COMPLEX REDUCTION OF CARDIOVASCULAR PROGNOSTIC RISK WITH TIME-RELEASED GARLIC POWDER TABLETS ALLICOR

Igor A. Sobenin[1,2], Valentin V. Pryanishnikov[1], Alexander N. Orekhov[1,2]

Institute of General Pathology and Pathophysiology, Russian Academy of Medical Sciences[1];
Institute for Atherosclerosis Research[2], Moscow, Russia.

Corresponding author:
Igor A. Sobenin, MD, PhD,
Institute of General Pathology and Pathophysiology
Russian Academy of Medical Sciences
125315 Moscow, Russia
E-mail: sobenin@cardio.ru

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SUMMARY

Polyetiological nature of atherosclerosis allows the suggestion that simultaneous complex reduction of several risk factors appears to be valid and clinically effective way to primary prevention of cardiovascular diseases. To test this hypothesis, double-blinded placebo-controlled study was performed in 167 mildly hyperlipidemic patients to evaluate the effectiveness of garlic-based drug Allicor treatment in primary coronary heart disease (CHD) prevention and reduction of multifunctional cardiovascular risk. Ten-year prognostic multifunctional cardiovascular risk that was calculated using algorithms derived from Framingham and Muenster Studies. It has been demonstrated that 12-months treatment with Allicor lowers 10-years prognostic risk of CHD development in men by 10.7% from the baseline level ($p<0.05$), and 10-years prognostic risk of acute myocardial infarction (fatal and non-fatal) and sudden death by 22.7% from the baseline level ($p<0.05$). In women, Allicor treatment prevented the rise of cardiovascular risk with ageing ($p<0.05$). The effects of treatment on the dynamics of cardiovascular risk were mainly due to a decrease in LDL cholesterol and partially due to the changes in HDL cholesterol and systolic blood pressure. The most prominent changes in serum lipids was the reduction of total and LDL cholesterol in men by 27.9 mg/dl ($p<0.05$) and 22.5 mg/dl ($p<0.05$), respectively, and in women by 11.4 mg/dl ($p<0.05$) and 10.8 mg/dl ($p<0.05$), respectively. In the subgroup of 79 intermediate- and high-risk patients 10-years prognostic risk of CHD development lowered by 13.2% from the baseline level in men ($p=0.005$), and by 7.1% in women ($p=0.040$). Ten-year prognostic risk of acute myocardial infarction (fatal and non-fatal) and sudden death was lowered by 26.1% from the baseline level in men ($p=0.025$), but in women did not change significantly. The effects of treatment on the dynamics of cardiovascular risk were mainly due to the decrease in LDL cholesterol by 0.61±0.17 mmol/L in men, and the rise in HDL cholesterol by 0.07±0.04

mmol/L in women. The results of the study have demonstrated the effectiveness of complex treatment of different risk factors in the reduction of the overall multivariate cardiovascular risk. Being the remedy of natural origin, garlic-based drug Allicor is safe with the respect to adverse effects and allows even perpetual administration, which may be quite necessary for primary prevention of atherosclerosis and atherosclerotic diseases.

INTRODUCTION

Clinical manifestations of atherosclerosis and especially coronary heart disease remain the number one killer and a leading cause of illness and disability worldwide. The social, medical and economical burden of CHD and the other complications of advanced atherosclerosis continue to increase in spite of the evident drop in cardiovascular death rates in the United States of America and several European countries. This fact is mostly due to population ageing, the rapid increase in the prevalence of type 2 diabetes mellitus, metabolic syndrome, overweight and obesity, as well as static or even increasing smoking prevalence rates. These unfavorable tendencies are characteristic for many industrial and developing countries, therefore CHD remains the major cause of mortality and morbidity in the world. By now, the results of prospective epidemiological studies allow us to reveal a number of clinical and biochemical conditions tightly associated with the development of atherosclerotic diseases and are therefore called “risk factors”. The traditional strategy for prevention of cardiovascular diseases is aimed at the reduction of risk factors.

