Antiatherosclerotic and Cardioprotective Effects of Time-Released Garlic Powder Pills

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Abstract: Garlic is believed to produce beneficial changes in different cardiovascular risk factors, thus possessing antatherosclerotic properties. The hypotensive and cholesterol-lowering effects were investigated in two studies in men with mild arterial hypertension and in men with mild hypercholesterolemia. Eight-week treatment resulted in the reduction of both systolic and diastolic blood pressure by 5.2% (P=0.008) and 4.0% (P=0.014), respectively. In a hyperlipidemic study, the 12-week treatment resulted in a decrease in LDL cholesterol by 11.8% (P=0.002), while HDL cholesterol increased by 11.5% (P=0.013). In men with cerebral atherosclerosis it has been demonstrated that 14-days treatment inhibited ADP-induced platelet aggregation by 25.4% (P<0.05) and increased plasma fibrinolytic activity by 22.4% (P<0.05).

One more study was performed in high-risk patients to evaluate the changes of prognostic cardiovascular risk that was calculated using algorithms derived from Framingham and Muenster Studies. Twelve-months treatment lowered 10-years prognostic risk of CHD by 13.2% in men (P=0.005), and by 7.1% in women (P=0.040). Ten-year prognostic risk of acute myocardial infarction and sudden coronary death was lowered by 26.1% in men (P=0.025).

The Atherosclerosis Monitoring and Atherogenicity Reduction Study (AMAR) was designed to estimate the effect of two-year treatment with garlic powder pills on the progression of carotid atherosclerosis in asymptomatic men. A significant correlation has been revealed between the changes in blood serum atherogenicity and the changes in carotid intima-media thickness (r=0.144, P=0.045). Evidence obtained from these studies as well as series of double-blinded placebo-controlled clinical trials indicates that garlic powder pills are effective for prevention of cardiovascular disorders.

Keywords: Atherosclerosis, coronary heart disease, prevention, treatment, garlic, Allicor.

INTRODUCTION

Garlic (Allium sativum) is one of the most popular botanicals used to reduce various risks associated with cardiovascular disease. Most of its popularity is based on the familiarity and the scientific research suggested benefits associated with the ingestion of the herb as a conventional food and as a dietary supplement. Garlic-based drugs and dietary supplements seem to be promising agents for the reduction of overall cardiovascular risk, as they possess a wide range of cardioprotective action and act towards many risk factors, reducing low density lipoprotein (LDL) cholesterol and triglycerides, increasing high density lipoprotein (HDL) cholesterol, lowering systolic and diastolic blood pressure, inhibiting platelet aggregation and activating fibrinolysis [1, 2].

It has been shown that garlic-based preparations are able to inhibit cholesterol biosynthesis, suppress LDL oxidation, lower plasma fibrinogen level and increase fibrinolytic activity, and thus to possess antatherosclerotic properties [3-7].

Atherosclerosis, by far the greatest killer in modern society, is a complex disease that develops due to many risk factors including alterations in plasma lipid and lipoprotein levels, blood pressure regulation, platelet function, clotting factors, arterial smooth muscle cell metabolism, etc. [8].

Clinical manifestations of atherosclerosis, mainly, coronary heart disease (CHD) and acute myocardial infarction, remain the leading cause of mortality and morbidity in most countries for decades.

Atherosclerosis can be described as an excessive fibro-fatty, proliferative, inflammatory response to damage of the artery wall, involving several cell types, such as smooth muscle cells, pericytes, monocyte-derived macrophages, lymphocytes and platelets. Although many factors appear to contribute to the development of atherosclerosis the precise mechanisms of atherogenesis are still unknown. At the level of arterial wall, the deposition of intracellular lipids, mainly free and esterified cholesterol, and subsequent foam cell formation is a typical feature of early atherosclerotic lesion [9]. Modified LDL is generally thought to be the source of accumulating lipids [10], and intracellular lipid deposition may act as a trigger mechanism for the development of advanced atherosclerotic lesions, implying an excessive production of connective tissue matrix components and, possibly, cellular proliferation and inflammatory reactions [11-14]. Subsequent formation of advanced atherosclerotic lesion finally results in widely spread clinical manifestations of atherosclerosis.

The prospective epidemiological studies have revealed a number of clinical and biochemical conditions tightly associated with the development of atherosclerotic diseases and therefore called “risk factors”, and the principal strategy for prevention of cardiovascular diseases is traditionally based on their reduction.

In recent years special algorithms for estimation of overall cardiovascular risk based on the results of major epidemiological studies have been developed, that allow for the complex impact of different risk factors [15].
Polyetiological nature of atherosclerosis allows suggesting that complex reduction of several risk factors may be valid and clinically effective way to primary prevention of cardiovascular diseases.

Several years ago we have established that blood serum from atherosclerotic patients is able to induce lipid accumulation in the primary culture of human intimal aortic cells, thus demonstrating the primary step in atherogenesis at the cellular level [16-19]. This phenomenon was termed “atherogenicity”. We have proposed that meaningful serum atherogenicity lowering may be the way to prevent lipid deposition in vascular wall, thus inhibiting the initial step of atherosclerosis lesion formation [20].

The results of our preliminary studies have shown that oral intake of garlic powder tablets Allicor resulted in the prevention of serum-induced cholesterol accumulation in cultured cells [21, 22]. We have also demonstrated that garlic components are able to stimulate the intracellular hydrolysis of esterified cholesterol and to inhibit the processes of intracellular cholesterol esterification, thus lowering the overall content of cholesterol esters in cells [23]. These data support an assumption that long-term treatment by garlic-based drug Allicor could produce a direct antiatherosclerotic effect at the level of vascular wall.

Clinical investigations focused on the effect of garlic-based preparations on arterial hypertension have revealed moderate hypotensive action of garlic in most studies [24-28]; however, controversial data exist [29].

These discrepancies may be possibly due to several factors, including a lack of consistency among studies in relation to dosage, standardization of garlic preparations and period of treatment.

It is notable that not all garlic preparations may be assumed equivalent in their composition and, more importantly, in biological response they may precipitate. In contrast to other products on the market, the recently developed garlic powder-based preparation Allicor has been characterized by the prolonged mode of action thereby promising more potent biological effects.

Some data support an assumption that long-term treatment by Allicor could produce a direct antiatherosclerotic effect at the level of vascular wall. Here we review indirect antiatherosclerotic effects of garlic preparations affecting atherosclerosis risk factors and its direct effect on atherosclerotic lesions.

PART I: INDIRECT ACTION

The approaches to the prevention and treatment of atherosclerotic diseases are based primarily on the reduction of risk factors or rather modifiable factors such as hyperlipidemia, hypertension, diabetes.

Hypolipidemic Effects

Among all risk factors of atherosclerosis, hypercholesterolemia is thought to be the most potent one to increase the cardiovascular risk [30]. Lipid hypothesis of atherosclerosis proposes that reduction of plasma cholesterol would lead to a fall in coronary disease [31].

To elucidate hypolipidemic effects of time-released garlic powder tablets, we have performed independent double-blinded placebo-controlled study. In mildly hypercholesterolemic subjects during acclimatization phase when patients stayed on hypolipidemic diet for 4 weeks and on hypolipidemic diet plus placebo for additional 4 weeks, moderate but statistically insignificant decrease in total and LDL cholesterol was observed; at the same time, no significant changes occurred in HDL cholesterol and triglyceride levels, as well.

Time-released garlic powder tablets 600 mg daily produced moderate but statistically significant decrease in total cholesterol level after 8 and 12 weeks of placebo-controlled phase (Table 1).

By the end of the study, total cholesterol lowered by 7.6%, as compared to the level at randomization, and was lower by 11.5% as compared to placebo group. The same dynamic of changes was observed for LDL cholesterol levels. By the end of the treatment, LDL cholesterol lowered by 11.8 and was lower by 13.8% as compared to placebo group.

Table 1. The lipid changes during the placebo-controlled phase of hypolipidemic study.

