Dnepropetrovsk, aged 30-69 years. It also included determination of the prevalence of very high risk using all variations of the Systematic COronary Risk Evaluation (SCORE) scale, recommended by the ESC.

Results

According to the results of this Ukrainian–Russian study, conducted between 2009 and 2013, cardiovascular risk factors were identified which can be merged into three main groups according to prevalence among the adult population.

* Corresponding author. Tel/Fax: +380442498810. E-mail: cardiom@bigmir.net
** The **Working Group** of the Ukraine-Russia study of 20 risk factors in Dnepropetrovsk:
Kovalenko V.N., Dzyak G.V., Oganov R.G., Mitchenko E.I., Mamedov M.N., Kolesnik T.V., Deev A.D., Ostanina T.D., Kolesnik E.L., Kosova A.A., Bulanaya T.M., Romanov V.Yu., Chulaevskaya I.V., Gelymedova M.M., Sopko E.V., Kulik O.Yu., Ilyushin A.Ya., Gvozdik M.V., Shkreba A.A., Pustovit Yu.A.
Doctors from Dnepropetrovsk's polyclinics: Ilyyashevich N.N., Manaenkova E.V., Borzova T.A., Dovbnya T.A., Sushkina V.M., Korobskaya S.G., Kovrizhina O.S., Sidorova O.A., Sytenko O.N., Tarasyeva I.P., Komleva N.V., Yaltanets V.A., Gorb I.V., Sinitsa I.V., Selezneva N.G., Zhuk V.A., Storozhuk S.V., Kirilenko M.Yu., Bratusy E.V., Mudrakova I.V., Petrik N.N., Nastoburko I.V., Stavitskaya O.S., Ruban A.N., Moskvinova N.N., Makovetskaya M.A., Kolodka A.G., Grabova Yu.V., Railko A.S.

The most prevalent group of risk factors in this population, found in approximately 70% of cases, in descending order, were: abdominal obesity (by ESC criteria); overweight and obesity (by BMI); hypercholesterolemia and increased low density lipoprotein (LDL) cholesterol.

The second most common group of risk factors, found in approximately 40–45% of the cases, in descending order, were: abdominal obesity (by the criteria of the Adult Treatment Panel (ATP) III (2001); hypertension; hyperinsulinemia and insulin resistance (IR) by the homeostatic model assessment (HOMA) index.

The third most common risk factors, found in up to 30% of the population, in descending order, were: hypertriglyceridemia; impaired glucose tolerance (IGT); smoking; decreased HDL cholesterol; hyperuricemia and diabetes.

Conclusion

According to results of the analysis on the prevalence of risk factors and calculations of cardiovascular risk in urban population in Ukraine, using recommendations of the ESC (2012) and all three versions of the SCORE risk scale, a prevalence of very high risk involving cardiovascular complications was found in 30% of the adult population. These findings should serve as a basis for further multicenter epidemiological studies and prompt long-term prevention programmes.

Keywords

Risk factors, cardiovascular disease, urban population

According to the *World Health Organization* (WHO), cardiovascular disease (CVD) is the main cause of death worldwide. The latest estimates have shown that in 2008 17.3 million people died from CVD and, of that number, 7.3 million people died from coronary (ischemic) heart disease and 6.2 million died from stroke. This problem mostly affects low-income and middle-income countries and it is predicted that by 2030 global mortality from CVD will reach 23.3 million people per year [9].

The peculiarity of the European Region is that, along with a decrease of overall mortality in recent years, which in 2010 reached an age-standardized mortality rate of 813 per 100,000 of population, there are still wide differences between countries. For example, according to *WHO*, the age-specific structure in 15 countries that joined the European Union (EU) before 2004 is characterized by an increase in mortality in older age groups by two times, and in 12 other countries that joined the EU after May 2004 and in the CIS countries, it increased by more than three times. On average about 50% of all deaths in Europe occur due to CVD , and of all deaths in the age group to 75 years old, 42% related are related to CVD in women and 38% in men [5].

Some decrease in age-standardized mortality rates from CVD was observed in the period from 1970s and 1990s, which was most pronounced in rich developed countries, demonstrating the potential for preventive measures to avoid premature death and to extend healthy life expectancy. The results of the international research project MONICA (Multinational MONItoring of trends and determinants in CArdiovascular disease) were quite demonstrative, and was conducted in 21 countries on four continents over the period 1976–1996 to monitor the trends and determinants of CVD under the aegis of *WHO*. The following risk factors were explored: smoking, cholesterol, systolic blood pressure and body mass index (BMI). The following dynamics were noted: the reduction of smoking in men, along with an increase in women; some tendency to lower cholesterol, which, however, significantly affected the CVD risk; a tendency to decrease blood pressure, along with a tendency to increase the body mass index, in half of women and two thirds of men.

Also, within the framework of the WHO MONICA project, from mid 1980s to mid 1990s, there was monitoring of the frequency of coronary heart disease (CHD), risk factors and treatment of coronary patients among selected populations in order to obtain an accurate picture of the levels and trends associated with CVD. The most significant reduction in the incidence of CHD in men occurred in three populations in northern Europe: North Karelia and Kuopio in Finland, and in Northern Sweden. An increase in the frequency of CHD was also observed among both male and female population in the countries of Eastern Europe.

The importance and effectiveness of a multifactorial approach to solving this problem was clearly demonstrated by the example of the North Karelia project in Finland. Thus, during the period from 1972 to 2007, the total cholesterol in men in North Karelia decreased from 6.9 mmol/L to 5.4 mmol/L (i.e., 1.5 mmol/L), diastolic blood pressure decreased from 92.6 mmHg to 83.9 mmHg (i.e. by 8.7 mmHg) and the prevalence of

smoking decreased from 51% to 30% (i.e. by 21%). As a result, based on the reduction in diastolic pressure, cholesterol and smoking, overall risk fell by 60%. At the same time, observed mortality from CHD decreased in the same geographical area by 80%.

In 2012, the *European Atherosclerosis Society* (EAS) once again highlighted the importance of risk factor modification using the results of a meta-analysis of 18 studies involving more than 250,000 men and women aged 55 years and older [7]. It was found that in individuals with optimal profile of risk factors (non-smoking, non-diabetic, with optimal level of cholesterol and blood pressure) enjoyed a more than 3 times reduced risk of major cardiovascular events, more than 6 times reduction in death from CVD, and more than 10 times reduction in the risk of developing CHD. None of the most advanced medical technologies, including interventional and surgical methods of treatment, has this degree of influence on cardiovascular risk.

In Ukraine, according to the latest official statistics, more than 440,000 people died from cardiovascular diseases in 2011, which represents 66.3% of all causes of death, and this figure continues to be one of the highest in the structure of mortality in Europe. Along with the available data on the prevalence in Ukraine of five traditional risk factors, including smoking, hypertension, obesity, dyslipidemia and lack of physical activity, there is no analysis of the new predictors of CVD, the importance of which is emphasized in policy documents published by the *European Society of Cardiology* (ESC) and the *EAS*. Firstly, the problems associated with carbohydrate metabolism and especially the prevalence of type 2 diabetes, a recognized equivalent of CHD; visceral fat distribution, not only overweight; hyperuricemia; level of C-reactive protein; thyroid disease, especially due to the accident at the Chernobyl Nuclear Power Plant and a number of other factors.

To solve this problem in 2009 the *M.D. Strazhesko Institute of Cardiology*, Kiev, Ukraine; the *Dnepropetrovsk State Medical Academy*, Dnepropetrovsk, Ukraine, and the *National Research Centre for Preventive Medicine*, Moscow, Russia started a joint Ukraine-Russia project to study 20 risk factors in an urban population of Dnepropetrovsk attending its five polyclinics. It should be noted that a similar protocol study was initiated in Russia in 2007 in multi-centres across five regions of the country. At present, the completed part of the study involves 20 risk factors in the urban population of the city of Cheboksary, the Chuvash Republic of the Russian Federation.

The study protocol included identification and assessment of the following parameters in 1,000 respondents (468 men and 532 women), living in five districts of Dnepropetrovsk, aged 30–69 years:

1. Anthropometric data (height, weight, BMI);
2. Definition of abdominal obesity (waist circumference, hip circumference, and their ratio);
3. Systolic (SBP) and diastolic blood pressure (DBP), a history of hypertension and its treatment;
4. Lipid profile (total (T) cholesterol, LDL cholesterol, cholesterol, very low density lipoprotein (VLDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, atherogenic index);
5. Smoking status;
6. Glycemic status (levels of fasting glucose and insulin, insulin sensitivity by the homeostatic model assessment (HOMA) index, history of diabetes);
7. Alcohol intake;
8. Social status (education, marital status);
9. Family history (hypertension, obesity, diabetes, CHD (including angina), stroke, heart attack in immediate family);
10. presence of CHD (Rose questionnaire, Minnesota code for electrocardiogram (ECG), including data on left ventricular hypertrophy, myocardial infarction);
11. Presence of cardiac arrhythmias and conduction abnormalities (extrasystole, atrial fibrillation);
12. Presence of heart failure;
13. Level of physical activity;
14. Eating pattern;
15. Levels of anxiety, depression and stress;
16. C-reactive protein level;
17. Uric acid level and urolithiasis history;
18. Presence of comorbidity on the thyroid gland, liver, and kidneys;
19. Presence of menopause in women;
20. Presence of peripheral vascular disease (atherosclerosis of the carotid arteries, atherosclerosis of the lower limbs and / or presence of varicose veins of the lower limbs).

There was a high response from the participants who took part in this project (72%). Consent to examination was given by 1,000 residents of Dnepropetrovsk from 1,388 people initially involved in the survey, which indicates a representative sample. Analysis of the data was conducted by the *National Research Centre for Preventive Medicine* in Moscow, in accordance with the standards of medical statistics involving the following methods of standardization:

• direct by age in accordance with the WHO MONICA project [11];

• regression – in general linear models (using SAS PROC GLM) [8].

According to the data obtained, we were able to analyze a number of epidemiological characteristics.

Hypertension

To analyze the prevalence of hypertension, data on blood pressure exceeding SBP≥140 mmHg and/or DBP≥90 mmHg were taken into account by measuring blood pressure 2 times: on the 1st and 2nd minute of the examination. The existing history of hypertension was also considered, including information on prescriptions for antihypertensive drugs. At the time of the survey, hypertension was diagnosed in 457 respondents (45.7%), including in 16 respondents (1.6%) for whom it was revealed for the first time. Sex distribution of hypertension was found in 37.6% of men and 52.8% of women. A progressive increase in the prevalence with age was noted. Hypertension was found in 31.5% of cases (29.5% men and 34.0% women) in the age group of 30–39 years, 29.8% (28.5% men and 31.5% women) in the age group of 40–49 years, 55.6% (43.6% men and 64.8% women) – followed by almost two-fold increase in the age group of 50-59 years, and 68.6% in the age group of 60–69 years (66.0% men and 69.7% women). A distinctive feature of our data is not only an increase in the overall percentage of hypertension prevalence in general population (45.7% vs. 29.3%) and in relevant age groups compared with the epidemiological data obtained earlier, but also a significant prevalence of hypertension among women in all age groups, not previously detected [1,2].