Many factors appear to contribute to the development of atherosclerosis including alterations in plasma lipid and lipoprotein levels, blood pressure regulation, platelet function and clotting factors, etc. In recent years special algorithms for the estimation of overall cardiovascular risk based on the results of major epidemiological studies have been developed, which allow for the complex impact of different risk factors [1]. On the other hand, current approaches to the prevention of atherosclerotic diseases usually employ the effect on isolated risk factors. However, the polyetiological nature of atherosclerosis allows for the suggestion that simultaneous complex reduction of several risk factors appears to be the most valid and clinically effective way for primary prevention of cardiovascular diseases. Theoretically, such approaches may decrease overall integral cardiovascular risk. To test this assumption, double-blinded placebo-controlled randomized study was performed in mildly hyperlipidemic patients. Garlic powder tablets, Allicor, were used as the drug capable of reducing different risk factors. Garlic contains a number of biologically active compounds and is widely used as traditional medicine of many cultures. In recent years, antiatherosclerotic and cardiovascular-protective effects of garlic have been extensively evaluated. Evidence from numerous studies demonstrate that garlic-based preparations can bring about the normalization of plasma lipids, along with the enhancement of fibrinolytic activity, inhibition of platelet aggregation and reduction of blood pressure.[2;3] The present study was performed to evaluate the effectiveness of Allicor treatment in primary CHD prevention and its effects on the estimates of multifunctional cardiovascular risk.

PATIENTS AND METHODS

This study was kept in accordance with the Helsinki Declaration of 1975, as revised in 1983, and approved by the local ethical committee. All participants gave their informed consent

prior to their inclusion in the study. Men and women aged 40-74 years who had serum cholesterol level above 200 mg/dl (5.2 mmol/L) upon primary examination were eligible for inclusion. The absence of documented CHD, high arterial hypertension (systolic blood pressure above 160 mm Hg or diastolic blood pressure above 95 mm Hg), or lipid-lowering drugs administration were also regarded as inclusion criteria. Patients were randomized according to gender, age, total cholesterol and smoking history as covariates into two groups, one who received Allicor (coated tablets containing 150 mg garlic powder, INAT-Farma, Moscow, Russia) one tablet twice a day for 12 months, and the other one who received a placebo in the same manner. Allicor and placebo looked identical.

Clinical and biochemical examination was performed upon the inclusion at the end of the study. Venous blood taken after overnight fasting was used for total cholesterol, triglycerides and high density lipoprotein (HDL) cholesterol measurements with commercial enzymatic kits (Boehringer Mannheim GmbH, Germany). Low density lipoprotein (LDL) cholesterol was calculated according to the Friedewald formula.

Ten-years prognostic risk of CHD development was calculated according to Weibull model derived from the results of Framingham study [4]. Following variables were used for risk determination: gender, age, systolic blood pressure, total cholesterol, HDL cholesterol, smoking status, diagnosed diabetes mellitus, left ventricular hypertrophy.

Ten-years prognostic risk of fatal or non-fatal myocardial infarction and sudden death was calculated with Cox proportional hazards model derived from PROCAM study [1], where following variables were used: gender, age, systolic blood pressure, total cholesterol, triglycerides, smoking status, diabetes mellitus, family history of acute myocardial infarction in 1st degree relative occurred before the age of 60 years. For this risk, the regional adjustment factor was applied. [5;6]

The significance of differences was estimated using SPSS 10.1.7 program package (SPSS Inc., USA). After examination of variable distribution, Mann-Whitney statistics or t-test was used for between-group comparisons, Wilcoxon statistics was used for within-group effect assessments, and Pearson's chi-square statistics was used for the comparison of nominal variables distributions. To estimate the relationship between changes in risk values and clinical and biochemical variables, Pearson's correlation analysis and regression analysis were used. The data are presented in terms of mean and S.E.M.; significance was defined at the 0.05 level of confidence.

RESULTS

Before the study, 278 patients were screened, and according to inclusion criteria 195 patients were recognized as eligible and randomized into two groups. The Allicor-treated group consisted of 98 patients (34 men, 64 women), and the placebo group consisted of 97 patients (33 men, 64 women). During the study, 12 patients (4 men, 8 women) dropped out of Allicor group, and 16 patients (6 men, 10 women) were lost in the placebo group. The reason for the exclusion from the study was the discontinuation of study medication. So, the retirement accounted for 12.2% and 16.5% in Allicor-treated and placebo groups, respectively, and the difference between groups was not statistically significant. By the end of the study, there were 86 evaluable patients in Allicor-treated group (30 men, 56 women) and 81 in the placebo group (27 men, 54 women).

The baseline clinical data on evaluable patients are presented in Table 1. It can be seen that groups of patients did not differ significantly in all clinical variables. In Allicor-treated patients, the mean age was higher in women than in men (P<0.05), and in placebo recipients, diastolic blood pressure was lower in women as well (P<0.05); with respect to other variables, men and women did not differ significantly within groups.

Allicor and the placebo groups did not differ significantly in mean total cholesterol, HDL and LDL cholesterol and triglycerides levels. Within groups, men and women differed significantly only with respect to HDL cholesterol (P<0.05). Serum triglycerides were higher in men as compared to women in both groups, but the difference did not reach statistical significance. The changes in lipid levels that occurred during the study are shown in Table 2. In the placebo group, no statistically significant changes were observed, except to triglycerides lowering in men by 21.2% (P<0.05). By the end of the study, the significant difference in HDL cholesterol between men and women was preserved (P<0.05).