<table>
<thead>
<tr>
<th>Time</th>
<th>Allicor</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total cholesterol, mmol/L</td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td>6.97±0.20</td>
<td>7.04±0.18</td>
</tr>
<tr>
<td>4 weeks</td>
<td>6.87±0.26</td>
<td>6.78±0.22 *</td>
</tr>
<tr>
<td>8 weeks</td>
<td>6.54±0.24 *</td>
<td>6.98±0.23</td>
</tr>
<tr>
<td>12 weeks</td>
<td>6.41±0.22 *#</td>
<td>7.24±0.18</td>
</tr>
<tr>
<td></td>
<td>Triacylglycerols, mmol/L</td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td>2.00±0.26</td>
<td>2.25±0.20</td>
</tr>
<tr>
<td>4 weeks</td>
<td>1.98±0.30</td>
<td>2.11±0.26</td>
</tr>
<tr>
<td>8 weeks</td>
<td>1.89±0.24</td>
<td>2.01±0.22</td>
</tr>
<tr>
<td>12 weeks</td>
<td>1.91±0.21</td>
<td>2.06±0.22</td>
</tr>
<tr>
<td></td>
<td>HDL cholesterol, mmol/L</td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td>1.06±0.07</td>
<td>1.20±0.09</td>
</tr>
<tr>
<td>4 weeks</td>
<td>1.13±0.07</td>
<td>1.12±0.09 *</td>
</tr>
<tr>
<td>8 weeks</td>
<td>1.16±0.08 *</td>
<td>1.07±0.10</td>
</tr>
<tr>
<td>12 weeks</td>
<td>1.17±0.09 *</td>
<td>1.16±0.10</td>
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<tr>
<td></td>
<td>LDL cholesterol, mmol/L</td>
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</tr>
<tr>
<td>Randomization</td>
<td>5.00±0.17</td>
<td>4.93±0.18</td>
</tr>
<tr>
<td>4 weeks</td>
<td>4.84±0.20</td>
<td>4.71±0.18 *</td>
</tr>
<tr>
<td>8 weeks</td>
<td>4.52±0.21 *</td>
<td>5.00±0.20</td>
</tr>
<tr>
<td>12 weeks</td>
<td>4.37±0.20 *#</td>
<td>5.07±0.16</td>
</tr>
</tbody>
</table>

* significant difference from the level at randomization, p<0.05; # significant difference from placebo, p<0.05.

Active treatment also resulted in significant increase in HDL cholesterol that was observed after 8 weeks of placebo-controlled phase and retained up to the end of 12-weeks follow-up. By the end of the study, HDL cholesterol increased by 11.5%, as compared to the level at randomization. Serum triacylglycerols lowered both in time-released garlic powder tablets and placebo recipients by 7.7% and 7.8%, respectively, but these changes did not reach statistical significance.

Several epidemiologic studies have indicated that certain diets with high garlic consumption are associated with low risk of cardiovascular disease [32]. The studies in which raw garlic was given orally for 2-4 months to healthy subjects and patients with ischemic heart disease have demonstrated significant reductions in blood cholesterol and triglyceride levels after garlic ingestion [3, 33].

However, the dosages required to obtain these effects in most of the studies were relatively high (from 7 to 28 cloves per day), so, it has been difficult to convince people to consume garlic regularly [34].
Standard garlic preparations that can be incorporated into controlled studies had been developed, and various commercial preparations of garlic have appeared on the market. Several clinical trials using commercially available garlic preparations were conducted, and most of these used dried garlic powder. The majority of these studies have also demonstrated the lipid-lowering effects of garlic; some also showed a significant decrease in serum triglyceride levels [6, 35].

Steiner, et al reported the results of a double-blinded crossover placebo-controlled study in moderately hypercholesterolemic men in which the effects of aged garlic extract (7.2 g daily) on blood lipids were demonstrated, namely, reductions of 6% in total cholesterol and 4% in LDL cholesterol [28]. The use of garlic in combination with fish oil in a 14-weeks single-blinded placebo-controlled crossover study resulted in the decreases of 11% in cholesterol, 34% in triglycerides, 10% in LDL and 19% in total cholesterol/HDL ratio were observed [36].

The reduction of total cholesterol by 7.6%, LDL cholesterol by 11.8% and increase in HDL cholesterol by 11.5% observed in our study stay in line with the results of the most successful trials where garlic preparations were investigated. However, the mechanisms of hypolipidemic action of garlic remain obscure.

Contradictory results exist that do not allow final conclusion on the beneficiary role of garlic-based preparations in the improvement of cardiovascular risk. Simons, et al investigated the effects of standard garlic powder tablets (Kwai®), 900 mg daily, on plasma lipids and lipoproteins in subjects with mild-to-moderate hypercholesterolemia in double-blinded placebo-controlled randomized crossover study, where no significant effect of garlic on lipids and lipoproteins have been demonstrated [37].

In another double-blinded randomized 6-months parallel trial the effect of 900 mg/d of dried garlic powder standardized to 1.3% allicin in reducing cholesterol was investigated [38]. The results of this study showed that this form of dried garlic powder was less effective in reducing total cholesterol than had been suggested by previous meta-analyses [27].

Two recent trials, one with garlic powder and the other with garlic oil, also failed to demonstrate any significant reduction in serum lipids. Issascsohn, et al conducted a randomized, placebo-controlled trial in which they investigated the effect of 900 mg/d of dried garlic powder (Kwai®) 12-weeks administration on serum cholesterol levels, and garlic powder was ineffective in lowering cholesterol levels in patients with hypercholesterolemia [39]. Steam-distilled garlic oil preparation (5 mg twice per day for 12 weeks) was used in a double-blinded randomized placebo-controlled study by Berthold, et al, and again had no influence on serum lipoproteins [40].

The inconsistencies in results obtained in different studies are usually tended to be explained by interference of several factors, such as the differences in the components occurring in the preparation, the quantity of the preparation provided and the duration of the study; moreover, the biological response to different preparations may vary greatly. Garlic contains a variety of organosulfur compounds, amino acids, vitamins and minerals [41].

Sulfur-containing compounds such as allicin, ajoene, cisleptanine and various sulfides may be responsible for hypotensive and lipid-lowering activity of garlic. It is known that allicin, biologically active substance from garlic that is supposed to possess antiatherosclerotic effect, is unstable and is very poorly absorbed on ingestion [42].

In addition, secondary compounds and metabolites that are formed in the body after the ingestion of garlic are not well studied with the respect of their lipid-lowering, hypotensive and antiatherosclerotic potency [43].

The manufacturing process can also markedly influence the composition of garlic product, and the proportions and amounts of various biologically active constituents may differ significantly [44, 45].

By far, a lot of garlic-based products are present on the market now. They can be classified into four groups, i.e., garlic essential oil, garlic oil macerate, garlic powder and garlic extract. As compared to other garlic preparations, dehydrated garlic powder is thought to retain the same ingredients as raw garlic, both water-soluble and organic-soluble [44, 45].

It has been shown that biological effects, such as blood serum atherogenicity reduction and improvement of serum fibrinolytic activity, produced by time-released garlic powder tablets last for 10-14 hours after single dose administration and exceeds that of ordinary garlic powder tablets [46-48].

### Hypotensive Effects

The clinical investigations focused on the effect of garlic in arterial hypertension have revealed its moderate hypotensive action in most studies [3, 5-7, 49]; however, controversial data exist [24].

It has been supposed that time-released garlic powder tablets may promise more potent pharmacological effects. To test this hypothesis, we have performed double-blind garlic powder tablets and placebo-controlled study of hypotensive action of Allicor in comparison with regular garlic powder tablets (Kwai) in men with mild and moderate arterial hypertension.

During 8-week placebo-treated run-in phase of the study SBP in the total group lowered by 3.2 mm Hg. Further dynamics of systolic blood pressure is shown in Fig. 1.