Dyslipidemias

Taking into account a need for a full lipid analysis of the surveyed respondents, as well as the fact that most prognostically significant levels of LDL cholesterol in Ukraine are determined by calculation based on the Friedewald formula, we analyzed the levels of total cholesterol >5.0 mmol/L in accordance with the recommendations of the ESC (2007), the *Ukrainian Society of Cardiology*, (2011) [3], and the *International Atherosclerosis Society* (2013) [6]. It was found that the prevalence of hypercholesterolemia in this urban population is on average 69.4% (62.3% men and 71.8% women), with prevalence increasing with age. An increased prevalence of hypercholesterolemia in men was observed from 56.8% in the age group of 30–39, to 69.8% in the age group of 50–59 years. There is a reduced prevalence of up to 54.3% in the prevalence of hypercholesterolemia in the age group of 60–69 years in men. It would be nice to believe that this did not happen due to the exclusion from the analysis of respondents due to increased mortality from CHD in men with hypercholesterolemia in the age range of 50–70 years, however it is not possible to exclude this possibility. There is a steady increase in the prevalence of hypercholesterolemia in women from 45.2% in the age group of 30–39 years to 86.0 % in the age group of 60–69 years.

The prevalence of low HDL cholesterol (<1.0 mmol/L for men and <1.3 mmol/L for women) was not a very specific characteristic for the studied population. Only 18.3% of respondents (10.4% men and 24.6% women) had an average risk factor for CVD in the form of lower HDL cholesterol levels, but for both men and women there was a slight increase of this risk factor with age: from 10.7% to 11.9% in men and from 22.0% to 24.0% in women.

Hypertriglyceridemia (>1.7% mol/L) was found on average in 31.7% of respondents (35.6% men and 26.2% women). For both men and women there was an increase of hypertriglyceridemia with age from 29.0% to 33.8% in men and more rapid in women, from 13.0% to 39.7%.

The prevalence of a high level of the most prognostically significant LDL cholesterol (>3.0 mmol/L) in the studied population was 68.1% (68.1% in men and 66.0% in women), and largely repeated the trend of hypercholesterolemia, which was certainly due to the calculation method. With regard to age, an increase was noted in the prevalence of this risk factor from 65.9% in the age group of 30–39 years to 71.9% in the age group of 50–59 years in men, with some reduction to 64.8% in the age group of 60–69 years. In women, by contrast, there was a steady increase in the prevalence of this risk factor from 43.6% to 75.8% in older age groups.

Smoking

The prevalence of smoking in the studied population averaged 24.2% (36.8% men and 13.1% women). There was a decrease of this risk factor with age, from 47.3% in the age group of 30–39 years to 18.1% in the age group of 60–69 years in men and from 20.5% to 5.03% in women. There was a big surprise for researchers to find such high prevalence (5.03%) of smoking in older age group of women (60–69 years), which is associated with the highest risk of CVD in this contingent.

Overweight and obesity

According to our data, normal weight with a BMI<25 kg/m2 (or 18.5–24.9 kg/m^2) in the studied population represented only 29.3% of the sample, while the total share of overweight and obesity was 70.1%

(69.6% men and 71.0% women). Moreover, in the population, according to BMI definition, overweight (25-29.9 kg/m^2) was detected in 42.3% men and 36.4% women, while classes I, II and III obesity was revealed in 20.0%, 6.3% and 1.0% men and 23.4%, 8.7% and 1.4% women, respectively.

In previously conducted epidemiological studies in Ukraine there are no data on the prevalence of abdominal type of obesity, measured by waist circumference. This risk factor is one of a cluster of factors called the metabolic syndrome, and received its mathematical interpretation in the *Adult Treatment Panel* (ATP) III, 2001 [10] as following measurements of waist circumference: >102 cm for men and >88 cm for women. Nevertheless, the recommendations of the *International Diabetes Federation* and recommendations for the prevention of CVD of the *ESC* (2012) [5] have more strict criteria for abdominal obesity as following measurements of waist circumference: >94 cm for men and >80 cm for women. We conducted an analysis using both the first and second values of the measurement. According to the less strict measurement, *ATP*-III (2001), abdominal obesity was found in 46.8% of the respondents (37.0% men and 56.6% women), while according to the more strict measurement, supported by the *ESC* (2012), abdominal obesity was found in 72.8% of respondents (62.3% men and 77.3% women). This represents an extremely high prevalence of cardiovascular and cardiometabolic risk not only for CVD, but also the manifestation of diabetes and a variety of metabolic disorders.

Type 2 diabetes mellitus, impaired glucose tolerance (IGT), insulin resistance (IR)

Data on the prevalence of diabetes, IGT and IR have not yet been presented in statistical reports in Ukraine. Taking into account the fact that diabetes is recognized throughout the world of cardiology as a CHD equivalent, i.e. this cohort of patients belongs to a group with very high cardiovascular risk, we analyzed glucose and fasting insulin levels, and also the HOMA index for IR in all respondents.

According to the results, the prevalence of all cases of diabetes, including first time identified diabetes, was 8% of the population – about the same proportion among men (7.9%) and women (8.1%). Interesting data was also discovered on the prevalence of IGT and IR. IGT was revealed in nearly one third of all respondents (28.0%), with clear predominance in the male cohort (38.9% vs. 19.1% women). This relationship was observed in all age groups. Thus, in the age group 30-39 years, it was found in 40.1% of men and only in 14.6% of women. With increasing age, the prevalence of IGT in men remained almost constant, whereas in women it increased up to 21.4% in the age group of 60–69 years due to lower estrogen, which has a strong antidiabetic effect. At the same time, the prevalence of hyperinsulinemia (>11 μU/kg) and IR, determined by the HOMA index, >2.77, was found in over one third of respondents (41.2%) with a primary detection in women (44.8%) compared with men (37.8%). This predominance was maintained in all age groups. Hyperinsulinemia, observed in the age group 30–39 years (31.9% men and 46.8% women) achieved a prevalence of 46.7% in men and 54.8% in women aged 60–69 years. This fact, together with the high prevalence of abdominal type of obesity in this urban population (46.8% according to the *ATP*-III (2001) criteria and 72.8% according the *ESC* (2012) criteria) suggests that the problem of the insulin resistance syndrome or metabolic syndrome, as well as all its associated cardiometabolic disorders, is highly relevant to Ukraine, which may not be fully appreciated by cardiologists.

Thyropathies

Thyroid dysfunction has first place in the structure of endocrinopathies in Ukraine. We did not carry out an additional screening of respondents' hormonal status, only information about previously diagnosed thyroid disease was analyzed. On average in this population, thyropathies had been diagnosed in 8.9% of cases (2.4% men and 14.5% women). This pathology should be considered in clinical and epidemiological developments, firstly, because of the close connection between hypothyroidism and atherogenic dyslipidemia; and, secondly, because of the significant increase in thyroid disorders after the Chernobyl accident.

Hyperuricemia

Elevated levels of uric acid in the blood are due to the consumption of foods rich in purines or chronic issues with a diet associated with consuming high calorie and fat foods. Increased levels of uric acid raise the predisposition toward gout and (at a very high level) renal insufficiency, and is also observed in the insulin resistance syndrome. The maximum values for a normal level are 360 μmol/L for women and 400 μmol/L for men. In the studied population, hyperuricemia was observed on average in 17.3% of cases with twice the predominance in the male population (23.0%) compared with female (11.5%).

Conclusion

It is difficult to analyze the prevalence of all 20 investigated risk factors in one article. However, as we touched on some of the traditional and identified new

predictors of CVD, we can try to characterize the profile of the main cardiovascular risk factors of this urban population in Ukraine (Figure 1). As shown in the diagram, the risk factors analyzed in this publication can be assigned to three main groups according to their degree of prevalence in the adult population. First, the most widespread group of risk factors in the population, represented in about 70% of cases, comprising, in decreasing order: abdominal obesity according to the *ESC* (2012) criteria; overweight and obesity according to BMI; hypercholesterolemia; and increased LDL cholesterol. The second most common group of risk factors (about 40–45% of the population) comprised: abdominal obesity, identified by the *ATP*-III (2001) criteria; hypertension; hyperinsulinemia and IR determined by the HOMA index. The third group of CVD risk factors (30% or less in the population), in descending order, comprised: hypertriglyceridemia; IGT; smoking; decreased HDL cholesterol; hyperuricemia and diabetes.

At the final stage of the study, in accordance with the recommendations of the *ESC* (2012), we tried to determine the prevalence of very high cardiovascular risk in this urban population in Ukraine using all three variations of the Systematic COronary Risk Evaluation (SCORE) scale, presented on-line on the *ESC* web page, using the scale for high-risk countries like Ukraine: https://escol.escardio.org/heartscore/calc.aspx?model=europehigh

Initially, calculating the number of respondents suffering from CHD (using only objective criteria like electrocardiogram (ECG), myocardial infarction, revascularization in anamnesis), as well as the number of respondents additionally identified with type 2 diabetes without history of coronary artery disease (CAD), which, in accordance with the *ESC* recommendations, is the equivalent of CAD, we discovered a group of 224 respondents with established very high risk.

During the next step, using the first SCORE1 scale, for which it is necessary to take into account the date of birth, sex, SBP, cholesterol, and smoking status, we further identified an additional 26 respondents. Consequently, using in addition the SCORE1 scale, we identified in the population 224+26=250 respondents at a very high risk.

Using the second SCORE2 scale to determine the risk according to which, in addition to all of the above, it is necessary to consider the level of HDL cholesterol, we got a slight decrease in the high-risk group, compared with the SCORE1 scale, identified in addition to CAD and diabetes, namely, the reduction of HDL cholesterol was noted only in 9 respondents. As we have already mentioned, this risk factor is not the lead in the Ukrainian urban population. Therefore, using the SCORE2 scale, we identified a group at a very high risk only in 224+9=233 respondents.

Using the third SCORE3 scale, to determine the risk in which, besides the date of birth and sex of a respondent, were used the parameters of height and weight to determine their BMI, and smoking status, we identified a further 67 respondents in addition to those with CAD and diabetes. Therefore, in total, using the SCORE3 scale we found a very high risk in 224+67=291 respondents.

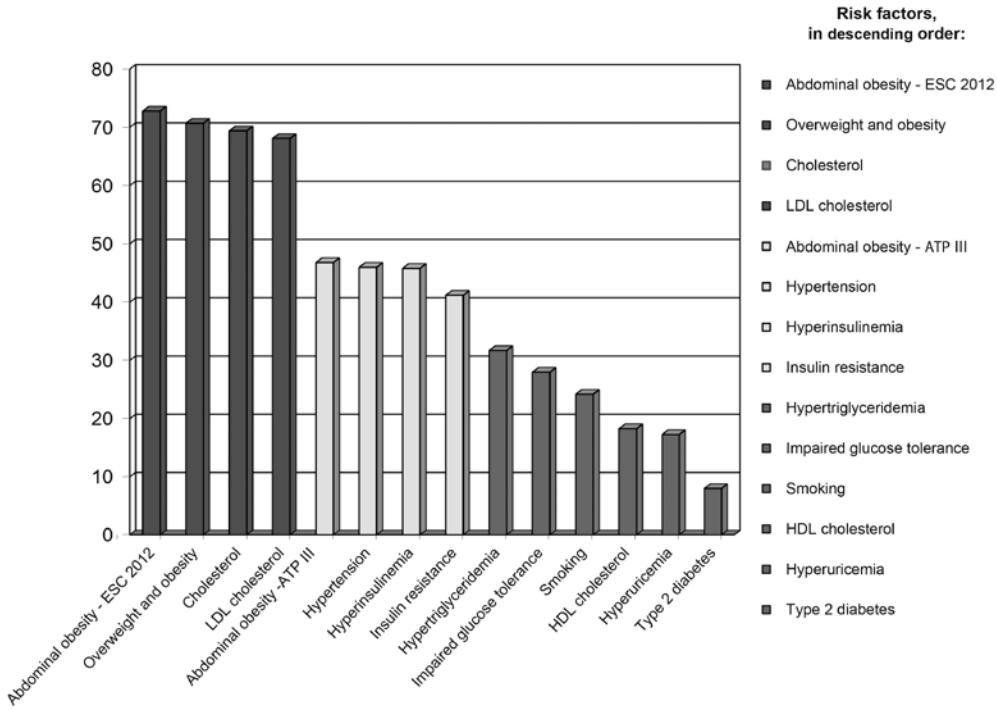

Figure 1. Prevalence of cardiovascular risk factors in an urban population in Ukraine

Attempting to determine the maximum cohort at a very high risk, we analyzed the possibility of defining this parameter, using all scales simultaneously, i.e. using every opportunity to determine the cohort threatened by the emergence of fatal CVD or SCOREmax, which was 71 respondents. Therefore, when using any possibility to determining SCORE more than 10%, which corresponds to a very high risk, we found it in total in 224+71=295 respondents. That is at the maximum consideration of all possible predictors in an adult urban population in Ukraine at the age of 30–69 years, the cohort with a very high risk of fatal complications comprised about 30% of the population, which, perhaps, is reflected in government statistics on the incidence and mortality of the *Ministry of Health* of Ukraine.