Table 1. Clinical characteristic of patients at the baseline.

Variable	Allicor			Placebo		
	All (n=86)	Men (n=30)	Women (n=56)	All (n=81)	Men (n=27)	Women (n=54)
Age, years	54.5±1.0	51.3±1.9	56.1±1.0$^{\$}$	54.7±1.0	52.0±2.1	56.1±1.1
SBP, mm Hg	134.0±2.1	137.2±4.4	132.3±2.2	136.9±2.0	139.1±3.1	135.7±2.6
DBP, mm Hg	84.2±1.0	86.3±2.0	83.1±1.2	84.3±1.0	87.4±1.4	82.7±1.3$^{\$}$
BMI, kg/m^2	25.9±0.4	25.8±0.5	26.0±0.4	27.1±0.5	26.8±0.6	27.2±0.6
DM, n	1	1	0	1	0	1
LVH, n	9	4	5	7	2	5
Smoking, n	13	10	3	12	8	4

SBP – systolic blood pressure; DBP – diastolic blood pressure; BMI – body mass index; DM – diabetes mellitus; LVH – left ventricular hypertrophy.
$^{\$}$ - a significant within-group difference between men and women, t-test, P<0.05.

In both men and women, there was some reduction in total and LDL cholesterol that did not reach statistical significance (95% CI: 0.8, 16.6 mg/dl for total cholesterol, and 1.8, 12.3 mg/dl for LDL cholesterol).

In Allicor recipients, the substantial decrease in total and LDL cholesterol was observed both in men and women (P<0.05). Total cholesterol decreased by 17.2±4.4 mg/dl (95% CI: 8.4, 26.5), and in men the effect was more prominent than in women (27.9±5.1 mg/dl vs. 11.4±6.1 mg/dl). LDL cholesterol decreased by 14.9±3.8 mg/dl (95% CI: 7.5, 22.8 mg/dl) in total group, by 22.5±2.0 mg/dl in men and by 10.8±5.0 mg/dl in women. So, Allicor treatment resulted in the reduction of total cholesterol by 6.4±1.7% and LDL cholesterol by 8.4±2.1% from the baseline. Hypolipidemic effects differed significantly in total group as well as in women, as compared to the placebo group (P<0.05). HDL cholesterol levels did not change significantly and the

difference between men and women still persisted (P<0.05). Triglycerides in Allicor-treated men lowered significantly by 24.9% (P<0.05), but the effect was similar to that observed in the placebo group.

At the baseline, 10-years prognostic risk of CHD in placebo group was low (below 5%) or moderate (from 5% to 10%) in 42 patients (51.9% of the total group), intermediate (from 10% to 20%) in 24 patients (29.6%), and high (above 20%) in 15 patients (18.5%). In Allicor recipients, the distribution of patients into the same cohorts of CHD 10-years risk was as follows: 46 patients (53.5% of the total group) vs. 27 patients (31.4%) vs. 13 patients (15.1%). Thus, placebo and Allicor-treated groups did not differ in the distribution of risk levels at the baseline (χ^2=0.353, P=0.950).

Baseline lipid values are presented in Table 2.

Table 2. The changes of serum lipid parameters.

Time	Allicor			Placebo		
	All (n=86)	Men (n=30)	Women (n=56)	All (n=81)	Men (n=27)	Women (n=54)
			Total cholesterol, mg/dl			
At the baseline	261.4±5.2	260.5±8.9	261.9±6.5	263.3±4.4	257.2±9.2	265.6±4.9
After 12 months	244.2±4.8*#	232.6±7.0*	250.4±6.3*#	254.1±4.1	241.6±8.3	260.4±4.8
			HDL cholesterol, mg/dl			
At the baseline	55.1±1.7	48.2±2.0	58.7±2.3$^{\$}$	54.7±1.7	47.2±2.5	58.4±2.1$^{\$}$
After 12 months	55.4±1.4	51.2±1.9	57.7±1.7$^{\$}$	53.9±1.8	48.9±2.2	56.5±2.4$^{\$}$
			Triglycerides, mg/dl			
At the baseline	141.7±11.0	167.2±23.0	128.0±11.4	139.3±9.9	161.7±19.8	128.2±10.8
After 12 months	128.6±8.0	125.6±10.3*	130.3±11.1	125.9±7.4	127.4±10.8*	125.2±9.8
			LDL cholesterol, mg/dl			
At the baseline	178.0±4.7	178.9±7.9	177.5±5.9	180.3±4.1	177.6±8.0	181.6±4.8
After 12 months	163.1±4.3*#	156.4±6.5*	166.7±5.5*#	175.0±4.6	167.3±8.8	178.9±5.3

* - a significant difference from the baseline, paired Wilcoxon test, P <0.05;
# - a significant difference from placebo, Mann-Whitney test, P <0.05;
$ - a significant within-group difference between men and women, t-test, P<0.05.