![Fig. (1). The dynamics of systolic blood pressure](image)
as well. The hypotensive effect of Allicor 2400 mg daily did not differ significantly from that of 600 mg daily.

In those patients who received Kwai 900 mg daily, SBP was lowered by 5.3 mm Hg after 4 weeks of treatment, and the same effect was observed at the end of the study (SBP decreased by 5.4 (Fig. 1). The difference in SBP changes between Kwai-treated and placebo groups was statistically significant after 4 and 8 weeks of treatment. The effect of Kwai 900 mg daily on SBP did not differ significantly from that of Allicor 600 or 2400 mg daily.

During 8-week placebo-treated run-in phase of the study DBP in the total group lowered by 1.0 mm Hg. Further dynamics of diastolic blood pressure is shown in Fig. 2. In those patients who received Allicor 600 mg daily, DBP was lowered by 2.5 mm Hg after 4 weeks. By the end of the study, DBP decreased by 3.8 (Fig. 2). The difference between DBP changes in Allicor and placebo groups was statistically significant.

The treatment with Allicor 2400 mg daily also resulted in statistically significant reduction in DBP. After 4 weeks of treatment DBP was lowered by 2.0 mm Hg, and after 8 weeks - by 3.2 mm Hg (Fig. 2). The difference in DBP changes between Allicor-treated and placebo groups was statistically significant after 4 and 8 weeks of treatment, as well. There was no statistically significant difference in the effects of Allicor 600 and 2400 mg daily on DBP.

![Fig. (2). The dynamics of diastolic blood pressure [5].](image)

Open circles / solid line, Allicor 600 mg daily; solid circles / long dash, placebo; open triangles / short dash, Allicor 2400 mg daily; solid triangles / solid line, Kwai 900 mg daily. Asterisk, significant difference from the beginning of treatment phase, p<0.05, Wilcoxon signed-rank test.

The treatment with Kwai 900 mg daily did not result in statistically significant decrease in DBP as compared to placebo. After 4 weeks of treatment DBP changed by 0.9 mm Hg, and after 8 weeks - by 1.0 mm Hg (Fig. 2). The difference in DBP changes between Kwai-treated patients and placebo recipients was observed after 4 weeks, but not after 8 weeks of treatment.

The results of this study have demonstrated that garlic-based dietary supplement Allicor produces statistically significant hypotensive effect on both systolic and diastolic blood pressure in men with mild and moderate arterial hypertension. These data are in good coincidence with the results from previous studies on hypotensive effects of garlic products [24-27, 50]. However, most of the previous studies were non-randomized and non-placebo-controlled.

Both Allicor and Kwai induced moderate but statistically significant decrease in systolic blood pressure that developed already after first 4 weeks of treatment, and garlic administration for further 4 weeks did not result in statistically significant additional hypotensive action. The effects of Kwai and Allicor on SBP did not differ significantly, in spite of the dosages recommended by manufacturers accounted for 900 and 600 mg per day, respectively. This fact may allow to suppose that maximum possible hypotensive effect of garlic was achieved already at the dosage of 600 mg per day, and further increase in dosage does not gain additional benefits. The latest preposition may be confirmed by another finding from this study that the 4-fold increase in Allicor dosage up to 2400 mg per day did not produce more prominent hypotensive effects on both systolic and diastolic blood pressure. Taken together, these findings show that the mechanisms of hypotensive action of garlic-based preparations may be quite different from those of conventional pharmacological agents used in the treatment of arterial hypertension and may be referred to complex biological regulation of blood pressure.

The mechanisms of hypotensive action of garlic-based preparations and garlic components remain rather obscure. The results from several animal studies demonstrate that garlic constituents are able to decrease blood pressure in hypertensive animals presumably by producing vasodilating effects at the level of arterial wall [51-65]. While allicin, an active ingredient released from garlic that is thought to be a systemic vasodilator, does not alter the activity of vascular prostacyclin synthase, it dilates the cat vascular wall independent of prostaglandin release or a beta adrenergic mechanism [52]. In terms of relative vasodilator activity, allicin was 100-fold less potent than sodium nitroprusside and many orders of magnitude less potent than isoproterenol, but significantly diminished the pulmonary pressor response to ventilatory hypoxia in the isolated perfused rat lung. Additionally, pulmonary vasodilator responses to allicin were independent of the synthesis of endothelial-derived relaxing factor or the activation of soluble guanylate cyclase [55].

Garlic can prevent chronic inhibition of nitric oxide synthesis by N-omega-nitro-L-arginine-methyl-ester (L-NAME) in rats, thus preventing L-NAME-induced arterial hypertension [62].

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In rats, garlic completely inhibited an acute hypoxic pulmonary vasoconstriction and induced significant dose-dependent vasorelaxation in both endothelium-intact and mechanically endothelium-disrupted pulmonary arterial rings, thus demonstrating a combination of endothelium-dependent and -independent mechanisms for the development of hypotensive effect [60].

It was also shown that garlic juice possesses a direct relaxant effect on smooth muscles of aorta, trachea, intestines and isolated rabbit hearts in vitro [66].

It has been demonstrated that garlic may provide a depressant effect on automaticity and tension development in the isolated rat heart, suggesting a beta-adrenoceptor blocking action [54].

Hypotensive effect of garlic constituents may be also explained in part by a significant biphasic diuretic and natriuretic response and inhibitory dose-dependent effect on kidney Na, K-ATPase [67-69].

At last, it has been demonstrated that aqueous garlic extract as well as allicin and ajoene can open potassium ion channels causing membrane hyperpolarization that closes about 20% of the L-type Ca2+ channels, consequence of which is vasodilatation [70, 71]. It is necessary to note that in our study Allicor, but not Kwai, induced statistically significant decrease in diastolic blood pressure. The inconsistencies in results obtained in different studies may be explained by the presence of remainders of the components occurring in the preparation, the quantity of the preparation provided, the duration of the study, and the influence of manufacturing process on the composition of garlic product; moreover, the biological response to different preparations may vary greatly.

Sulfur-containing compounds such as allicin, ajoene, cyclediamine and various sulfoxides may be responsible for hypotensive
activity of garlic. Both Allicor and Kwai contain just garlic powder, but Allicor is a time-released preparation, as its biological effect lasts for 12-16 hours after single dose administration [46].

DBP lowering in Allicor treated participants may be explained by presents of remainders of bioactive compounds in circulation. There is a difference between Kwai and Allicor in their biological effects which is due to slower disintegration of Allicor tablets during digestion. This process results in absorption of bioactive compounds in a dispensed way, consequently low and steady concentration of active metabolites in circulation. The different effects of Allicor and Kwai on diastolic blood pressure may be due to the prolonged action of Allicor that may allow better bioavailability of vasoactive constituents of garlic powder.

Hypertension is an acknowledged major risk factor for cardiovascular disease and death in both men and women. Despite a historical focus by clinicians on the importance of diastolic blood pressure risks, epidemiologic data from numerous large-scale studies have clearly demonstrated that both systolic and diastolic blood pressure are important determinants of cardiovascular risk even in mild and moderate arterial hypertension [72-74]. Additionally, even high-normal blood pressure is associated with an increased risk of cardiovascular disease [75].

It is generally thought that rigid normalization of blood pressure may prolong life and reduce cardiovascular sequela of hypertension, possibly including coronary heart disease [76].

So, moderate but statistically significant hypotensive effect of time-released garlic-based dietary supplement Allicor may suggest considerable benefits in dietary prevention of cardiovascular diseases.

**Anti-Aggregatory and Fibrinolytic Effects**

The results of preliminary in vitro studies have shown that Allicor produces a direct effect on platelet aggregation and plasma fibrinolytic activity. Namely, plasma incubation with Allicor (80 µg/ml) resulted in a significant inhibition of ADP-induced platelet aggregation by 36.0% as compared to the same plasma samples incubated without Allicor addition. Additionally, incubation of plasma with Allicor also increased its fibrinolytic activity by 2.8-fold (from 11.6 to 32.5 mm²).