The results of this research allows us to conclude that there is a serious epidemiological situation with the prevalence of cardiovascular risk factors in the urban population in Ukraine. This may include about 30% of population aged 30–69 years being categorised at a very high risk.

This data should serve as an incentive for large-scale multicenter epidemiological studies, with the support of government organizations, to follow the example of Western countries. This would include a full assessment of the entire population and study of the population aged from 18 to 70 years living in industrialized regions and cities, deprived of large industrial enterprises, to evaluate the situation objectively and carry out appropriate preventive measures.

Acknowledgment

Conducting this research has required the involvement of a large number of participants, as evidenced by the list of authors and support from sponsoring companies that funded not only a range of laboratory studies, but also several technical requirements of the project. The authors express their sincere appreciation to the main sponsor of this study, pharmaceutical company Dr. Reddis, and other commercial sponsors Borshchahivskiy Chemical Pharmaceutical Plant, EGIS, Kiev Vitamin Plant, Abbott, Queisser, Sanofi, and Health Promotion.

References

1. Gorbas IM. Epidemiolohiya osnovnykh faktoriv ryzyku sertsevo-sudynnykh zakhvoryuvan [The epidemiology of major risk factors for cardiovascular disease]. Arterialna hipertenziya. 2008;2:15–18. Ukrainian.
2. Gorbas IM, Barna OM, Sakalosh VYu, et al. Otsinka poshyrenosti ta kontrolyu faktoriv ryzyku sertsevo-sudynnykh zakhvoryuvan sered naselennya ta likariv [Assessing the prevalence and control of risk factors for cardiovascular diseases among the population and doctors]. Liky Ukrayiny. 2010;1:4–9. Ukrainian.
3. Mitchenko OI, Lutaj MI. Dyslipidemiyi: Diahnostyka, Profilaktyka Ta Likuvannya. Metodychni rekomendatsiyi Asotsiatsiyi kardiolohiv Ukrayiny [Dyslipidemia: Diagnosis, Prevention and Treatment. Guidelines of the Ukrainian Association of Cardiology] [Internet]. Kyiv (Ukraine): Instytut Kardiologii Imeni Akademika M.D. Strazheska; 2011. 25 p. Available from: http://strazhesko.org.ua/inc/materials/Guidelines_dyslipid_2011_new.pdf/. Ukrainian.
4. Kornatsky VM, redactor. Certsevo-sudynna zakhvoryuvanist v Ukrayini ta rekomendatsiyi shchodo pokrashchennya zdorovya v suchasnykh umovakh. Analitichno-statistichnij posibnik [Cardiovascular morbidity in Ukraine and recommendations to improve health in the modern world. Analytical Statistical Manual]. Kyiv (Ukraine): [publisher unknown]; 2012. 117 p. Ukranian.
5. 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;33:1635–1701.
6. Global Recommendations for the Management of Dyslipidemia [Internet]. [place unknown]: International Atherosclerosis Society; [updated 2013 July 25]. Available from: http://www.athero.org/IASPositionPaper.asp
7. Reducing lifetime cardiovascular risk. Key paper on lifetime cardiovascular risk. Featured Commentary [Internet]. [place unknown]: European Atherosclerosis Society; No.1, 2012. Available from: http://www.eas-society.org/featured-commentary,-no.1-reducing-lifetime-cardiovascular-risk.aspx
8. SAS/STAT User's Guide. 4th ed. Cary (USA): SAS Institute Inc.; 1990. Version 6, Vol.1 & 2.
9. The European health report 2012: charting the way to well-being [Internet]. [place unknown]: World Health Organization; 2013. Available from: http://www.euro.who.int/ru/what-we-do/data-and-evidence/european-health-report-2012
10. Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III Final Report) [Internet]. [place unknown]: National Heart, Lung and Blood Institute; 2002. Available from: http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3_rpt.htm
11. WHO MONICA Project. MONICA Manual [Internet]. [place unknown]: World Health Organization; 1999 Mar 31. Available from: http://www.thl.fi/publications/monica/manual/index.htm

International Heart
and Vascular Disease Journal • Volume 2, Number 2, February 2014 **ORIGINAL ARTICLES**
Journal of the Cardioprogress Foundation

Echocardiographic prediction of preservation of left ventricular function after surgical correction for severe aortic regurgitation

Yamaguchi K., Tanabe K.,* Takahashi A., Nakashima R., Sugamori T., Endo A., Takahashi N., Tani T., Okada Yu.

Authors:

Kazuto Yamaguchi, RMS, The Fourth Department of Internal Medicine, Shimane University Faculty of Medicine, Izumo, Japan
Kazuaki Tanabe, MD, The Fourth Department of Internal Medicine, Shimane University Faculty of Medicine, Izumo, Japan
Ayako Takahashi, MD, The Division of Cardiology Kobe City Medical Center General Hospital, Kobe, Japan
Ryuma Nakashima, MD, The Fourth Department of Internal Medicine, Shimane University Faculty of Medicine, Izumo, Japan,
Takashi Sugamori, MD, The Fourth Department of Internal Medicine, Shimane University Faculty of Medicine, Izumo, Japan
Akihiro Endo, MD, The Fourth Department of Internal Medicine, Shimane University Faculty of Medicine, Izumo, Japan
Nobuyuki Takahashi, MD, The Fourth Department of Internal Medicine, Shimane University Faculty of Medicine, Izumo, Japan
Tomoko Tani, MD, The Division of Cardiology Kobe City Medical Center General Hospital, Kobe, Japan
Yukikatsu Okada, MD, Cardiovascular Surgery, Kobe City Medical Center General Hospital, Kobe, Japan

Background

Left ventricular (LV) dysfunction is an indication for surgical correction of aortic valve in patients with severe aortic regurgitation (AR). This study sought to determine whether echocardiographic variables before surgery for AR predict postoperative LV dysfunction.

* Corresponding author. Tel: +81-853-20-2249; Fax: +81-853-20-2201. E-mail: kaz@med.shimane-u.ac.jp

Methods and Results

We studied 55 patients (20–85 years old, mean age 58 years old) with isolated AR who underwent surgical correction (aortic valve replacement or repair). Echocardiographic studies were performed in preoperative and postoperative (14.3±1.8 months after surgery) periods. The incidence of postoperative LV dysfunction (left ventricular ejection fraction (LVEF) <50%) was 25% (14/55). The incidence of postoperative LV dysfunction was high in patients with preoperative LVEF<50% (11/24, 46%), preoperative LV end-systolic dimension (LVESD) >50mm (6/14, 43%), preoperative LV end-diastolic dimension (LVEDD) >70mm (2/3, 67%), preoperative LVESD normalized to body surface area (LVESD/BSA) ≥25mm/m2 (12/28, 42%). The optimal cutoff value for LVESD/BSA to predict the postoperative normalization of LVEF (LVEF≥50%) was 26.5mm/m2 with a sensitivity of 86% and a specificity of 70%, whereas LVEDD of 62mm had 64% sensitivity and 71% specificity, LVESD of 47mm had 79% sensitivity and 77% specificity.

Conclusion

In patients with AR, LVEF<50% and/or LVESD/BSA≥26.5mm/m^2 should be carefully considered for surgical intervention, which reduces the risk of post operative LV dysfunction.

Key words

Aortic regurgitation, echocardiography, function

Current guidelines suggest surgical intervention in severe aortic regurgitation (AR) if there are significant symptoms or at the onset of signs of LV dysfunction, such as an ejection fraction (EF) of ⩽50% or significant left ventricular (LV) dilatation with an end-diastolic dimension (EDD) of >70–75 mm and/or end-systolic dimension (ESD) of >50–55 mm [1,2]. Previous studies demonstrated that patients with severe or moderately severe AR and conservative management incur excess mortality compared with expected, excess mortality in patients with severe symptoms, and excess mortality rate in patients asymptomatic with LVEF<55% or LVESD normalized to body surface area ≥25 mm/m^2 [2,3–5].

The postoperative outcome for patients with a reduced EF depends on the magnitude of the reduction of EF. These patients generally have an improvement in the EF postoperatively as a result of relief of the high afterload [6,7]. In contrast, LVEF is a powerful predictor of cardiovascular outcome in heart failure patients across a broad spectrum of ventricular function [8,9]. It still remains a clinical dilemma when a physician should recommend surgery to a patient experiencing AR with minimal symptoms in order to preserve the postoperative LV function. The purpose of this study was to determine whether echocardiographic indices before aortic valve surgery are predictive of postoperative LV function and useful for deciding the optimal timing of aortic valve surgery.

Methods

Patients

This study was based on a retrospective review of our experience with aortic valve surgery for isolated AR. The inclusion criteria were (1) surgical correction (repair or replacement) of AR performed between January 1, 2001 and December 31, 2005; and (2) immediate postoperative survival allowing for observation of late after surgery. Patients with associated coronary artery bypass graft surgery or ascending aortic surgery were included. The exclusion criteria were (1) moderate to severe aortic stenosis; (2) aortic dissection; (3) previous operation for AR; (4) previous or associated mitral valve replacement (tricuspid valve repair was not excluded); (5) infective endocarditis; and (6) operative death, defined as occurring during the first postoperative month or within the same hospitalization.

Fifty-five patients had aortic valve operations due to isolated severe AR and had echocardiographic studies immediately before surgery and late after surgery (at least 6 months after surgery). Of the 55 patients, the mean age was 58±16 years, 42 (76%) were men, and 11 (20%) were in atrial fibrillation. The cause of AR was defined as degenerative (33 patients), rheumatic (8 patients), aortic root dilatation (6 patients), bicuspid aortic valve (5 patients), and aortic valve prolapse (3 patients). Before surgery, 24 patients were

in *New York Heart Association* functional class III or class IV. The surgical procedure performed was valve repair in 11 patients and valve replacement in 44 (bioprosthesis in 11 patients and mechanical prosthesis in 30). Coronary artery bypass graft surgery was performed in 4 patients and ascending aortic surgery was performed in 7 patients.