After 12 months of the treatment, no significant changes in the distribution of patients into risk categories in placebo group were observed: 50.6% patients had low or moderate CHD risk, 29.6% - intermediate risk, and 19.8% - high risk. However, the dynamic of changes demonstrated that the category of CHD risk did not change in 53 patients (65.4%), while in 11 patients (13.6%) risk category decreased, and in the other 17 patients (21.0%), it increased. Thus, during the one-year follow-up, a significant redistribution of placebo recipients into different CHD risk categories occurred, and an overall increase of risk prevailed (χ^2=86.875, P<0.001).

In the Allicor-treated group, the amount of patients who had low or moderate 10-years prognostic risk of CHD increased up to 60.5%, while 25.5% patients had intermediate risk, and other 14.0% patients had high CHD risk. The redistribution of patients into risk categories was as follows: 68 patients (79.1%) had the same category of CHD risk as at the baseline, 13 patients (15.1%) have demonstrated the decrease in risk category, and only in 5 patients (5.8% of the group) the category of risk increased. Thus, under the Allicor treatment, the tendency of decrease of CHD risk prevailed (χ^2=143.748, P<0.001). However, by the end of the study, the Allicor-treated group did not differ significantly from placebo group with the respect to patients' distribution into CHD risk cohorts (χ^2=2.121, P=0.548), but the trends to redistribution of patients within groups differed significantly in Allicor and placebo recipients (χ^2=8.429, P=0.015).

The data on the changes of absolute 10-years CHD risk that are presented in Table 3 seem even more informative. It is necessary to note that men and women looked quite different with respect to CHD prognostic risk values. In men, the mean CHD risk was 1.9-fold higher, and 10-years prognostic risk of acute myocardial infarction and sudden death was 9.4-fold higher than in women. Thus, the analysis of absolute risk changes in total groups without subdivision according to gender would be incorrect. It can be seen that in the placebo group, both men and women did not demonstrate significant changes in 10-years CHD risk. On the contrary, in Allicor-treated men the mean level of CHD risk decreased by 10.7±4.3% from the baseline (P<0.05); in women the decrease of risk did not reach statistical significance.

Table 3. The dynamics of absolute cardiovascular risk.

Time	Allicor			Placebo		
	All (n=86)	Men (n=30)	Women (n=56)	All (n=81)	Men (n=27)	Women (n=54)
	10-years prognostic risk of CHD, %					
At the baseline	11.55±1.05	17.26±2.11	9.09±1.08$^{\$}$	12.54±1.09	18.15±2.01	9.73±1.12$^{\$}$
After 12 months	10.98±1.03*#	15.41±1.99*	9.00±1.08$^{\$}$	12.38±1.07	17.49±2.12	9.82±1.05$^{\$}$
	10-years prognostic risk of myocardial infarction and sudden death, %					
At the baseline	5.02±1.2	11.79±3.17	1.39±0.28$^{\$}$	5.40±1.01	13.58±2.30	1.32±0.27$^{\$}$
After 12 months	4.19±0.93*#	9.11±2.31*#	1.56±0.41#$^{\$}$	5.15±1.04	12.51±2.56	1.47±0.25*$^{\$}$

* - a significant difference from the baseline, paired Wilcoxon test, P <0.05;
# - a significant difference from placebo, Mann-Whitney test, P <0.05;
$ - a significant within-group difference between men and women, t-test, P<0.05.

The changes occurred with CHD prognostic risk correlated with the dynamics of systolic blood pressure (r=0.419; P<0.001), diastolic blood pressure (r=0.233; P=0.003), total cholesterol (r=0.432; P<0.001), triglycerides (r=0.394; P<0.001), HDL cholesterol (r= -0.419; P<0.001) and LDL cholesterol (r=0.469; P<0.001). The analysis of regression has revealed that the dynamics of CHD risk depended on the changes in systolic blood pressure (P<0.001), LDL cholesterol (P<0.001), HDL cholesterol (P<0.001) and triglycerides (P=0.001). The leading factors that determined CHD risk dynamics both in men and women were the changes in LDL and HDL cholesterol, and in women the changes in systolic blood pressure and serum triglycerides played an additional role.