In patients with cerebral atherosclerosis and chronic cerebrovascular insufficiency, the 14-days treatment with Allicor resulted in sufficient improvement of general condition, reduced hits of giddiness and headaches.

At the beginning of treatment, all patients were characterized with increased levels of ADP-induced platelet aggregation and fibrinogen, and lowered plasma fibrinolytic activity and index of fibrinolysis. At the baseline, the patients randomized to Allicor were characterized by higher values of ADP-induced platelet aggregation as compared to placebo recipients. After 14-days treatment, ADP-induced platelet aggregation in Allicor-treated patients was lowered by 25.4%, whereas in placebo group there were no significant changes. By the end of the study the beneficial difference in ADP-induced platelet aggregation between Allicor and placebo recipients accounted for 10%, although did not reach statistical significance.

Baseline levels of plasma fibrinogen were comparable between Allicor and placebo recipients. After 14-days treatment, fibrinogen level in Allicor-treated patients was lowered by 8.9% as compared to baseline, whereas in placebo group it remained stable. By the end of the study the beneficial difference in plasma fibrinogen level between Allicor and placebo recipients accounted for 8.8%, but was not significant.

Plasma fibrinolytic activity was lowered both in Allicor and placebo randomized patients at the baseline. Allicor treatment resulted in a significant increase in plasma fibrinolytic activity by 22.4% as compared to baseline level, and in placebo group there were no significant changes. By the end of the study the difference in plasma fibrinolytic activity between Allicor and placebo recipients accounted for 35.4% and was statistically significant. Additionally, the index of fibrinolysis in Allicor-treated patients increased by 44.8% as compared to baseline level. After treatment period, the index of fibrinolysis in Allicor recipients was higher by 67.2% as compared to placebo group.

The results of the study demonstrate that garlic powder tablets possess antplatelet effects and can normalize plasma fibrinolytic activity in atherosclerotic men suffering from chronic cerebrovascular insufficiency. These data are in good coincidence with previously reported effects of garlic-based products on coagulation-related parameters [5, 77-80].

The direct inhibition of ADP-induced platelet aggregation by Allicor in vitro was more prominent than in clinical study. This discrepancy in the results of in vitro and ex vivo studies may reflect the biochemical transformations that biologically active components of garlic undergo in gastrointestinal tract, and the extent of bioavailability of active compounds can also play a role. Some of the sulfur-containing compounds such as allicin, ajoene, S-allyleystene, S-methylleystene, diallyl disulfide and sulfoxides may be responsible for antithrombotic activity of garlic.

The effect of garlic on platelet aggregation is proposed to be due to inhibition of cyclooxygenase that plays a key role in arachidonic acid metabolism [81]. This results in a decreased synthesis of thromboxane B2 and decreased production of potent vasoconstrictors leukotriene C4 and prostaglandin E2 by platelets [82-85].

Additionally, the data exist that garlic, unlike aspirin, does not affect the prostacycl synthesis in vascular wall, thus sustaining antithrombogenic properties of endothelial cells [82, 83].

It may be also proposed that moderate anti-aggregatory effect of garlic may be due to regulation of activity of membrane phospholipases that prevents the liberation of arachidonic acid from phospholipids [86]. Garlic-based preparations are also able to regulate the processes of serotonin and coagulation factor IV liberation from platelets [87].

The treatment of patients with cerebral atherosclerosis with garlic powder tablets provided moderate but statistically significant decrease in plasma fibrinogen level. It is known that commonly used aspirin treatment along with the inhibition of platelet aggregation may provoke the increase in plasma fibrinogen that may be regarded as unfavorable side effect. Taking into account the possible role of inflammation in atherosclerosis, it may be proposed that garlic preparations while lowering fibrinogen - an acute phase protein, can play a positive antiatherosclerotic role.

The treatment with Allicor also contributes to normalization of blood plasma fibrinolytic activity that was significantly lowered at the baseline, and this effect favorably complies with antithrombotic effects of garlic. These data confirm the previous findings from different studies [78, 88] where the ability of garlic-based preparations to increase plasma fibrinolytic activity was demonstrated in patients with coronary artery disease.

Evidence obtained from these studies indicates that garlic has potential in the prevention and control of cardiovascular disorders and is beneficial when taken as a dietary supplement.

**Metabolic Effects in Type 2 Diabetes Mellitus**

Type 2 diabetes mellitus is characterized by premature accelerated atherosclerosis development leading to early invalidization and high mortality in this category of patients [89, 90].

Among all risk factors of atherosclerosis, diabetes mellitus is thought to be one the most potent that greatly increases the risk of cardiovascular diseases of atherosclerotic origin [91, 92] and garlic
is used in the traditional medicine of many cultures for the treat-
ment diabetes [93].

The study was performed to evaluate the glucose- and lipid-
lowering potency of new garlic-based formulation, namely, time-
released garlic powder tablets Allicor, in type 2 diabetic patients.
The results of the study are shown in Tables 2 and 3. In Type 2
diabetic patients who received monotherapy with Allicor, a signifi-
cant decrease in serum triglyceride levels was observed after 3
weeks of treatment, and by the end of the study the difference from
baseline levels accounted for 36%. At the same time, the levels of
total cholesterol, HDL cholesterol and LDL cholesterol did not
change significantly (Table 2).

The improvement of metabolic control was also observed in
Allicor-treated patients. Serum fructosamine levels were signifi-
cantly lower after 3 and 4 weeks of treatment as compared to pla-
cebo group, and decreased significantly as compared to baseline
levels by the end of the study (Table 3). Additionally, fasting blood
glucose levels decreased and were maintained at the mean levels
below than 7.0 mmol/l during the whole period of the study (Table
3). The significant difference in mean fasting blood glucose levels
from placebo patients was observed after 2, 3 and 4 weeks of treat-
ment. None of Allicor-treated patients was excluded from the study
due to the impairments in fasting glucose levels. In placebo group,
no significant changes in lipid levels were observed (Table 2).

There were no significant changes in serum fructosamine lev-
els, as well (Table 3). However, fasting blood glucose levels began
increasing after the withdrawal of oral hypoglycaemics, and this led
to the discontinuation of the study in six patients out of ten due to
the steady increase of fasting blood glucose above 9.5 mmol/l.

Table 2. The dynamics of blood lipid changes.

<table>
<thead>
<tr>
<th>Group</th>
<th>0 days</th>
<th>7 days</th>
<th>14 days</th>
<th>21 day</th>
<th>28 days</th>
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<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Total cholesterol, mmol/l</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Allicor</td>
<td>6.42±0.18</td>
<td>6.57±0.47</td>
<td>6.29±0.21</td>
<td>6.36±0.31</td>
<td>6.23±0.47</td>
</tr>
<tr>
<td>Placebo</td>
<td>6.52±0.34</td>
<td>6.23±0.34</td>
<td>6.36±0.49</td>
<td>6.21±0.39</td>
<td>6.36±0.44</td>
</tr>
<tr>
<td><strong>Triglycerides, mmol/l</strong></td>
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<td>2.16±0.34</td>
<td>1.99±0.47*</td>
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<tr>
<td><strong>HDL cholesterol, mmol/l</strong></td>
<td></td>
<td></td>
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<tr>
<td>Allicor</td>
<td>1.27±0.11</td>
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<tr>
<td>Placebo</td>
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<td>1.25±0.06</td>
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<td>1.42±0.09</td>
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<td><strong>LDL cholesterol, mmol/l</strong></td>
<td></td>
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<tr>
<td>Allicor</td>
<td>3.86±0.21</td>
<td>4.15±0.29</td>
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<td>Placebo</td>
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<td>3.91±0.32</td>
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</tr>
<tr>
<td><strong>Combined therapy</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Total cholesterol, mmol/l</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Allicor</td>
<td>6.81±0.26</td>
<td>6.18±0.31</td>
<td>6.05±0.23</td>
<td>6.26±0.44</td>
<td>6.52±0.42</td>
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<tr>
<td>Placebo</td>
<td>6.29±0.31</td>
<td>6.52±0.42</td>
<td>6.05±0.44</td>
<td>6.47±0.44</td>
<td>6.31±0.44</td>
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<td><strong>Triglycerides, mmol/l</strong></td>
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<td>Allicor</td>
<td>3.03±0.31</td>
<td>2.45±0.32</td>
<td>2.57±0.60</td>
<td>2.21±0.42*</td>
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<td>2.88±0.30</td>
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<td>2.60±0.32</td>
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<tr>
<td><strong>HDL cholesterol, mmol/l</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Allicor</td>
<td>1.30±0.11</td>
<td>1.27±0.14</td>
<td>1.22±0.10</td>
<td>1.22±0.10</td>
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<td>Placebo</td>
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<td>1.44±0.11</td>
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<td><strong>LDL cholesterol, mmol/l</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Allicor</td>
<td>4.19±0.27</td>
<td>3.84±0.32</td>
<td>3.71±0.27</td>
<td>4.08±0.45</td>
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<td>Placebo</td>
<td>3.66±0.32</td>
<td>4.12±0.41</td>
<td>3.77±0.42</td>
<td>3.90±0.42</td>
<td>3.76±0.45</td>
</tr>
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</table>