Echocardiography

Echocardiographic examinations were performed within 1 month before and late after surgery (at least 6 months after surgery). Before surgery, the degree of AR was determined by color flow Doppler method and 2 quantitative methods: 1) quantitative Doppler using aortic and mitral stroke volumes, allowing calculation of regurgitant volume and regurgitant fraction, and 2) the proximal isovelocity surface area method to calculate ERO area [10]. LV end-diastolic dimensions (LVEDD) and end-systolic dimensions (LVESD) were measured using 2D parasternal long-axis view. LV end-diastolic and end-systolic volumes and EF were measured by the biapical Simpson's disk method [11].

Statistical Analysis

Results are presented as mean ± SD. To determine whether the difference in the values between the 2 groups was statistically significant, a paired t test was performed; the level of significance was set to $P<0.05$. Receiver-operating curves were generated for comparison of pre-operative echocardiographic indices for discriminating patients with or without LV dysfunction late after aortic valve replacement (AVR).

Results

The preoperative and late after surgery (mean 14.8±1.8 months) echocardiographic data of the study patients are displayed in Table 1. After aortic valve surgery, both LVEDD and LVESD decreased significantly. The LVEF was 54±12% before surgery and was 55±12% late after surgery. The incidence of postoperative LV dysfunction (LVEF<50%) was 25 % (14/55).

Table 1. **Echocardiogaphic indices**

	Before surgery	After surgery
	(14.8±1.8 months)	
LVEF (%)	52±13	56±11
LVEDD (mm)	60±8	46±7*
LVESD (mm)	43±9	31±9*
LVESD/BSA (mm/m^2)	26±5	19±6*

LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; BSA, body surface area
*$P<0.001$ vs. Before surgery

Table 2. **A comparison of clinical characteristics of patients whose postoperative LVEF≥50% or postoperative LVEF<50%**

	Post-operative LVEF		
	≥50%	**<50%**	***P* value**
No. of patients	41	14	
Male (%)	32 (78)	10 (74)	
Age (years)	55±16	65±10	0.03
NYHA III-IV (%)	16 (39)	8 (57)	0.12
Hypertension (%)	26 (63)	8 (57)	0.84
Dyslipidemia (%)	5 (12)	4 (29)	0.42
Diabetes (%)	5 (12)	3 (21)	0.28
Creatinine >1.5 mg/dl	0 (0)	3 (21)	0.001
Medication			
ACEI/ARB (%)	19 (46)	4 (29)	0.22
Beta-blocker	8 (20)	1 (7)	0.28

A comparison of clinical characteristics of patients whose postoperative LVEF≥50% or postoperative LVEF<50% is shown in Table 2. Patients with postoperative LV dysfunction were significantly older than those with postoperative LVEF>50%.

Table 3 shows the incidence of postoperative LV dysfunction according to the preoperative echocardiographic indices. The incidence of postoperative LV dysfunction was high in patients with preoperative LVEF<50% (11/24, 46%), preoperative LVESD>50 mm (6/14, 43%), preoperative LVEDD>70 mm (2/3, 67%), LVESD/BSA≥25mm/m^2 (12/28, 42%). On univariate analysis, the preoperative LVEF (r=0.61, $P<0.0001$, Figure 1), LVESD (r=–0.29, P=0.02, Figure 2) and LVESD/BSA (r=–0.48, $P<0.0001$, Figure 3) were predictive of postoperative LVEF. The optimal cutoff value for LVESD/BSA to predict the postoperative LV dysfunction was 26.5mm/m^2 with a sensitivity of 86%

Table 3. **Incidence of postoperative LVEF<50% according to the preoperative echocardiographic indices**

	Post-operative LVEF	
	≥50%	**<50%**
Preoperative LVEF		
LVEF≥50%	28	3 (10%)
LVEF<50%	13	11 (46%)
Preoperative LVEDD		
LVEDD>70 mm	1	2 (67%)
LVEDD≤70 mm	40	12 (23%)
Preoperative LVESD		
LVESD>50 mm	8	6 (43%)
LVESD≤50 mm	33	8 (20%)
Preoperative LVESD/BSA		
LVESD/BSA≥25 mm/m^2	16	12 (42%)
LVESD/BSA<25 mm/m^2	25	2 (7%)

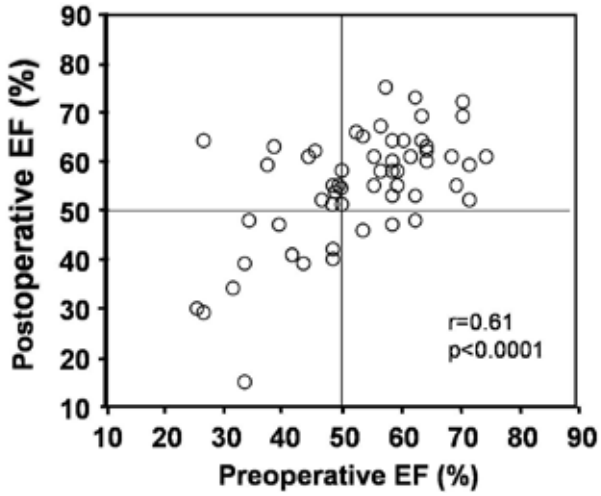

Figure 1. Relationship between preoperative and postoperative left ventricular (LV) ejection fraction (EF). The preoperative EF<50% is predictive of postoperative LV dysfunction

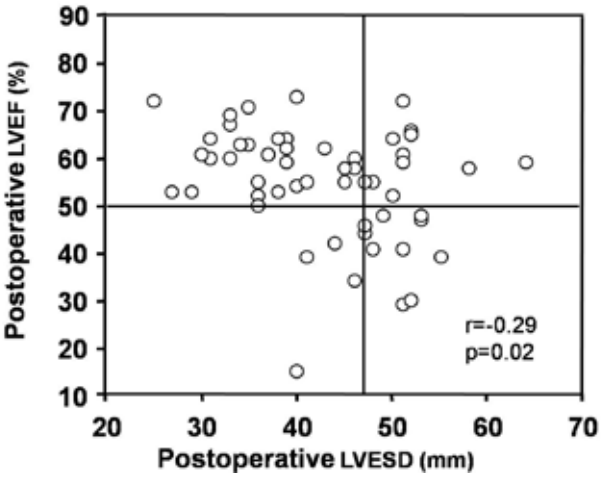

Figure 2. Relationship between preoperative left ventricular (LV) end-systolic dimension (ESD) and postoperative LV ejection fraction (EF). The preoperative ESD≥47 mm is predictive of postoperative LV dysfunction

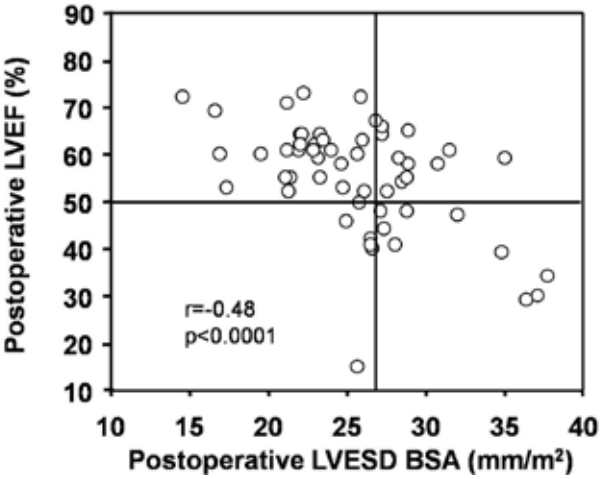

Figure 3. Relationship between preoperative left ventricular (LV) end-systolic dimension (ESD) normalized to body surface area (BSA) and postoperative LV ejection fraction (EF). The preoperative ESD/BSA≥26.5 mm is predictive of postoperative LV dysfunction

and a specificity of 70%, whereas LVEDD of 62 mm had 64% sensitivity and 71% specificity and LVESD of 47 mm had 79% sensitivity and 77% specificity.

Discussion

The timing of surgical correction for AR has traditionally been relied on symptoms or indexes of LV size or function associated with poor outcome. LVEF is an important predictor of cardiovascular outcomes in a broad spectrum of patients with heart failure [8]. Thus, to determine the timing, we must take into consideration not only postoperative survival but also the incidence of postoperative LV dysfunction.

We found that an LVEF of 50% and LVESV of 47 mm or LVESD/BSA of 26.5 mm/m^2 identified Japanese patients with a higher risk of postoperative LV dysfunction. The values of LVESD were lower than those recommended in the *American College of Cardiology* and the *American Heart Association* and the *European Society of Cardiology* guidelines [1,2]. These echocardiographic measures in Japanese patients may not be applied directly to patients in other countries, because the normal size of the heart is different [12]. Previous studies demonstrated that after surgery for AR, women exhibit an excess late mortality. The generalization to women of the unadjusted LV diameter surgical criteria established in men results in irrelevant criteria almost never reached in women [13,14]. This undoubtedly was related to the fact that women have smaller body sizes. Recent study has demonstrated that asymptomatic patients with severe AR and LV end-systolic volume index ≥45 ml/m^2 had higher cardiac event rates and surgery for AR reduced cardiac events [15]. These results emphasize the importance of normalization of LV size to body size in patients with AR.

A preoperative LVEF<50% is associated with a poor postoperative LV function and, despite the controversy about the prognostic usefulness of LV variables [13], should remain an indicator for surgical correction of AR. When the LVEF is reduced preoperatively because of increased afterload with preserved contractile function, the decrease in afterload and wall stress leads to an improvement in LVEF and this mechanism may explain the favorable effects of aortic valve replacement on LVEF [16–18]. However, in some patients, the persistent LV damage after aortic valve replacement is presumably resulting from irreversible myocardial contractile dysfunction before AVR. These findings indicated the need for surgical intervention for AR before the development of irreversible myocardial damage. In this study, LVESD normalized to

body surface area manifested as excessive LV dilatation raises the concern that irreversible LV contractile dysfunction might have already occurred. Although there is no ideal clinical measure of ventricular contractility, end-systolic indices are less load dependent than diastolic or ejection phase measurements [19].

Study Limitations

We defined LV dysfunction as LVEF<50%. However, postoperative LV performance is not determined by LVEF alone. We studied postoperative LVEF, which was easy to measure, but it is only aspect of LV performance. We did not take into account the effect of medications. Recent studies including the experimental study demonstrated that unloading therapy or beta-blocker therapy has a beneficial effect on LV remodeling and function [20,21]. Long-term vasodilator therapy with nifedipine or enalapril, however, did not reduce or delay the need for AVR in patients with asymptomatic severe AR [22]. The possible benefit of medical treatment still remains a matter of controversy and further study is needed to clarify this problem. It might be wondered if newer prostheses or surgical advances could, in the future, decrease the incidence of late postoperative LV dysfunction.

Conclusion

In Japanese patients with severe AR, echocardiographic parameters of LVEF and LVESD are good predictors of postoperative LV dysfunction and useful as objective markers to decide the timing of surgery. LVEF<50% and/or LVESD/BSA≥26.5 mm/m^2 should be carefully considered for surgical intervention, which reduces the risk of postoperative LV dysfunction.