The relative 10-years risk of CHD in women from placebo group increased by 10.7±5.4% (95% CI: 0.0, 21.6, P<0.05); in Allicor-treated women there was no significant changes of risk (P<0.05 vs. placebo). In placebo-treated men, the relative CHD risk did not change, while in Allicor-treated men the risk lowered significantly by 9.2±4.2% (95% CI: 0.6, 17.8, P<0.05).

The data on the changes in 10-years prognostic risk of fatal and non-fatal myocardial infarction and sudden death are presented in Table 3. In placebo-treated men, mean level of absolute risk did not change; in placebo-treated women there was an increase by 11.4% from the baseline (P<0.05). On the other hand, in Allicor-treated women, the increase of risk was insignificant, while in men the significant reduction of risk by 22.7±15.5% from the baseline was observed (P<0.05). Both in men and women, the dynamic of changes differed significantly from placebo recipients (P<0.05).

The changes of risk of myocardial infarction and sudden death correlated with the dynamics of systolic blood pressure (r=0.185; P=0.017), total cholesterol (r=0.530; P<0.001), serum triglycerides (r=0.295; P<0.001), HDL cholesterol (r= -0.173; P=0.025) and LDL cholesterol (r=0.544; P<0.001). Regression analysis revealed that the leading factors in men were the changes of LDL cholesterol (P<0.001) and HDL cholesterol (P=0.027), and in women, the changes of LDL cholesterol (P<0.001) and triglycerides (P<0.001).

The relative risk of myocardial infarction and sudden death increased in placebo-treated women by 45.1±13.9% (95% CI: 17.4, 72.9, P<0.05). In Allicor-treated women, the relative risk also increased by 14.2±11.8% (95% CI: -9.4, 37.8, P<0.05), but the increase was lower than in placebo group (P<0.05). In placebo-treated men, there was no significant increase in relative risk, while in Allicor recipients the relative risk of myocardial infarction and sudden death decreased by 11.9±11.2% (P<0.05).

Additional data set was obtained from this study based on the data on those patients with high (above 10%) 10-year prognostic risk of CHD development. There were 40 patients (20 men, 20 women) in Allicor-treated group, and placebo group consisted of 39 patients (20 men, 19 women) in this subgroup.

In placebo-treated high-risk men, serum triacylglycerols tended to decrease by 25.0±7.2%, or by 0.49±0.26 mmol/L from the baseline (p=0.054), and HDL cholesterol increased significantly by 9.0±5.4%, or 0.10±0.04 mmol/L from the baseline (p=0.037). The changes in total and LDL cholesterol in placebo-treated men did not reach statistical significance (95% CI: -

1.16; 0.28 and -0.93; 0.23 mmol/L for total and LDL cholesterol, respectively). At the same time, no significant changes in lipid parameters in placebo-treated women were observed.

In Allicor-treated high-risk patients, all lipid parameters changed significantly. Total cholesterol decreased by 6.1±2.9%, or 0.42±0.21 mmol/L from the baseline ($p<0.001$). Serum triacylglycerols lowered by 20.1±7.2%, or 0.46±0.17 mmol/L from the baseline ($p=0.001$). HDL cholesterol level increased by 8.2±3.5%, or 0.10±0.04 mmol/L from the baseline ($p=0.005$). Accordingly, LDL cholesterol level lowered by 4.4±3.7%, or 0.31±0.18 mmol/L ($p=0.002$). The most prominent changes were observed in men: total cholesterol decreased by 0.82±0.17 mmol/L ($p=0.001$), LDL cholesterol decreased by 0.61±0.17 mmol/L ($p=0.004$), serum triacylglycerols decreased by 0.72±0.28 mmol/L from the baseline ($p=0.004$), and HDL cholesterol tended to increase by 0.12±0.07 mmol/L ($p=0.062$). In Allicor-treated women, total and LDL cholesterol levels did not change significantly, serum triacylglycerols tended to decrease by 0.20±0.18 mmol/L ($p=0.067$), and only HDL cholesterol increased significantly by 6.5±4.3%, or 0.07±0.04 mmol/L from the baseline ($p=0.040$).

The data on the changes in prognostic cardiovascular risk levels are presented in Table 4. It is notable that 10-year prognostic risk of acute myocardial infarction and sudden death in women was 8.7-fold lower than in men. At the same time, 10-year prognostic risk of CHD development in women was only 1.3-fold lower. Thus, further estimation of changes in the risk of myocardial infarction had to be gender-oriented, whereas the changes in CHD prognostic risk could be also analyzed without subdivision into men and women.