* significant difference from baseline levels, p<0.05.
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In type 2 diabetic patients who received combined therapy with Allicor and oral hypoglycaemics, serum triglyceride levels decreased, and significant changes were observed after 3 weeks of treatment, similar to the patients who received monotherapy with Allicor. By the end of the study the difference from baseline levels accounted for 26%. The levels of total cholesterol, HDL cholesterol and LDL cholesterol did not change significantly (Table 2). Moreover, the significant difference in mean fasting blood glucose as compared to baseline levels was observed after the first week of treatment and by the end of the study (Table 3). Fasting blood glucose was maintained at the mean levels below or equal to 9.0 mmol/l during the whole period of the study (Table 3). Moreover, the significant difference in mean fasting blood glucose as compared to baseline levels was observed after the first week of treatment and by the end of the study (Table 3). Fasting blood glucose was maintained at the mean levels below or equal to 9.0 mmol/l during the whole period of the study (Table 3). Moreover, the significant difference in mean fasting blood glucose as compared to baseline levels was observed after the first week of treatment and by the end of the study (Table 3). Fasting blood glucose was maintained at the mean levels below or equal to 9.0 mmol/l during the whole period of the study (Table 3).

Additionally, improvement of metabolic control was observed, namely, serum fructosamine levels were significantly lower after 1, 3 and 4 weeks of treatment as compared to placebo group, and decreased significantly as compared to baseline levels after 3 weeks of treatment and by the end of the study (Table 3). Moreover, the significant difference in mean fasting blood glucose as compared to baseline levels was observed after the first week of treatment, and some patients experienced hypoglycaemic episodes that demanded the correction of daily dosage of oral hypoglycaemics. By the end of the study the daily dosage of glucose-lowering drugs was decreased by 15% on an average, as compared to baseline. Nobody of Allicor-treated patients discontinued the study in placebo group, no significant changes in lipid levels were observed (Table 2). There were no significant changes in fasting blood glucose and serum fructosamine levels, as well (Table 3).

Little is known on the possible beneficial effects of garlic-based preparations in type 2 diabetes mellitus, one of the major risk factors of premature atherosclerosis development. Late complications of diabetes mellitus include various syndromes associated with damage to large and small arteries, i.e., micro- and macroangiopathies. It was suggested that macroangiopathies result from atheroembolism [94], although some pathomorphological alterations typical especially for diabetes mellitus have been described [95]. Premature development and accelerated progression of atherosclerosis are the specific features of diabetes mellitus, as was confirmed by epidemiological studies [96-98]. Hyperglycemia occurring in diabetes mellitus leads to an increase in the concentration of the non-enzymatic glycosylation products in circulation [99].

Non-enzymatic glycosylation of proteins is a cascade of chemical reactions yielding stable covalent bonds between glucose molecule and free amino groups of protein. Enhanced glycosylation in diabetes mellitus can lead to the formation of modified atherogenic LDL as well as advanced glycation end products, including glycated collagen in arterial wall, the factors that could be attributed to accelerated atherogenesis in diabetics.

Particularly, it is known that non-enzymatic glycosylation impairs LDL metabolism, which manifests as a reduced affinity of LDL to the classical LDL-receptor [99], lower rate of LDL clearance from blood plasma [100], increased LDL uptake by macrophages [101], enhanced covalent binding of LDL to the connective tissue matrix of the vessel wall [102] and generation of free radicals participating in oxidative damage to lipid and proteins moieties of a lipoprotein particle [103]. It is quite obvious that improved metabolic control in diabetic patients can lead to the reduction in non-enzymatic glycosylation and therefore decrease biochemical risk for atherosclerosis development and progression [104]. The possibility of glucose-lowering effects of garlic was supported experimentally in the number of studies.

The first report considering the beneficial effects of allicin, biologically active sulfoxide from garlic, in alloxan-induced diabetic mice was published as far back as in 1973 [105]. Further studies have demonstrated that sulphur-containing amino acids from garlic possess a direct hypoglycaemic action, potentiate the effects of insulin in blood serum and increase the hepatic glycogen synthesis in alloxan-induced diabetes in mice and rabbits [106-110]. Additionally, garlic constituents decreased significantly the concentration of serum lipids, blood glucose and activities of serum enzymes like alkaline phosphatase, acid phosphatase and lactate dehydrogenase and liver glucose-6-phosphatase [111, 112].

Treatment of alloxan diabetic rats with the antioxidant Sallyl cysteine sulfoxide isolated from garlic, ameliorated the diabetic condition almost to the same extent, as did glibenclamide and insulin. In addition, S-allyl cysteine sulfoxide controlled lipid peroxidation and significantly stimulated in vitro insulin secretion from B cells isolated from normal rats [113-151]. The effect of garlic-based preparations was also demonstrated in streptozotocin-induced diabetes in mice and rats [114-117].

So, the anti-diabetic action of garlic established in animal studies provided a background for further investigations concerning possible clinical implications for garlic-based preparations. However, the use of garlic compounds as antidiabetic remedies in clinical practice is not well recognized, although dried garlic is widely

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>0 days</th>
<th>7 days</th>
<th>14 days</th>
<th>21 day</th>
<th>28 days</th>
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</thead>
<tbody>
<tr>
<td><strong>Fasting blood glucose, mmol/l</strong></td>
<td><strong>Monotherapy</strong></td>
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<td>6.5±0.7</td>
<td>6.2±0.5*</td>
<td>5.9±0.5*</td>
<td>6.3±0.4*</td>
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</tr>
<tr>
<td>Placebo</td>
<td>7.6±0.6</td>
<td>8.5±0.9</td>
<td>8.6±0.7</td>
<td>9.3±0.2*</td>
<td>9.3±0.4*</td>
<td></td>
</tr>
<tr>
<td><strong>Serum fructosamine, µmol/l</strong></td>
<td><strong>Allicor</strong></td>
<td>276±16</td>
<td>270±15</td>
<td>261±12</td>
<td>243±13 #</td>
<td>228±14 #*</td>
</tr>
<tr>
<td>Placebo</td>
<td>284±20</td>
<td>303±18</td>
<td>285±12</td>
<td>310±22</td>
<td>300±11</td>
<td></td>
</tr>
<tr>
<td><strong>Combined therapy</strong></td>
<td><strong>Fasting blood glucose, mmol/l</strong></td>
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<td></td>
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</tr>
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<td>Allicor</td>
<td>9.7±0.4</td>
<td>8.1±0.3*</td>
<td>8.9±0.5</td>
<td>9.0±0.5</td>
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</tr>
<tr>
<td>Placebo</td>
<td>10.1±0.8</td>
<td>9.9±0.7</td>
<td>9.7±0.6</td>
<td>9.7±0.7</td>
<td>10.2±0.7</td>
<td></td>
</tr>
<tr>
<td><strong>Serum fructosamine, µmol/l</strong></td>
<td>Allicor</td>
<td>396±16</td>
<td>359±14 #</td>
<td>355±20</td>
<td>340±17 #*</td>
<td>322±16 #*</td>
</tr>
<tr>
<td>Placebo</td>
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<td>414±16</td>
<td>382±17</td>
<td>402±11</td>
<td>404±14</td>
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</tbody>
</table>

* significant difference from baseline levels, p<0.05;
# significant difference from placebo group, p<0.05.