Conflict of interest: None declared

References

1. Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease. A report of the American College of Cardiology/ American Heart Association task force on practice guidelines (writing committee to revise the 1998 guidelines for the management of patients with valvular heart disease). J Am Coll Cardiol. 2006;48:e1–148
2. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012). The task force on the management of valvular heart disease of the European Society of Cardiology (ESC) and the Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2012;33:2451–2496
3. Dujardin KS, Enriquez-Sarano M, Schaff HV, et al. Mortality and morbidity of aortic regurgitation in clinical practice. A long-term follow-up study. Circulation. 1999;99:1851–1857
4. Klodas E, Enriquetz-Sarano M, Tajik AJ, et al. Aortic regurgitation complicated by extreme left ventricular dilataion: long-term outcome after surgical correction. J Am Coll Cardiol. 1996;27:670–677
5. Klodas E, Enriquetz-Sarano M, Tajik AJ, et al. Optrimal timing of surgical correction in patients with severe aortic regurgitation: role of symptoms. J Am Coll Cardiol. 1997;30:746–752
6. Chaliki HP, Mohty D, Avierinos JF, et al. Outcomes after aortic valve replacement in patients with severe aortic regurgitation and markedly reduced left ventricular function. Circulation. 2002;106:2687–2693
7. Tornos P, Sambola A, Permanyer-Miralda G, et al. Long-term outcome of surgically treated aortic regurgitation. J Am Coll Cardiol. 2006;47:1012–1017
8. Solomon SD, Anavekar N, Skali H, et al. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. Circulation. 2005;112:3738–3744
9. Vasan RS, Larson MG, Benjamin EJ, et al. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction. J Am Coll Cardiol. 1999;33:1948–1955
10. Enriquez-Sarano M, Tajik AJ. Aortic regurgitation. N Engl J Med. 2004;351:1539–1546
11. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18:1440–1463
12. Daimon M, Watanabe H, Abe Y, et al. Normal values of echocardiographic parameters in relation to age in a healthy Japanese population. The JAMP study. Circ J. 2008;72:1859–1866
13. Klodas E, Enriquez-Sarano M, Tajik AJ, et al. Surgery for aortic regurgitation in women. Contrasting indications and outcomes compared with men. Circulation. 1996;94:2472–2478
14. McDonald ML, Smedira NG, Blackstone EH, et al. Reduced survival in women after valve surgery for aortic regurgitation: effect of aortic enlargement and late aortic rupture. J Thorac Cardiovasc Surg. 2000;119:1205–1215
15. Detaint D, Messika-Zeitoun D, Maalouf J, et al. Quantitative echocardiographic determinants of clinical outcome in asymptomatic patients with aortic regurgitation. A prospective study. J Am Coll Cardiol Img. 2008;1:1–11
16. Gaasch WH, Carroll JD, Levine HJ, Criscitiello MG. Chronic aortic regurgitation: prognosis value of left ventricular end-systolic dimension and end-diastolic radius/thickness ratio. J Am Coll Cardiol. 1983;1:775–782

17. Starling MR, Kirsh MM, Montgomery DG, Gross MD. Mechanisms for left ventricular systolic dysfunction in aortic regurgitation: importance for predicting the functional response to aortic valve replacement. J Am Coll Cardiol. 1991;17:887–897
18. Borer JS, Hochreiter C, Herrold EM, et al. Prediction of indications for valve replacement among asymptomatic or minimally symptomatic patients with chronic aortic regurgitation and normal left ventricular function. Circulation. 1998;97:525-534
19. Borow KM. Surgical outcome in chronic aortic regurgitation: A physiologic framework for assessing preoperative predictors. J Am Coll Cardiol. 1987;10:1165–1170
20. Plante E, Lachance D, Gaudreau M, et al. Effectiveness of β-blockade in experimental chronic aortic regurgitation. Circulation. 2004;110:1477–1483
21. Scognamiglio R, Negut C, Palisi M, et al. Long-term survival and functional results after aortic valve replacement in asymptomatic patients with chronic severe aortic regurgitation and left ventricular dysfunction. J Am Coll Cardiol. 2005;45:1025–1030
22. Evangelista A, Tornos P, Sambola A, et al. Long-term vasodilator therapy in patients with severe aortic regurgitation. N Engl J Med. 2005;353:1342–1349

International Heart
and Vascular Disease Journal • Volume 2, Number 2, February 2014 **ORIGINAL ARTICLES**
Journal of the Cardioprogress Foundation

Genetic polymorphism of endothelial nitric oxide synthase in coronary artery disease

Hasanzad M., Imeni M., Mohammadhasani M.R., Hassanzad M., Jamaldini S.H.*

Authors:

Mandana Hasanzad, PhD, Medical Sciences Research Center, Tehran Medical Branch, Islamic Azad University, Tehran, Iran
Mahdieh Imeni, Msc, Medical Sciences Research Center, Tehran Medical Branch, Islamic Azad University, Cardiogenetics Research Center, Tehran University of Medical Sciences, Tehran, Iran
Mohammad Reza Mohammadhasani, MD, Medical Sciences Research Center, Tehran Medical Branch, Islamic Azad University, Tehran, Iran
Maryam Hassanzad, MD, Pediatric Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
Seyed Hamid Jamaldini, MD, Cardiogenetics Research Center, Tehran University of Medical Sciences, Tehran, Iran

Background

Coronary artery disease (CAD) is a leading cause of mortality and morbidity in the Iranian population. Interaction between genetic and environmental factors determines susceptibility of an individual to develop CAD. Nitric oxide (NO) is an important endogenous vasodilator that is produced by endothelial nitric oxide synthase (eNOS) from L-arginine in endothelial and plays a critical role in the regulation of cardiovascular homeostasis.

Objective

The purpose of this study was to analyze the eNOS C786T polymorphism in CAD.

Materials and Methods

The study included 213 patients and 106 controls. eNOS rs41322052 polymorphism was genotyped using PCR-RFLP protocol.

Results

Previous eNOS T786C polymorphism studies suggested this polymorphism has an important role in cardiovascular disorders and especially in its association with the risk of CAD. We determined the prevalence of eNOS T786C polymorphism in healthy volunteers from an Iranian population and in patients suffering from CAD. Distribution

* Corresponding author. Tel/Fax: +98-21-22663213. E-mail: hjam1358@yahoo.co.uk

of genotypes CC was around 100% for patients and control groups, so the C allele was not the susceptible allele for CAD subjects in this study.

Conclusion

According to the current study, there were no significant differences in endothelial nitric oxide synthase gene C786T polymorphism between healthy volunteers and patients with CAD. Therefore, genetic variation in eNOS may not contribute to etiology and risk of CAD.

Key words

Coronary artery disease, endothelial nitric oxide synthase, Iranian patients

Introduction

Coronary artery disease (CAD) is one of the leading causes of death worldwide. Many epidemiological studies show that both environmental and genetic factors have influence, but genetic factors play a more important role in susceptibility to CAD [2,1].

It is clear that endothelial cells play a critical role in the progression and clinical manifestation of the atherosclerotic process [3,4]. One of the most important products of endothelial cells is nitric oxide (NO), a major mediator of endothelium dependent vasodilation made in the endothelial cells from L-arginine through the action of the homodimeric enzyme endothelial nitric oxide synthase (eNOS). In addition to vasodilation, NO inhibits platelet aggregation, proliferation of vascular smooth muscle cells, and leukocyte adhesion to endothelial cells [5,6]. eNOS may have an atheroprotective role by these functions [7].

Nitric oxide production can be influenced by polymorphisms of the eNOS gene. The gene is located on chromosome 7q35–36 [8]. The eNOS gene is expressed and functionally regulated through multiple regulatory steps [9,10] and also by several polymorphisms [11].

The substitution of T to C nucleotide at position 786 in the 5' flanking region of eNOS gene, leading to reduce of promoter activity of this gene, is associated with CAD [12].

The purpose of the present study was to assess the association of genetic variants of eNOS 786C>T (rs41322052) polymorphism with the risk of CAD.

Materials and methods

A total of 319 subjects including 213 patients with CAD and 106 controls participated in this study.

The inclusion criteria for the patients were: (1) age at the time of CAD diagnosis: 55 years or younger in men and 65 years or younger in women; and, (2) at least 50% stenosis in a major coronary artery, or one of their branches, as determined by angiography. The extent of the disease was defined according to the number of arteries with a minimum of 50% stenosis, whether in a single vessel or in multiple vessels. Diagnosis of myocardial infarction (MI) was confirmed through patients' records using the *World Health Organization* (WHO) criteria [13] based on symptoms, elevation in cardiac enzymes or electrocardiographic changes.

All patients provided information about coronary risk factors such as diabetes mellitus, hypertension, hypercholesterolemia and cigarette smoking. Triglycerides, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels were measured by conventional methods of clinical chemistry. Hypertension was defined as systolic blood pressure equal to or greater than 140 mmHg and/or diastolic blood pressure equal to or greater than 90 mmHg on more than one occasion. Patients with a history of diabetes or basal glycaemia higher than 120 mg/dL were defined as diabetics.

Genotyping

Genomic DNA was extracted from 10 ml of EDTA anticoagulated peripheral blood leucocytes using salting out method.

Screening for the eNOS 786C>T polymorphism was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The primers used were 5'-TGGAGAGTGCTGGTGTACCCCA -3' (forward) and 5'-GCCTCCACCCCCACCCTGTC -3' (reverse).

DNA is amplified for 40 cycles, each cycle comprising denaturation at 94 °C for 1 min, annealing at 62 °C for 1 min, extension at 70 °C for 1 min with final extension time of 5 min at 70 °C. The initial denaturation stage was carried out at 95 °C for 7 min. PCR products were digested with the restriction enzyme BsmAI at 37 °C overnight. In the presence of C

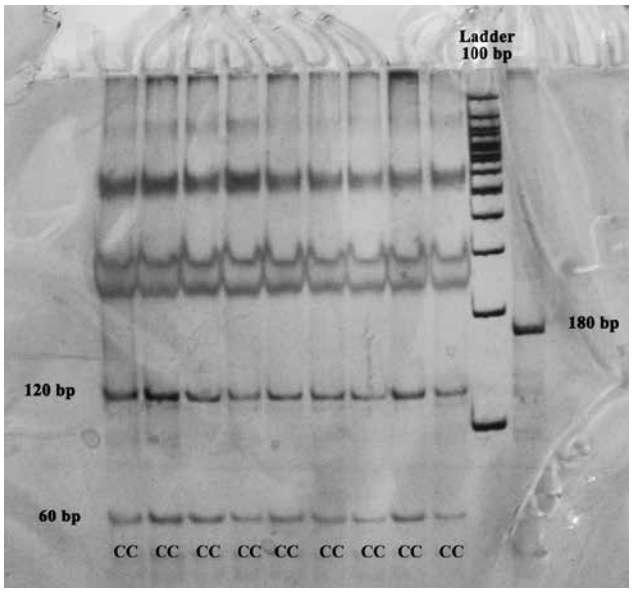

Figure 1. Representative screening for the endothelial nitric oxide synthase C786T polymorphism; 180-bp band, genotype TT; 120 & 60-bp band, genotype CC; 180, 120 & 60-bp bands, genotype CT

at nucleotide 786, the 180 base pair (bp) PCR product is cleaved into two fragments of 120 and 60 bp. The PCR products are separated on 8% acrylamid gel (Figure 1).

The validity of this PCR-RFLP analysis was confirmed by direct sequencing of several PCR samples with each genotype (Figure 2).

Results

The CAD patient group had a higher prevalence of hypertension, diabetes, smoking and family history of premature CAD compared with the controls. The patients also had higher body mass index (BMI), total cholesterol, LDL and triglycerides levels. According to our results, family history, hypertension, diabetes, smoking, obesity, high total cholesterol, LDL and triglycerides levels and low HDL significantly increased risk of CAD.

Distribution of CC genotypes was around 100% between patients and control groups.