In placebo-treated patients, no significant changes in cardiovascular prognostic risks were observed. On the opposite, Allicor treatment resulted in a significant decrease in CHD prognostic risk calculated by systolic blood pressure algorithm, in spite of gender differences. In Allicor-treated high-risk men CHD prognostic risk decreased by 13.2% from the baseline ($p=0.005$), in women – by 7.1% ($p=0.040$), and in total group – by 10.7% from the baseline ($p<0.001$). When diastolic blood pressure algorithm was used, the decrease of CHD prognostic risk by 6.7% from the baseline was observed ($p=0.010$), but the subdivision into men (CHD risk decrease by 7.1%) and women (CHD risk decrease by 6.3%) resulted in the loss of significance ($p=0.058$ and $p=0.057$, respectively), obviously due to the insufficient sample size.

Ten-year prognostic risk of myocardial infarction (fatal and non-fatal) and sudden death did not change in placebo-treated men and women (Table 4). On the opposite, in

Table 4. The dynamics of absolute cardiovascular risk in high-risk subgroup.

Time	Allicor recipients			Placebo recipients		
	All (n=40)	Men (n=20)	Women (n=20)	All (n=39)	Men (n=20)	Women (n=19)
10-year prognostic risk of CHD, % (systolic blood pressure algorithm)						
At the baseline	19.6±1.6	22.8±2.3	16.4±2.1	20.4±1.4	22.5±1.9	18.3±1.9
After 12 months	17.5±1.6*	19.8±2.4*	15.1±2.1*	19.5±1.5	21.5±2.2	17.5±1.8
10-year prognostic risk of CHD, % (diastolic blood pressure algorithm)						

At the baseline	19.4±1.7	22.6±2.6	15.9±1.8	20.7±1.4	22.6±2.0	18.7±1.9
After 12 months	18.1±1.7*	21.0±2.5	14.9±2.0	20.2±1.6	21.9±2.4	18.3±2.0
10-year prognostic risk of myocardial infarction and sudden death, %						
At the baseline	9.7±2.4	16.5±4.4	3.0±0.6	10.3±1.8	17.3±2.6	2.9±0.6
After 12 months	7.8±1.8*#	12.2±3.2*	3.4±1.0	9.5±1.9	15.7±3.1	3.0±0.5

* - a significant difference from the baseline, paired Wilcoxon test, $p < 0.05$;
# - a significant difference from placebo, Mann-Whitney test, $p < 0.05$.

Allicor-treated high-risk men the risk of myocardial infarction and sudden death decreased by 26.1% from the baseline ($p=0.025$). In Allicor-treated women there were no significant changes in prognostic risk level.

DISCUSSION

The probability of the development of cardiovascular diseases is determined by the mutual action of different risk factors that can be classified into non-modifiable (such as gender, age, family history of CHD, diabetes mellitus, etc.) and modifiable ones (dyslipidemia, arterial hypertension, smoking status, abdominal obesity, etc.) Furthermore, a number of other factors have been attributed to the development of CHD, such as elevated plasma fibrinogen, lipoprotein(a), homocysteine, and microalbuminuria in patients with diabetes mellitus or insulin resistance. It is possible that physical inactivity, heavy alcohol consumption, hyperglycemia, fasting hyperinsulinemia, insulin resistance, social and psychologic stress, different thrombogenic factors etc. may also play a role [7]. Some of these are not definitely shown to be independent risk factors, and for some of them, measurements and analysis are not widely performed or considered to be useful. The strategy of primary prevention of cardiovascular diseases is fairly based on the modification of independent major risk factors. In the Framingham Study, the 44% decrease in the CHD rate in men between 1950 and 1989 could be attributed to improvements of risk factors by one third to one half, at least [8]. The reductions of risk factors in USA could account for 50% of the drop in CHD death rate between 1980 and 1990, while the improvements in other treatments could account for 43% of the decline [9]. In the Netherlands, 44% of the decline in CHD mortality rate between 1978 and 1985 could be attributed to effective primary prevention [10]. The decrease in plasma cholesterol and blood pressure along with smoking prevalence resulted in 48% effect on the reduction of CHD death rate across 20 years of the North Karelia Project [11].

The main approach to CHD primary prevention is traditionally based on blood cholesterol lowering. Indeed, the increased level of LDL cholesterol possesses the highest prognostic significance as compared to other isolated risk factors with the respect of its sensitivity and specificity. However, modern algorithms of calculation of the prognostic risks based on several risk factors measurements provide much better estimates,[12] since different factors may cluster and interact synergistically, increasing the probability of CHD development.[13;14] For example, the presence of three major risk factors triples the risk for CHD event and nearly doubles the risk of