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used in traditional medicine of many cultures in the treatment of diabetes mellitus.

There are few clinical data on the effects of garlic in the improvement of metabolic control in diabetic patients. The results of the clinical study performed in South-East Asia more than 15 years ago were first to demonstrate the effectiveness of garlic in diabetes mellitus [118]. The beneficial effects of garlic-based dietary supplement in diabetes were also supported in a recent study by Melchinskaya, et al [119].

The study seems to be the first placebo-controlled trial aimed to estimate the effects of garlic-based drug on the parameters of metabolic control and plasma lipids in type 2 diabetes mellitus. In patients receiving monotherapy with Allicor, time-released garlic powder tablets, fasting blood glucose level tended to decrease. More remarkably, serum fructosamine that is considered to be a reliable and stable measure of long-term compensation of metabolic control, decreased significantly. Similar results were obtained in patients receiving Allicor along with continuing treatment with oral hypoglycaemics.

Hypertriglyceridaemia is the common pattern of dyslipidemia in type 2 diabetics. The observed reduction of serum triglycerides may also be related to antioxidant action of biologically active compounds from garlic that may inhibit generation of free radicals and stimulate catalase, superoxide dismutase and glutathione peroxidase activities [120], so that they might increase insulin sensitivity in peripheral and hepatic cells via the inhibition of lipid peroxidation in cell membranes.

Thus, glucose-lowering and triglyceride-lowering effects of garlic may be possibly due to its peripheral action through the lowering of insulin resistance in target tissues. It is notable that in diabetic patients receiving the combined therapy with Allicor and oral hypoglycaemics the moderate but statistically significant reduction in the daily dosage of glucose-lowering drugs occurred. This can be regarded as an additional beneficial effect of Allicor, since sulfonylurea derivatives may possess some unfavorable side effects that can be regarded as proatherogenic. It has been shown that oral hypoglycaemics produce a direct proatherogenic effect in cultured cells, inducing a substantial intracellular cholesterol accumulation [121]. So, the use of minimally possible dose of antidiabetic drugs to sustain adequate metabolic control is theoretically and experimentally justified and may be the rationale for Allicor assignment for complex therapy of type 2 diabetes mellitus.

Protection from Acute Respiratory Diseases

Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death [122]. Systemic infections may cause exaggerated local inflammation in atherosclerotic coronary arteries, representing the triggering effect of acute infections on acute coronary syndromes [123].

So the use of dietary supplements possessing the effects on non-specific natural immunity is well justified. Many of them may induce the enhancement of natural immunologic non-specific resistance to all types of viruses responsible for acute respiratory diseases (ARD) morbidity, and garlic-based preparations deserve the most thorough attention [124-127].

In spite of commonly spread positive opinion about the antibacterial and antiviral properties of garlic, very few and fragmented data exist on the benefits of garlic and garlic-based preparations in the prevention of acute respiratory viral diseases.

Lately the studies were performed to investigate the effect of time-released garlic powder tablets Allicor in prevention of ARD in children, in comparison with benzimidazole (Dibazole). It has been demonstrated that Allicor reduced ARD morbidity by 2.4-fold as compared to placebo, and by 1.7-fold as compared to benzimidazole. The results of investigation have demonstrated that garlic powder tablets are effective in non-specific prevention of ARD in children and possess no side effects. Two population-based studies have been performed in different regions. In 4,245 Muscovite adults 36-months Allicor treatment resulted in the reduction of ARD yearly morbidity (including influenza) by 59%. Most convincing results have been obtained in the study carried out in Putivl (Ukraine), where 4,413 participants (children and adults) vs 5,161 controls have been followed-up for 12 months. ARD rate (including influenza) in Allicor recipients was lowered by 7-fold, total morbidity was lower by 5.5-fold. Interestingly, coronary heart disease and hypertonic morbidity was also reduced (by 3.6- and 4.1-fold, respectively), that may be due to cardioprotective effects of garlic. It is also important that both high and low doses of garlic preparation (600 mg and 300 mg daily) provided similar beneficial effect. This study seems to be the one of the first clinical trials to investigate the effects of garlic-based preparation on ARD morbidity.

The mechanisms underlying antimicrobial effects of garlic are not well elucidated yet. However, it is known that sulfur-containing amino acids from garlic may play the decisive role, among them are alliin, allicin and ajoene [128].

The authors recommended Allicor for long-term prevention of acute respiratory diseases as the effective, low-cost and safe approach to the improvement of immunity and resistance to viral infections.

Primary Prevention of Cardiovascular Disease in High-Risk Patients

The double-blind placebo-controlled randomized study was performed to evaluate the effectiveness of time-released garlic powder tablets Allicor in primary coronary heart disease (CHD) prevention and its effects on the estimates of multifunctional prognostic cardiovascular risk in intermediate- and high-risk patients.

There were 40 patients (20 men, 20 women) in Allicor-treated group, and placebo group consisted of 39 patients (20 men, 19 women). The groups did not differ significantly with the respect to age, arterial blood pressure, body mass index, left ventricular hypertrophy, diabetes mellitus and smoking status. Additionally, no gender-related differences were revealed within groups, except for the increased body mass index in Allicor-treated women.

Baseline lipid levels are presented in Table 4. There were no significant differences between groups and gender-specific differences within groups with the respect to any measured parameter.

Table 4 also summarizes the changes in lipid levels that occurred during 12-months follow-up. In placebo-treated men serum triacylglycerols tended to decrease by 25.0%, or by 0.49 mmol/L from the baseline, and HDL cholesterol increased significantly by 9.0%, or 0.10 mmol/L from the baseline. The changes in total and LDL cholesterol in placebo-treated men did not reach statistical significance. At the same time, no significant changes in lipid parameters in placebo-treated women were observed.

In Allicor-treated patients all lipid parameters changed significantly. Total cholesterol decreased by 6.1%, or 0.42 mmol/L from the baseline. Serum triacylglycerols lowered by 20.1%, or 0.46 mmol/L from the baseline. HDL cholesterol level increased by 8.2%, or 0.10 mmol/L from the baseline. Accordingly, LDL cholesterol level lowered by 4.4%, or 0.31 mmol/L. The most prominent changes were observed in men: total cholesterol decreased by 0.82 mmol/L, LDL cholesterol decreased by 0.61 mmol/L, serum triacylglycerols decreased by 0.72 mmol/L from the baseline, and HDL cholesterol tended to increase by 0.12 mmol/L. In Allicor-treated women total and LDL cholesterol levels did not change significantly, serum triacylglycerols tended to decrease by 0.20 mmol/L, and only HDL cholesterol increased significantly by 6.5%, or 0.07 mmol/L from the baseline.

The data on the changes in prognostic cardiovascular risk levels are presented in Table 5. 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. So, 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 men CHD prognostic risk decreased by 13.2% from the baseline, in women - by 7.1%, and in total group - by 10.7% from the baseline. When diastolic blood pressure algorithm was used, the decrease of CHD prognostic risk by 6.7% from the baseline was observed, 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, obviously due to the insufficient sample size.

The beneficial changes in 10-year CHD prognostic risk correlated with the changes in systolic blood pressure, diastolic blood pressure, serum triacylglycerols, HDL cholesterol and LDL cholesterol. Regression analysis confirmed the role of the changes in systolic blood pressure, LDL cholesterol and HDL cholesterol, whereas the changes of serum triacylglycerols played additional role in men, and the improvements in diastolic blood pressure - in women.