Discussion

Recently, several studies revealed that there were various mutations on eNOS gene and these mutations might be a risk factor for CAD, MI, and hypertension. They also found that these polymorphisms differed largely among races due to large differences in the linkage pattern of –786T/C, Glu298Asp, and 4a/4b polymorphisms of eNOS among races. In this study, we investigated the relationship between T786C mutation of eNOS gene and CAD for first time in the Iranian population.

Our results demonstrated no association between C allele and CAD in the Iranian population.

A study carried out in Caucasian patients reported that eNOS (T786C) gene polymorphism is a major risk factor for CAD in this population [14]. Masafumi Nakayama *et al*. showed that an association between this gene polymorphism reduces the endothelial NO synthesis and predisposes the patients with the mutation to coronary spasm in a Japanese population [12].

Çiftçi *et al*. examination of a Turkish population indicated significantly high frequency of eNOS -786C/C genotype in acute coronary syndrome (ACS) patients than in those of controls that indicated genotype association between eNOS (786C/C) with ACS. In addition, the finding of significantly high frequency of T/T genotype in the coronary heart disease (CHD) group may support the relationship of CC genotype with ACS without CHD [15].

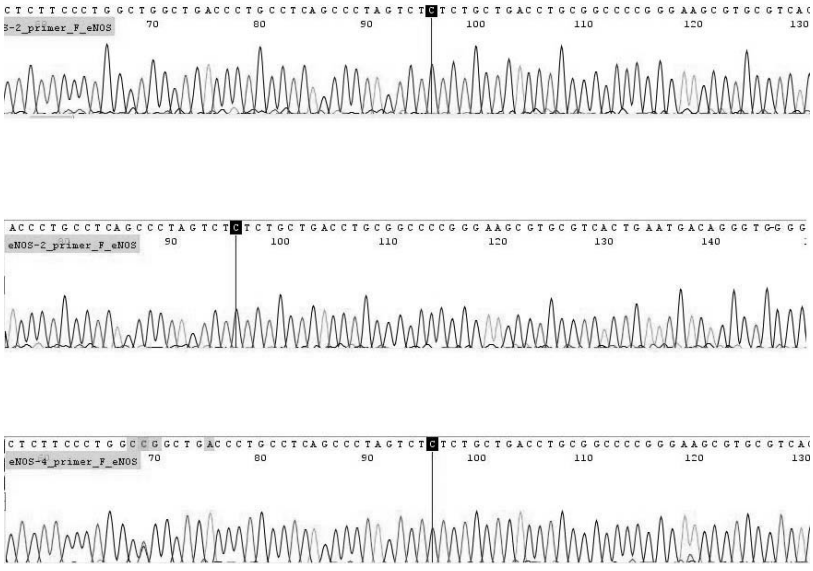

Figure 2. A sample of sequencing result for confirming eNOS genotyping. The vertical blue line indicates the position of C786T SNP

There are no more studies on this polymorphism in other populations. Future studies should seek more single nucleotide polymorphisms (SNPs) in our population and create a panel of SNPs which can be used as genetic risk markers.

In the present study, the eNOS C786T polymorphism seems to have no significant association with the risk of CAD in our patients.

Acknowledgment

The authors thank all those who collaborated with us in this survey.

Conflict of interest: None declared

References

1. Marenberg ME, Risch N, Berkman LF, et al. Genetic susceptibility to death from coronary heart disease in a study of twins. N Engl J Med. 1994;330:1041–6.
2. Ramakrishnan L, Sachdev HS, Sharma M, et al. Relationship of APOA5, PPARg and HL gene variants with serial changes in childhood body mass index and coronary artery disease risk factors in young adulthood. Lipids Health Dis. 2011;10:68.
3. De Caterina R. Endothelial dysfunctions: common denominators in vascular disease. Curr Opin Lipidol. 2000;11:9–23.
4. Gimbrone Jr MA. Vascular endothelium, hemodynamic forces, and atherogenesis. Am J Pathol. 1999;155:1–5.
5. Moncada S, Higgs A. The l-arginine-nitric oxide pathway. N Engl J Med 1993;329:2002–12.
6. Luscher TF. The endothelium as a target and mediator of cardiovascular disease. Eur J Clin Investig. 1993;23:670–85.
7. Hingorani AD. Polymorphisms in endothelial nitric oxide synthase and atherogenesis: John French Lecture 2000. Atherosclerosis. 2001;154:521–7.
8. Marsden PA, Heng HHQ, Scherer SW, et al. Structure and chromosomal localization of the human constitutive endothelial nitric oxide synthase gene. J Biol Chem. 1993;268:17478–88.
9. Rossi GP, Seccia TM, Nussdorfer GG. Reciprocal regulation of endothelin-1 and nitric oxide: relevance in the physiology and pathology of the cardiovascular system. Int Rev Cytol. 2001;209:241–72.
10. Andrew PJ, Mayer B. Enzymatic function of nitric oxide synthases. Cardiovasc Res. 1999;43:521–31.
11. Hingorani AD, Liang CF, Fatibene J, et al. A common variant of the endothelial nitric oxide synthase (Glu298-Asp) is a major risk factor for coronary artery disease in the UK. Circulation. 1999;100:1515–20.
12. Masafumi Nakayama, Hirofumi Yasue, Michihiro Yoshimura, et al. C 786 → T Mutation in the 5'-Flanking Region of the Endothelial Nitric Oxide Synthase Gene Is Associated With Coronary Spasm. Circulation 1999;99:2864–2870.
13. Nomenclature and criteria for diagnosis of ischemic heart disease. Report of the Joint International Society and Federation of Cardiology/World Health Organization task force on standardization of clinical nomenclature. Nomenclature and criteria for diagnosis of ischemic heart disease. Circulation.1979;59:607–8.
14. Rossi GP, Cesari M, Zanchetta M. The T-786C endothelial nitric oxide synthase genotype is a novel risk factor for coronary artery disease in Caucasian Patients of the GENICA study. J Am Coll Cardiol. 2003 Mar 19;41(6):930-7.
15. Ciftçi C, Melil S, Cebi Y, et al. Association of endothelial nitric oxide synthase promoter region (T-786C) gene polymorphism with acute coronary syndrome and coronary heart disease. Lipids Health Dis. 2008 Feb 25;7:5

International Heart
and Vascular Disease Journal • Volume 2, Number 2, February 2014 **ORIGINAL ARTICLES**
Journal of the Cardioprogress Foundation

The relationship between blood pressure and physical activity without induced programmes

Ozpelit E. *, Şimşek M.A., Kangül H., Akdeniz B., Goldeli Ö., Barış N.

Authors:

Ozpelit Ebru, MD, Department of Cardiology, School of Medicine, Dokuz Eylul University, İzmir, Turkey
Şimşek Mustafa Aytek, MD, Department of Cardiology, School of Medicine, Dokuz Eylul University, İzmir, Turkey
Kangül Hande, MD, Department of Cardiology, School of Medicine, Dokuz Eylul University, İzmir, Turkey
Akdeniz Bahri, MD, Professor, Department of Cardiology, School of Medicine, Dokuz Eylul University, İzmir, Turkey
Goldeli Özhan, MD, Professor, Department of Cardiology, School of Medicine, Dokuz Eylul University, İzmir, Turkey
Barış Nezihi, MD, Professor, Department of Cardiology, School of Medicine, Dokuz Eylul University, İzmir, Turkey

Objective

Scheduled exercise programmes improve cardiovascular risk profile. However, long-term attendance in these programmes is extremely low. In this study, we aimed to investigate the association between habitual daily activity levels of the subjects and their cardiovascular risk profile with particular attention to blood pressure (BP) levels.

Materials and Methods

292 subjects were enrolled in the study. All of the subjects completed the International Physical Activity Questionnaire. Their cardiovascular risk profile and BP levels were also recorded. Subjects were divided into 3 subgroups according to their weekly total metabolic equivalent count as low, moderate and high activity groups. Comparison of these three groups with regard to cardiovascular risk status and BP levels was performed. The effect of physical activity level on BP control was also assessed.

Results

The numbers of subjects with low, moderate and high exercise level were 154, 91 and 47 respectively. Two hundred and thirty subjects were hypertensive and 105 of them had uncontrolled hypertension. The cardiovascular risk status and BP levels did not differ among low, moderate and high activity groups. Among the hypertensive

* Corresponding author. Tel: + 90 (232) 412 4134, fax: +90 (232) 279 2565. E-mail: ebru.ozpelit@gmail.com

population, those with uncontrolled hypertension were significantly less active those with controlled hypertension.

Conclusion

Blood pressure control in this hypertensive population was found to be associated with their weekly physical activity levels. This finding is important to highlight the effects of daily lifestyles on cardiovascular outcomes.

Key words

Hypertension, physical activity, sedentary life, blood pressure control

Introduction

Economic development and modern technology have simplified life for humanity. In the modern world, we have reduced use of our muscles and generally replaced many of our basic functions with machines. We invest much mental effort in how we can walk less (escalators, elevators, conveyor belts, etc.).

Sedentary lifestyle is known to be related to hypertension, hypercholesterolemia, atherosclerosis and atherosclerosis-related cardiovascular diseases [1]. Regular physical activity can reduce cardiovascular risk. Some studies show the effect of physical activity in reducing blood cholesterol levels and BP [2,3]. Success of scheduled programmes and induced physical activities has been demonstrated in previous studies [4,5]. However, each person has different daily physical activity in normal life and it is not well established whether the BP levels differ according to daily physical activity of individuals in the absence of any scheduled programme.

Hypertension is one of the leading causes of death in the world. Its prevalence in Turkey is 31.8% [6]. Achieving optimal control of high BP is difficult. Usually more than two drugs are needed to control BP [7]. Among patients on antihypertensive therapy, only 20% of patients have controlled BP. The ratio of controlled BP in general population is only 8% [6].

In this cross-sectional study, we aimed to investigate whether the weekly physical activity status of patients has an impact on BP control. Additionally, we aimed to determine the physical activity status and ratio of antihypertensive drugs usage in our geographical area.

Methods

The study was conducted in Balcova, Izmir, which is an urban area at the western site of Turkey. A total of 340 subjects were examined for this study; 190 of those through clinic visits and 150 through home visits. After excluding ineligible subjects due to inadequate medical information, 292 subjects were enrolled in the study. Home visits were conducted at different times of a day. Cases for home visits were selected from local elective lists via a random numbers method. Educated medical school students and two investigators (Şimşek MA, Kangül H) did home visits. Hypertensive to normotensive volunteer ratio was planned as 3/1. All subjects gave informed consent and the study protocol was approved by our Institutional Review Board.

Inclusion criteria:

- People older than 18 years old
- Hypertensive patients (according to the Seventh Report of the *Joint National Committee* (JNC 7): mean systolic BP≥140 mmHg or mean diastolic BP≥90 mmHg, or previously diagnosed and/or taking antihypertensive drugs) [8].

Exclusion criteria:

- People with scheduled sportive programme
- Physical disability
- Answering the *International Physical Activity Questionnaire* (IPAQ) inappropriately
- Active systemic disease

Blood pressure was measured according to the *JNC-7* recommendations with aneroid sphygmomanometer (Riester, Rudolf Reister GmbH&Co, Jungingen, Germany). Validated short Turkish version of IPAQ was used to measure weekly physical activity [9]. Mean weekly physical activity was calculated as metabolic equivalent (MET) for each person. Less than 600 MET was defined as low physical activity level; 600–1500 MET as moderate level; and, more than 1500 MET as high level.