dying of any cause; having four or five risk factors increases the risk for CHD event by 5-fold and risk for death by 3-fold during the 20 years of follow-up [15]. Thus, no CHD risk factor can be judged in isolation, and if any risk factor is present in patient, it is necessary to assess for other risk components and, more importantly, to treat all of them vigorously [7]. Presently, multivariate cardiovascular risk estimation is developed from findings of Prospective Cardiovascular Münster Study (PROCAM) and the Framingham Study data sets. Such approach, to a certain extent, emphasizes the polyetiological nature of atherosclerotic diseases, although the algorithms do not include the assessment of all definitely known risk factors. Quite naturally, algorithms derived in one population may provide incorrect estimates of absolute risk when applied in another geographical region.[16;17] Ideally, the solution lies in the performance of similar prospective studies in different countries and regions, but the more pragmatic approach is the recalibration of existing algorithms based on cross-sectional observational data. So, the MONICA project has provided recalibration of the PROCAM algorithm using the observed CHD morbidity, mortality and case fatality data from many countries [5;6]. Thus, the relevant recalibration coefficients which are characteristics of Russia have been used in our study.

The results of the given study have demonstrated that 12-months treatment with garlic-based drug Allicor resulted in significant reduction of multivariate prognostic risk of cardiovascular diseases or, at least, prevents its rise with aging. These effects were observed as well for absolute and relative risk estimates. In placebo-treated women risk values increased during the follow-up, and Allicor treatment obviously prevented this rise. In men, risk values remained stable in placebo group, and Allicor treatment resulted in significant risk reduction. So, the men differed from women not only by risk level at the baseline, but also by its dynamics during the one-year follow-up. The favorable dynamics of lipid profile observed not only in Allicor recipients but also in the placebo group may be attributed, at least partially, to the placebo-controlled design of the study, since the patients were motivated to give more attention to the improvement of diet and lifestyle. The similar reduction of serum triglycerides observed in men both in Allicor-treated and placebo group indirectly confirms this suggestion. It is notable that much better beneficial changes in cardiovascular risk estimates were observed in the subgroup of patients who were at a high risk at the baseline.

The main effect that underlies the dynamics of multivariate cardiovascular risks in Alicor-treated patients is a hypolipidemic action of the drug. Cholesterol lowering potential of garlic-based preparations is studied rather well [2;18;19]. In spite of several controversial data, [20] the meta-analysis has demonstrated moderate lipid-lowering effect of garlic that is comparable with rational dietary improvement.[2;21] However, the association of beneficial effects of Allicor exclusively with its action on LDL cholesterol is incorrect, since the regression analysis has revealed the relation of cardiovascular risk dynamics with the changes in arterial blood pressure, HDL cholesterol and even triglycerides. Although the last effects did not reach statistical significance, they have provided benefits upon the calculation of individual multivariate risks. It is known that garlic-based preparations possess moderate hypotensive action, and in some studies the increase in HDL cholesterol has been demonstrated.[3;22-25] Additionally, it is necessary to note that garlic-based drugs can affect the processes of platelet aggregation and fibrinolysis substantially, that is especially important in the prevention of CHD events, such as myocardial infarction.[19;26] The last parameters are not considered in the algorithms of multivariate cardiovascular risk estimation, but independently influence on the probability of fatal and not-fatal events.

Garlic contains a variety of organosulfur compounds, amino acids, vitamins and minerals.[27] Some of the sulfur-containing compounds such as allicin, ajoene, S-allylcysteine, S-methylcysteine, diallyl disulfide and sulfoxides may be responsible for antiatherosclerotic activity of garlic that can be realized through different mechanisms of action.[20] Allicor contains dehydrated garlic powder that is thought to retain the same biologically active ingredients as raw garlic, both water-soluble and organic-soluble.[28;29] On the other hand, it possesses a prolonged mode of action, as its biological effect lasts for 12-16 hours after a single dose is administered.[30] Being the remedy of natural origin, Allicor is safe with the respect to adverse effects and allows even perpetual administration, which may be quite necessary for primary prevention of atherosclerosis and atherosclerotic diseases.