Ten-year prognostic risk of myocardial infarction (fatal and non-fatal) and sudden death did not change in placebo-treated men and women (Table 5). On the opposite, in Allicor-treated men the risk of myocardial infarction and sudden death decreased by 26.1% from the baseline. In Allicor-treated women there were no significant changes in prognostic risk level.

The changes in 10-years prognostic risk of myocardial infarction and sudden death correlated with the changes in systolic blood pressure, serum triacylglycerols and LDL cholesterol. In Allicor-treated men the only factor that could be assigned to risk reduction was the decrease of LDL cholesterol level.

Cardiovascular risk is generally predetermined by mutual action of different risk factors, such as dyslipidemia, arterial hypertension, smoking, abdominal obesity, etc. Thus, no CHD risk factors in particular patient cannot be judged in isolation; moreover, when some risk factor is present in patient, it is necessary to analyze other components of cardiovascular risk and treat all of them vigorously [129].

The modern strategy of prevention of cardiovascular diseases is fairly based on complex modification of independent major risk factors. The effectiveness of such approach is supported in the number of epidemiological studies. In the Framingham Study, 44% decrease in the CHD rate in men observed between 1950 and 1989 could be attributed to improvements of risk factors at least by one third to one half [130].

Additionally, 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 effect [131]. In Netherlands, 44% of the decline in CHD mortality rate between 1978 and 1985 could be attributed solely to effective primary prevention [132]. Finally, 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 [133].

Most comprehensive epidemiological studies provided the evidence that in high-risk patients without manifested CHD the probability of acute myocardial infarction and sudden death may be comparable or even higher than in CHD patients [134, 135]. So, the concept of absolute cardiac risk estimation that reflects actual probability of cardiovascular event began to prevail in preventive cardiology.

At present, multivariate cardiovascular risk estimation is developed from findings of Prospective Cardiovascular Münster Study.
PART II: DIRECT ACTION

Direct action is aimed not to risk factor elimination but to reducing an atherosclerotic lesion in the artery.

Table 5. The dynamics of absolute cardiovascular risk changes.

<table>
<thead>
<tr>
<th>Time</th>
<th>Allicor recipients</th>
<th>Placebo recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n=40)</td>
<td>Men (n=20)</td>
</tr>
<tr>
<td>10-year prognostic risk of CHD, % (systolic blood pressure algorithm)</td>
<td>19.4±1.7</td>
<td>22.6±2.6</td>
</tr>
<tr>
<td>After 12 months</td>
<td>18.1±1.7*</td>
<td>21.0±2.5</td>
</tr>
<tr>
<td>10-year prognostic risk of CHD, % (diastolic blood pressure algorithm)</td>
<td>19.4±1.7</td>
<td>22.6±2.6</td>
</tr>
<tr>
<td>After 12 months</td>
<td>18.1±1.7*</td>
<td>21.0±2.5</td>
</tr>
<tr>
<td>10-year prognostic risk of myocardial infarction and sudden death, %</td>
<td>9.7±2.4</td>
<td>16.5±4.4</td>
</tr>
<tr>
<td>After 12 months</td>
<td>7.8±1.8*#</td>
<td>12.6±3.2*</td>
</tr>
</tbody>
</table>

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

(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 [136, 137].

Ideally, the solution lies in the performing of similar prospective studies in different countries and regions, but 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 [134, 138]. The relevant recalibration coefficients that are characteristic for Russia have been used in our study.

The results of the double-masked placebo-controlled randomized study have demonstrated that 12-months treatment with time-released garlic powder tablets Allicor results in a significant reduction of multivariate prognostic cardiovascular risk in high-risk patients. It is notable that 10-year prognostic risk of CHD was reduced better in men than in women, and the reduction of 10-year prognostic risk of myocardial infarction and sudden death was observed only in men. These gender-related differences were mainly due to prominent decrease of LDL cholesterol in men as compared to women, as well as to extremely low probability of acute cardiovascular events in women.

The main effect that underlies the beneficial dynamics of multivariate cardiovascular risks in Allicor-treated patients is a hypolipidemic action of the drug, namely, the sufficient reduction of LDL cholesterol. 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 HDL cholesterol, serum triacylglycerols and arterial blood pressure. Although the last effects did not reach statistical significance, they have provided benefits upon the calculation of individual multivariate risks.

**PART II: DIRECT ACTION**

Direct action is aimed not to risk factor elimination but to reducing an atherosclerotic lesion in the artery.

**Direct Antiatherosclerotic Effect in Carotid Atherosclerosis**

Several years ago we have established that blood serum from atherosclerotic patients is able to induce lipid accumulation in the primary culture of human intimal aortic cells, thus demonstrating the primary step in atherogenesis at the cellular level [16-19].

This phenomenon was termed “atherogenicity”. We have proposed that meaningful serum atherogenicity lowering may be the way to prevent lipid deposition in vascular wall, thus inhibiting the initial step of atherosclerosis lesion formation [20].

The results of our preliminary studies have shown that oral intake of garlic powder tablets Allicor resulted in the prevention of serum-induced cholesterol accumulation in cultured cells [22, 46]. So, the use of Allicor seemed to be the promising approach to lowering atherogenicity. We have also demonstrated that garlic components are able to stimulate the intracellular hydrolysis of esterified cholesterol and to inhibit the processes of intracellular cholesterol esterification, thus lowering the overall content of cholesterol esters in cells [23]. These data support an assumption that long-term treatment by garlic-based drug Allicor could produce a direct antiatherosclerotic effect at the level of vascular wall.

To test it, the double-blinded placebo-controlled multicenter study was performed to estimate the effect of Allicor on the evolution of carotid atherosclerosis in asymptomatic men.

Atherosclerosis is characterized by a number of morphological, histological and hemorheological changes in large arteries [8].

The pathogenetic treatment of atherosclerosis seems to consider at least the prevention of growth of atherosclerotic lesions, diminishing the lipid core mass and further plaque stabilization. Taken together, these approaches could theoretically result in the regression of lesions.

Atherosclerosis affects most vascular beds, and noninvasive imaging of superficial arteries by ultrasound has been recognized as a surrogate measure of atherosclerosis in numerous studies. Extra-coronary atherosclerotic lesion can be quickly and safely evaluated in the carotids, femoral arteries, and the abdominal aorta. The grade of atherosclerosis in extracoronary sites correlates with a greater number of standard risk factors and, more important, with greater cardiac risk [139]. Of the peripheral arterial surrogates, carotid...
Atherosclerosis has been most closely correlated with coronary artery disease [140-144]. Peripheral arterial ultrasonography is regarded to be a sensitive tool for the detection of early atherosclerosis and may be useful in assessing response to therapy. Thickening of the intima-media of the arterial wall is the earliest detectable anatomic change in the development and progression of atherosclerosis. High-resolution B-mode ultrasonography is widely used for noninvasive quantification of carotid IMT (intima-media thickening) as a measure of subclinical atherosclerosis [145]. Carotid IMT is believed to be a marker of generalized atherosclerosis and is predictive of clinical cardiovascular events [146-150]. So, ultrasound imaging of intima-media thickening in carotid arteries is an applicable method for atherosclerosis monitoring during Allicor long-term treatment.

IMT changes in individual patients were formally classified as progression, regression or stability on the basis of statistically significant difference of the mean of three measurements at the end of the study from the mean of three examinations at the baseline. In Allicor recipients, IMT significant increase either in one or both carotid arteries was observed in 30 (32.2%) patients, and IMT either of one or both carotid arteries decreased significantly in 44 (47.3%) patients. In 8 patients (8.6%) there were no significant IMT changes in both carotid arteries, and in the rest 11 patients (11.8%) diverse changes were observed, i.e. one carotid artery demonstrated a significant increase in IMT, and in other one IMT decreased. In placebo group, the progression was observed in 50 (48.5%) cases, and IMT decreased significantly in one or both arteries in 31 (30.1%) patients. Stable situation was observed in 11 (10.7%), and diverse changes occurred in the rest 7 (6.8%) patients. The difference in the direction of IMT changes between Allicor and placebo recipients was statistically significant. So, spontaneous atherosclerosis progression prevailed in placebo group, and Allicor treatment yielded a beneficial impact on early atherosclerosis in carotids demonstrating the significant increase in the number of observed regressions mainly for account of diminishing the number of cases with progression.