Statistical Analysis

SPSS statistical software (SPSS for Windows 15.0, Chicago, IL, USA) was used for all statistical calculations. Continuous variables were given as mean ± SD, and categorical variables were defined as a percentage. Differences between groups were tested using

one-way analysis of variance (ANOVA), t-test and x^2 test when appropriate. Pearson correlation was used to evaluate the association between the parameters. Statistical significance was defined as $P<0.05$.

Results

230 hypertensive and 62 normotensive volunteers were enrolled in this study. The mean age of total study population was 56.5±13.5 (19–86). Among the entire studied group, 154 (52.7%) were female; 59 (20.2%) were diabetic; 101 (34.6%) were hyperlipidemic; and, 95 (32.5%) were active smokers. Mean body mass index (BMI) of the 292 subjects was 27.8±4.4 (16.5–41.0). Both hypertensive and normotensive volunteers have comparable physical activities but normotensive ones were significantly younger and thinner (Table 1).

Hypertensive patients were divided into two groups according to the presence of optimal BP control. One hundred and twenty five patients with BP<140/90 mmHg were accepted as regulated and 105 patients with BP≥140/90 mmHg as unregulated. The regulated group was younger than unregulated but the difference was not significant. Weekly physical activity of regulated group was significantly higher than unregulated. Regulated group has significantly lower BMI than unregulated (Table 2).

Systolic and diastolic BP was analyzed for correlation with weekly physical activity level. Both have opposite relations with weekly physical activity level; however, the correlations were not significant (Table 3).

The studied population was divided into 3 groups, according to their weekly physical activity, as low, moderate and high. There were no significant differences between groups in respect of systolic and diastolic BP (Table 4). Among the hypertensive population, the rates of controlled BP levels were also similar between groups (Table 5).

Antihypertensive drug usage was applicable in 199 of 230 hypertensive patients. The ratio of antihypertensive drugs is shown in Table 6. Sixty nine patients were on beta-blockers and 130 were not. Patients taking beta-blockers had less weekly physical activ-

Table 1. **Physical activity, age and BMI of hypertensive and normotensive volunteers**

	Hypertensive (n=230)	Normotensive (n=62)	*P*
Physical activity (MET)	995.7 ± 1206.2	712.3 ± 990.5	0.14
Age (years old)	59.1 ± 12.0	47.1 ± 14.8	<0.05
BMI (kg/m²)	28.4 ± 4.4	25.8 ± 4.0	<0.05

Table 2. **Physical activity, age and BMI of regulated and unregulated groups in hypertensive patients**

	Regulated (n=125)	Unregulated (n=105)	*P*
Physical activity (MET)	1099.4 ± 1480.4	784.8 ± 732.6	<0.05
Age (years old)	57.7 ± 12.7	60.7 ± 10.9	0.053
BMI (kg/m²)	27.5 ± 4.2	29.4 ± 4.5	<0.05

Table 3. **Correlation of systolic and diastolic blood pressures with weekly physical activity**

	R	*P*
Hypertensive patients (n=230)		
Systolic BP (mmHg)	– 0.05	0.36
Diastolic BP (mmHg)	– 0.07	0.24
All cases (n=292)		
Systolic BP (mmHg)	– 0.90	0.17
Diastolic BP (mmHg)	– 0.92	0.16

BP = blood pressure

Table 4. **Systolic and diastolic blood pressures. Difference between low, moderate and high physical activity groups**

	Low	Moderate	High	*P*
All cases (n=292)	(n=154)	(n=91)	(n=47)	
Systolic BP (mmHg)	132.3 ± 16.7	131.4 ± 18.9	132.4 ± 17.5	0.91
Diastolic BP (mmHg)	78.6 ± 10.9	79.5 ± 9.9	77.5 ± 11.8	0.58
Hypertensive (n=230)	(n=120)	(n=70)	(n=40)	
Systolic BP (mmHg)	134.8 ± 17.7	135.3 ± 19.5	133.9 ± 16.8	0.93
Diastolic BP (mmHg)	79.8 ± 11.2	81.6 ± 10.4	77.8 ± 11.8	0.20
Normotensive (n=62)	(n=34)	(n=23)	(n=5)	
Systolic BP (mmHg)	123.7 ± 9.1	119.6 ± 10.3	117.0 ± 14.8	0.19
Diastolic BP (mmHg)	74.6 ± 8.6	73.5 ± 5.7	70.4 ± 7.1	0.50

BP = blood pressure

Table 5. **Ratio of patients with regulated and unregulated blood pressure between low, moderate and high physical activity groups**

	Low (n=120)	Moderate (n=70)	High (n=40)	*P*
Unregulated group	54 (45%)	33 (47%)	18 (45%)	0.95
Regulated group	66 (55%)	37 (53%)	22 (55%)	0.95

Table 6. **Antihypertensive drug usage**

Antihypertensive drugs	Patients number (n=199)*
ACEI	30 (15.1%)
ACEI + D	13 (6.5%)
ARB	44 (22.1%)
ARB + D	38 (19.1%)
BB	69 (34.7%)
CCB	38 (19.1%)
ARB + CCB	6 (3.0%)
ACEI + CCB	1 (0.5%)
D	9 (4.5%)
AB	4 (2.0%)

* There was no patient with beta blocker + diuretic. Some patients use more than one drug.
ACEI = angiotensin converting enzyme inhibitor;
D = diuretic;
ARB = angiotensin receptor blocker;
BB = beta blocker;
CCB = calcium channel blocker;
AB = alpha blocker

ity than others but the difference was not significant (952.5±1191.3 vs. 1022.0±1221.8, *P*=0.70).

Discussion

This study examined the relation between BP and weekly physical activity level obtained via IPAQ. There was no significant difference between hypertensive and normotensive volunteers with regard to their physical activity status. However, in the hypertensive group, physical activity level was found to be associated with BP control. Among hypertensive patients, the ones with optimal BP control were significantly more active than the patients with unregulated hypertension.

We found that normotensive patients were significantly younger than hypertensive. This was not an unexpected finding as the prevalence of hypertension increases with aging [6]. Although the BMI in normotensive patients was significantly lower than in hypertensive, their weekly physical activity level was surprisingly low. It is speculated that, as human metabolism gets slower with aging, the elderly people who have higher BP, BMI, cholesterol, etc. try to apply the offered lifestyle changes, causing them to be more active than they were.

When we focused on the hypertensive group, the weekly physical activity level of patients with regulated BP was significantly higher than of unregulated ones. Their BMI was significantly lower than unregulated patients, as expected. We have previously demonstrated that arterial stiffness was associated with resistant hypertension [10]. Arterial stiffness is known to be a primary reason for increased cardiac afterload and unregulated BP in the elderly. Shibata and co-workers demonstrated that aortic stiffening was not improved even after 1 year of progressive endurance exercise training in elderly patients, while left ventricular afterload was reduced [5]. Scheduled exercise programmes can improve some cardiovascular outcomes, but healthy aging can be related more with basal physical activity status of person than with scheduled exercise programmes. So we think that, increased basal physical activity yielded a better BP control probably due to an improvement in arterial stiffness. Although sedentary behaviours are closely associated with mortality, moderate-vigorous physical activity does not fully mitigate cardiovascular risks associated with sedentary life [1]. Our understanding is that, improvement of a sedentary lifestyle via basic lifestyle changes could be more effective than scheduled exercise programmes in decreasing cardiovascular risks. The more that people increase activity in their daily lives, the better their cardiovascular risk profile. To make certain conclusions, optimal energy expenditure via daily activities should be defined more clearly [11].

When the whole studied population was divided into 3 subgroups according to weekly physical activity level as low, moderate and high, no significant difference was found between the groups with regard to systolic and diastolic BP. The percentages of patients with unregulated hypertension were also not statistically different among these 3 groups. Quantification of physical activity level of the groups was achieved according to a MET value criteria recommended by IPAQ. However, categorizing the physical activity via this classification may not be as valuable as the total MET count. Celis-Morales and co-workers compared the accelerometer and IPAQ. Although they found an over-reporting of physical activity with IPAQ, many data proved the validity of IPAQ [12].

In our population, beta-blockers and rennin-angiotensin system blockers were the most frequently used antihypertensive drugs. Another interesting finding of our study was that there was no significant physical activity difference between the patients with and without beta-blockers. Although beta-blocker therapy is a well-known cause of decreased functional status, this was not the case in our study group.

In conclusion, this study illustrates how minor changes in sedentary lifestyles can cause better BP control. It is not always mandatory to apply strict exercise programmes to improve the cardiovascular risk profile. As long-term attendance to scheduled physical training is extremely low among patients, it is better to increase the physical activity level through habitual alterations of patients' daily lives. For assessment and quantification of the patients' physical activity level, IPAQ is a simple and valid tool. However, it depends on the patient's self-reporting and no definitive threshold level exists to define if a patient is physically active or not. More data are needed for optimal assessment of patients' physical activity level and for defining the targets.

Limitations

The parameters assessed in this study, other than the measured BP levels, are based on patients self-reporting. Almost half of the patients were evaluated via clinical visits. Thus, a "white coat" effect cannot be excluded in this population. The relatively small number of normotensive patients and mismatched basal characteristics of the normotensive and hypertensive patients can limit the accuracy of the comparison be-

tween these groups with regard to their physical activity status. However, this study was not designed for such a distinct purpose and therefore we did not seek to make the groups matched. In the hypertensive population, BP control was evaluated according to the measured BP levels. Variables, other than physical activity status, were not considered when assessing the level of BP control.

Conflict of interest: None declared

References

1. Charles EM, Stephanie MG, Steven CM, et al. Amount of time spent in sedentary behaviors and cause-specific mortality in US adults. Am J Clin Nutr. 2012;95:437–445.
2. Pinto Pereira SM, Ki M, Power C. Sedentary behaviour and biomarkers for cardiovascular disease and diabetes in mid-life: the role of television-viewing and sitting at work. PLoS One. 2012;7:e31132.
3. Rossi A, Dikareva A, Bacon SL, Daskalopoulou SS. The impact of physical activity on mortality in patients with high blood pressure: a systematic review. J Hypertens. 2012;30:1277–1288.
4. Fletcher GF, Balady G, Blair SN, et al. Statements on exercise: benefits and recommendations for physical activity programmes for all Americans: a statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. Circulation. 1996;94:857–862.
5. Shibata S, Levine BD. Effect of exercise training on biologic vascular age in healthy seniors. Am J Physiol Heart Circ Physiol. 2012 Mar 15;302:H1340–1346.
6. Altun B, Arici M, Nergizoglu G, et al. Prevalence, awareness, treatment and control of hypertension in Turkey (the PatenT study) in 2003. J Hypertens. 2005;23:1817–1823.
7. Kjeldsen SE, Dahlöf B, Devereux RB, et al. Lowering of blood pressure and predictors of response in patients with left ventricular hypertrophy: the LIFE study. Losartan Intervention for Endpoint. Am J Hypertens. 2000;13:899–906.
8. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003 Dec;42:1206–1252.
9. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003;35:1381–1395.
10. Pabuccu T, Baris N, Ozpelit E, et al. The relationship between resistant hypertension and arterial stiffness. Clin Exp Hypertens. 2012;34:57–62.
11. Owen N, Sparling PB, Healy GvN, et al. Sedentary behavior: emerging evidence for a new health risk. Mayo Clin Proc. 2010;85:1138–1141.
12. Celis-Morales CA, Perez-Bravo F, Ibanez L, et al. Objective vs. self-reported physical activity and sedentary time: effects of measurement method on relationships with risk biomarkers. PLoS One. 2012;7:e36345.