REFERENCES

1. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Münster (PROCAM) study. Circulation 2002;105(3):310-315.
2. Ackermann RT, Mulrow CD, Ramirez G, Gardner CD, Morbidoni L, Lawrence VA. Garlic shows promise for improving some cardiovascular risk factors. Arch Intern Med 2001;161(6):813-24.
3. Agarwal KC. Therapeutic actions of garlic constituents. Med Res Rev 2003;16:111-24.
4. Odell PM, Anderson KM, Kannel WB. New models for predicting cardiovascular events. J Clin Epidemiol 1994;47(6):583-92.
5. Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. Lancet 1999;353(9164):1547-57.
6. International Task Force for Prevention of Coronary Heart Disease. Pocket guide to prevention of coronary heart disease. Grunwald, Germany: Borm Bruckmeier Verlag GmBH, 2003.
7. Gotto AM, Jr., Assmann G, Carmena R et al. The ILIB lipid handbook for clinical practice. Blood lipids and coronary heart disease. New York: International Lipid Information Bureau, 2000.
8. Sytkowski PA, Kannel WB, Agostino RB. Changes in risk factors and the decline in mortality from cardiovascular disease. The Framingham Heart Study. N Engl J Med 1990;322(23):1635-41.
9. Hunink MG, Goldman L, Tosteson AN et al. The recent decline in mortality from coronary heart disease, 1980-1990. The effect of secular trends in risk factors and treatment. JAMA 1997;277(7):535-42.
10. Bots ML, Grobbee DE. Decline of coronary heart disease mortality in The Netherlands from 1978 to 1985: contribution of medical care and changes over time in presence of major cardiovascular risk factors. J Cardiovasc Risk 1996;3(3):271-76.
11. Ginter E. Prevention of cardiovascular diseases: the Finnish experience and current situation. Bratisl Lek Listy 1997;98(2):67-72.
12. Voss R, Cullen P, Schulte H, Assmann G. Prediction of risk of coronary events in middle-aged men in the Prospective Cardiovascular Münster Study (PROCAM) using neural networks. Int J Epidemiol 2002;31(6):1253-62.

13. Kannel WB, Neaton JD, Wentworth D et al. Overall and coronary heart disease mortality rates in relation to major risk factors in 325,348 men screened for the MRFIT. Multiple Risk Factor Intervention Trial. Am Heart J 1986;112(4):825-36.
14. Stamler J, Dyer AR, Shekelle RB, Neaton J, Stamler R. Relationship of baseline major risk factors to coronary and all-cause mortality, and to longevity: findings from long-term follow-up of Chicago cohorts. Cardiology 1993;82(2-3):191-222.
15. Yusuf HR, Giles WH, Croft JB, Anda RF, Casper ML. Impact of multiple risk factor profiles on determining cardiovascular disease risk. Prev Med 1998;27(1):1-9.
16. Empana JP, Ducimetiere P, Arveiler D et al. Are the Framingham and PROCAM coronary heart disease risk functions applicable to different European populations? The PRIME Study. Eur Heart J 2003;24(21):1903-11.
17. Hense HW, Schulte H, Lowel H, Assmann G, Keil U. Framingham risk function overestimates risk of coronary heart disease in men and women from Germany - results from the MONICA Augsburg and the PROCAM cohorts. Eur Heart J 2003;24(10):937-45.
18. Berthold HK, Sudhop T. Garlic preparations for prevention of atherosclerosis. Curr Opin Lipidol 1998;9(6):565-69.
19. Bordia A, Verma SK, Srivastava KC. Effect of garlic (Allium sativum) on blood lipids, blood sugar, fibrinogen and fibrinolytic activity in patients with coronary artery disease. Prostaglandins Leukot Essent Fatty Acids 1998;58(4):257-63.
20. Yeh YY, Liu L. Cholesterol-lowering effect of garlic extracts and organosulfur compounds: human and animal studies. J Nutr 2001;131(3s):989S-93S.
21. Silagy C, Neil A. Garlic as a lipid lowering agent - a meta-analysis. J R Coll Physicians Lond 1994;28(1):39-45.
22. Bordia A. Effect of garlic on blood lipids in patients with coronary heart disease. Am J Clin Nutr 1981;34(10):2100-2103.
23. Ernst E. Cardiovascular effects of garlic (Allium sativum): a review. Pharmatherapeutica 1987;5(2):83-89.
24. Auer W, Eiber A, Hertkorn E et al. Hypertension and hyperlipidaemia: garlic helps in mild cases. Br J Clin Pract Suppl 1990;693-6.
25. Silagy CA, Neil HA. A meta-analysis of the effect of garlic on blood pressure. J Hypertens 1994;12(4):463-68.
26. Bordia A, Verma SK, Srivastava KC. Effect of garlic on platelet aggregation in humans: a study in healthy subjects and patients with coronary artery disease. Prostaglandins Leukot Essent Fatty Acids 1996;55(3):201-5.
27. Block E. The chemistry of garlic and onions. Sci Am 1985;252(3):114-19.
28. Iberl B., Winkler G., Müller B., Knobloch K. Quantitative determination of allicin and alliin from garlic by HPLC. Planta Med 1990;56320-326.
29. Amagase H, Petesch BL, Matsuura H, Kasuga S, Itakura Y. Intake of garlic and its bioactive components. J Nutr 2001;131(3s):955S-62S.
30. Orekhov AN, Tertov VV, Sobenin IA, Pivovarova EM. Direct anti-atherosclerosis-related efects of garlic. Ann Med 1995;27(1):63-65.