International Heart
and Vascular Disease Journal • Volume 2, Number 2, February 2014
Journal of the Cardioprogress Foundation

CLINICAL CASE

A case of infective endocarditis after coronary stenting in myocardial infarction patients

Alekperov E.Z.*

Author:
Elman Zaur oglu Alekperov, MD
Senior Researcher of the Department of Myocardial Infarction of the Scientific-Research Institute of Cardiology named after J.Abdullayev, Baku, Azerbaijan

Summary

A clinical analysis was conducted of a patient who developed infective endocarditis after percutaneous coronary intervention with stenting of the right coronary artery. Despite a large amount of vegetation on the aortic valve (23 mm), it underwent a complete regression within 22 days. In addition, an interesting fact was the absence of prior aortic valve lesions, suggesting iatrogenic aortic insufficiency developed in this patient, and infective endocarditis.

Keywords

Coronary artery stenting, infective endocarditis, aortic valve

Infective endocarditis is a dangerous and severe inflammatory disease of the endocardium with a septic course. The disease most commonly affects the endocardium of modified valves and intracardiac defects of the heart. In addition, in the literature there are quite a lot of data on inflammatory changes of the endocardium in the area adjoining implantable endocardial electrodes [1]. Some interventional cardiologists believe that there is a possibility of developing bacterial endocarditis immediately after an invasive procedure, although there are limited conclusive data on this assumption in the available sources of literature [2]. There is some evidence that bacterial endocarditis involves unaffected heart valves [3]. In this regard, this case may be of some clinical and scientific interest.

Patient M, 61 years old, was admitted to the *Cardiology Department of the Central Hospital of Oilmen* (CHO) on 4 August 2012, complaining of fever, malaise, general weakness, pain in the lower back and left knee. Twenty years ago, during prophylactic examination in the *Scientific-Research Institute of Cardiology named after J.Abdullayev*, Baku, Azerbaijan, pathological changes in electrocardiogram (ECG) in the form of negative T waves (v1-v4) were found. The veloergometry conducted at the time had negative results, negative T waves in the ECG during exercise, which underwent reversion and became positive. The tolerance to the load was high, no subjective sensations during the test were observed. There were no echocardiographic signs of structural changes in the heart and valves. All that time, the patient main-

* Corresponding author. Tel: +99412 4653401 (work); +99450 3282456 (mobile). E-mail: azelman56@mail.ru

tained daily activity. His work had often been associated with physical exercise, without any discomfort in the heart. Two years ago, he first experienced a rise in blood pressure (BP) up to 180/100 mmHg. He was prescribed a fixed-dose maintenance therapy with lisinopril and hypothiazide after consultation at the *Scientific-Research Institute of Cardiology*. After this prescription, his condition was stable for a long time and BP readings remained within the target values. Once a year, the patient had a medical check-up in the *Outpatient Department of the CHO*.

Three months earlier, 11 May 2012, after emotional stress, the patient felt a searing pain in the chest, weakness, periodical cold sweat with an episode of short-term loss of consciousness. Due to the progressive deterioration, he was admitted to the *Cardiology Department of the CHO* with a diagnosis of developing acute lower myocardial infarction. X-ray examination showed a moderate expansion of the heart's shadow to the left. Echocardiogram revealed that systolic and diastolic dimensions and function of the left ventricle (LV) were normal; there was a moderate concentric LV hypertrophy. Laboratory tests detected the dynamics of troponin I going from 0.44 ng/mL to 10.19 ng/mL. Other indicators of the laboratory and instrumental methods were normal. During coronary angiography he was diagnosed with coronary subtotal occlusion of the right coronary artery, and stenting of infarct-related coronary artery was conducted. Three days later, he had a sub-febrile temperature, which normalized on the fourth day after intramuscular injection of ceftriaxone 1.0g per day. The patient was discharged from hospital in satisfactory condition a week after admission.

In spite of regular check-ups in the *Outpatient Department of the CHO*, after 1.5 months, 4 July 2012, his temperature started to rise, increasing to 38.8º C accompanied by strong chills. A total blood test showed increased erythrocyte sedimentation rate to 66 mm/h, C-protein levels to 39.8 mg/L (normal <3.1 mg/L), moderate monocytosis and anemia. Repeat blood cultures for sterility were negative. An ECG showed signs of myocardial infarction in the form of scarring of the lower wall of the LV myocardium. X-ray examination of the chest did not show any pathology, there was a slight enlargement of the heart to the left. An ultrasound examination of the internal organs: the liver, gallbladder, pancreas, urinary bladder and prostate showed that everything was in normal range; the kidneys had visible salt crystals. Echocardiography: systolic and diastolic dimensions and systolic function of LV were normal; ejection fraction - 60%; segmental function of LV walls – normal; aortic valve cusps had visible small single vegetation. The patient was re-admitted to the *CHO* with a diagnosis of subacute infective endocarditis. Despite the conducted forced comprehensive treatment with adequate doses of antibiotics, the vegetation on the aortic valve was progressively increasing and, by the 12th day, it reached 23 mm. This size of vegetation persisted up to 20 days, but then regression to 17 mm was recorded on day 25, 14 mm on day 28, and 7.5 mm on day 34 of the treatment (Figure 1). Contractile function of the myocardium and the size of the heart chambers during inpatient treatment remained within normal limits, although the echocardiography had signs of moderate aortic valve insufficiency of II degree. Echocardiography, performed on the 42nd day of inpatient treatment, showed a dense calcified area on the site of vegetation. The patient was discharged home in a satisfactory condition. Over two weeks he continued to take rifampicin and fluconazole. Currently, his condition is satisfactory and his ability to work has been completely restored. Ventricular extrasystoles of II graduation (according to Lown classification) are periodically observed. Hemodynamic signs of aortic valve insufficiency of II degree can still be seen on echocardiography. He takes regularly statins, aspirin, clopidogrel, ACE inhibitors, amiodarone, and has periodical check-ups in the Outpatient Departments of the *CHO* and *Scientific-Research Institute of Cardiology named after J.Abdullayev*.

The above data suggest that the patient has no previous signs of aortic insufficiency, as he repeatedly underwent complete preventive examination prior to the disease. According to the patient's history, he suffered from rheumatism in his youth, but the previous echocardiographic studies had not detected the presence of valvular heart disease, including aortic insufficiency. An interesting fact is that the LV dimensions remained in normal range, which is not typical for the long-term pre-aortic regurgitation; in other words, the problems emerged immediately after percutaneous coronary intervention (PCI). We can assume that PCI has contributed to traumatic injury of the aortic valve cusps and the appearance of moderate regurgitation of blood from the aorta, which was seen on echocardiography as aortic valve insufficiency of II degree. The genesis for the temperature (37-38°C), which appeared on the third day after PCI and lasted for 5 days, is not clear. The temperature became normal only after parenteral administration of the anti-

biotic. It is possible that during the procedure infection was primarily localized on the injured aortic valve cusp.

Thus, the analysis of this clinical case suggests the development of iatrogenic infective endocarditis. Perhaps such clinical situations require much closer analysis. If there is a need for an invasive intervention, interventional cardiologists should consider the potential for development of such complications.

References

1. Habib G, Hoen B, Tornos P, et al. The Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009) [Internet]. [place unknown]: Oxford University Press; 2009. p. 2369–2413. Available from: http://escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-IE-FT.pdf
2. Friedman ND, Kaye KS, Stout JE, et al. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med. 2002;137:791–797.
3. Hoen B, Alla F, Selton-Suty C, et al. Changing profile of infective endocarditis: results of a 1-year survey in France. JAMA. 2002;288:75–81.

International Heart
and Vascular Disease Journal • Volume 2, Number 2, February 2014
Journal of the Cardioprogress Foundation

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).

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

1. Submission requirements and publishing policy

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

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

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

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

1.4. Submission of the manuscript to the Editors implies that the Author agrees to transfer the exclusive property rights for the manuscript and other objects of the copyright, like photos, drawings, graphics, tables, etc., to the Editors. The Editors obtain the right to reproduce (partly or fully) all the content submitted, including objects of the copyright, in press and on the Internet; to distribute; to translate the manuscript and other provided content into any language; to export and import copies of the issue where the article of the Author was published; and to revise the manuscript.

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

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

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

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

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

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

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

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

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

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

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

2. General recommendations for submission of original scientific works

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

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

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

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

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

3. Publication of uncontrolled trials results

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

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

4. Ethical aspects

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

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

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

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

5. Authorship

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

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

6. Conflict of interests/financing

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

7. Manuscript content

7.1. Title page

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

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

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

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

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

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

7.2. Summary

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

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

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

7.3. List of abbreviations and their definitions

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

7.4. Text

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

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

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

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

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

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

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

7.5. Statistics

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

7.6. Acknowledgements

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

7.7. References

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

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

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

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

7.7.5. In order to increase the citing of authors, transliteration of sources in non-English languages are made in the **International Heart and Vascular Disease Journal** using official coding. Names of authors and journals are transliterated by means of coding, and semantic transliteration (translation) is used for the titles of articles. If a source has an original transliteration, the latter is used. The Editors will be grateful if authors provide the transliterated variant of the list of references. You can use online services: http://translit.ru for making transliteration.

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

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

Periodicals

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

Sources in non-English languages with transliteration:

Baevskiy RM, Ivanov GG, Chireykin LV, et al. Analiz variabelnosti serdechnogo ritma pri ispolzovanii razlichnykh elektrokardiograficheskikh sistem (metodicheskiye rekomendatsii) [Analysis of heart rate variability using different ECG systems (guidelines)]. Vestnik aritmologii. 2002;24:65–86. Russian.

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

Punctuation in the list of references should be considered. A comma should not be put between the name of the journal and the year of its release. After the year of release a semicolon is put without a space, then a colon follows the volume

number, and finally page numbers are given. There are no indications like "volume", "№", "pages".

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 non-English languages with transliteration:

Belenkov YuN. Kardiomiopatii [Cardiomyopathies]. In.: Chazov EI, Belenkov YuN., editors. Ratsionalnaya farmakoterapiya serdechno-sosudistykh zabolevaniy: Rukovodstvo dlya praktikuyushchikh vrachey [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 non-English languages with transliteration:

Shlyakhto EV, Konradi AO, Tsyrlin VA. Vegetativnaya nervnaya sistema i arterialnaya gipertenziya [The autonomic nervous system and hypertension]. St. Petersburg (Russia): Meditsinskoe izdatelstvo; 2008. Russian.

Websites

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

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

7.8. Diagrams, charts, and drawings

7.8.1. Diagrams, charts, and drawings should be submitted electronically in the following formats: «MS Excel», «Adobe Illustrator», «Corel Draw» or «MS PowerPoint». Diagrams, charts, and drawings must be allocated on separate pages, numbered in order of citation, and have names and notes if necessary. They must not repeat the content of tables. Please indicate the names and units of measurement for graph axes. Provide the legend for each graph (denote lines and filling). If you compare diagrams, provide significance of differences. Do not use 3-D models for histograms. If appropriate, please identify places in the text where you wish graphics, drawings and graphs to be inserted.

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

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

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

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

7.9. Tables

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

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

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

PEDIM 2014

Prague European Days of Internal Medicine 18–20 September, 2014

www.pedim2014.org

FOUNDATION FOR THE ADVANCEMENT OF CARDIOLOGY

"CARDIOPROGRESS"

knowledge, observation, action

Official website: www.cardioprogress.ru

Tel: 007 965 236 1600

Email: inf.cardio@gmail.com

Moscow, Russia