The dynamic of changes in intima-media thickness in Allicor-treated and placebo groups is demonstrated in Figure 3. The tendency to IMT decrease in Allicor recipients was observed already after first 3 months of the study, but statistically significant difference from the baseline as well as from placebo group was achieved only after first 12 months of treatment. Upon the following examinations up to the end of the two-year study, the difference between placebo and Allicor recipients increased and remained statistically significant. For the common carotid artery, there was a moderate yearly IMT increase of 0.015 mm overall mean baseline IMT of 0.931 mm in placebo group, whereas in Allicor-treated patients the rate of IMT changes was -0.022 mm per year that was significantly different from placebo recipients.

The mean rate of IMT changes in placebo group was similar in both years of the study, and in Allicor-treated patients the beneficial effect seemed to be more pronounced in the first year of treatment (-0.028 mm vs -0.016 mm for the first and the second year, respectively), but the difference did not reach statistical significance.

The beneficial effects of Allicor were also revealed upon the analysis of data from subgroups of patients who had either significant increase or reduction in IMT. So, in Allicor-treated patients with atherosclerosis progression (n=30) IMT increased by 0.029 mm, while in placebo recipients (n=50) the increase accounted for 0.070 mm. Similarly, the spontaneous atherosclerosis regression in placebo recipients (n=31) was characterized by significant decrease in IMT by 0.041 mm, but in Allicor-treated patients (n=44) the rate of IMT decrease over two years was 0.082 mm.

At the baseline, the sera from 17 patients in placebo group (16.5%) did not induce significant cholesterol accumulation in cultured cells, while the sera from other 86 patients were atherogenic, i.e. induced statistically significant (1.21- to 3.91-fold) increase in intracellular cholesterol content (mean result, 166.3% of control value). In Allicor-treated patients, 23 patients (24.7%) had nonatherogenic sera, and in other 70 patients the sera increased intracellular cholesterol by 1.22- to 3.53-fold (mean result, 172.1% of control value).

Among patients with non-atherogenic sera at the baseline, in placebo recipients blood serum atherogenicity arrived in 11 cases during the study; in Allicor-treated patients at the end of the study serum atherogenicity was revealed in 9 cases, and in other 14 patients the sera remained non-atherogenic. The difference between Allicor and placebo recipients was statistically significant. Thus, Allicor treatment prevented the uprise of blood serum atherogenicity.

Among patients with initially atherogenic sera, in placebo group blood serum atherogenicity spontaneously decreased in 26 patients, did not change significantly in 28 patients, and in 32 cases there was further increase in blood serum atherogenic potential. On the opposite, in Allicor group serum atherogenicity was decreased in 39 patients by the end of the study, remained unchanged in 18 patients, and further increase in serum ability to induce intracellular cholesterol accumulation was observed only in 13 cases. Again, the difference between Allicor and placebo recipients was statistically significant. Thus, Allicor also induced a fall in blood serum atherogenicity, if it existed at the beginning of treatment.

The overall dynamic of changes in serum atherogenicity is presented in Figure 4. At the baseline, serum taken from patients was able to induce 1.56-fold increase in intracellular cholesterol content in cell culture test. In the placebo group, the mean level of serum atherogenic potential did not change significantly during two years of the study. On the opposite, in Allicor-treated patients the mean value for the ability of serum to induce intracellular lipid accumulation was significantly lowered approximately by 30% of the initial level already after first 3 months of study, and this effect was maintained during the study. General linear model analysis has demonstrated the statistically significant difference in the dynamic of changes in serum atherogenicity between Allicor-treated and placebo groups.
The presence or absence of serum atherogenicity at the baseline, as well as the extent of serum-induced intracellular cholesterol accumulation at the baseline, did not correlate with the following changes in IMT. However, the statistically significant correlation has been revealed between the changes in blood serum atherogenicity during the study and the changes in intima-media thickness of common carotid arteries. Upon the separate analysis of placebo and Allicor recipients, correlation coefficients for these two parameters did not reach statistical significance. In patients with initially non-atherogenic sera, the correlation between changes in atherogenicity and IMT was rather stronger, obviously due to those patients in placebo group in whom serum atherogenicity arrived during the study. In patients with initially atherogenic sera, the correlation between changes in atherogenicity and IMT in total group did not reach statistical significance, but in Allicor-treated patients in most of whom the decrease in serum atherogenicity was observed, the above parameters correlated well.

The observed changes in serum lipid levels are presented in Table 6. Serum total cholesterol levels remained stable in the Allicor-treated group, whereas in the placebo group the moderate but significant increase by 4.4% was observed by the end of the study as compared to baseline level. However, there was no significant difference between groups at any time of the study. For serum triglycerides, in both groups moderate decrease was observed that was statistically significant; in Allicor group serum triglycerides lowered by 13.4%, and in placebo recipients by 15.2% by the end of the study. There was no significant difference between groups at any time of the study except for examination after 3 months of treatment. For HDL cholesterol, the similar changes were observed both in Allicor-treated and placebo groups. By the end of the study, HDL cholesterol levels increased by 0.27 mMol/L and 0.13 mMol/L, respectively. The calculated levels of LDL cholesterol demonstrated statistically significant decrease in Allicor-treated group after 12 months of treatment, and by the end of the study it accounted for 5.2%. On the opposite, in placebo group there was moderate elevation in LDL cholesterol by 9.3% by the end of the study. So, there was significant difference in LDL cholesterol levels between Allicor-treated and placebo groups after 3, 18 and 24 months of the study.

We have revealed no significant correlations between baseline IMT and its changes over two years of the study and baseline lipid parameters. However, some correlations were revealed between the changes in lipid parameters and IMT during the study. There was a tendency to negative correlation between HDL cholesterol changes and IMT dynamics in total group, and in placebo group this correlation was statistically significant. In those patients with initially non-atherogenic sera, HDL cholesterol changes also correlated negatively with the changes in IMT, but upon separation into placebo and Allicor recipients this correlation has lost significance but remained as a tendency. In the patients with initially atherogenic sera similar tendency existed in placebo recipients. Additionally, in the subgroup of patients in whom serum atherogenicity did not change over the time of study, the correlation between the increase of IMT and increase of LDL cholesterol existed, and the tendency to such correlation was observed in placebo recipients.

The main scientific goal of the double-masked placebo-controlled randomized study was to test the hypothesis that long-term lowering of serum atherogenicity may prevent the initial stage of atherogenesis, namely, the excessive deposition of cholesterol in the cells of the arterial wall, thus inhibiting further formation of atherosclerosis lesion [11, 12, 20].

At the clinical level, inhibition of the processes of atherogenesis could be monitored by ultrasound examination of common carotid arteries and the measurements of intima-media thickness.

For this purpose, asymptomatic men who regarded themselves as “apparently healthy” but had ultrasonographic evidence for early atherosclerosis were recruited for this study. The obtained results clearly indicate that long-term treatment with garlic-based drug Allicor results in a significant decrease in intima-media thickness of carotid arteries as compared to measurements made at baseline either to placebo group, respectively. Overall, the regression of subclinical atherosclerosis was much more frequently observed in asymptomatic men who randomly received Allicor than in those who received placebo.

This anti-atherosclerotic effect goes in parallel with serum atherogenicity lowering, and the statistically significant correlation has been revealed between the changes in blood serum atherogenicity during the study and the changes in IMT of common carotid arteries. However, those correlations revealed between IMT changes and the changes in HDL cholesterol, especially in placebo recipients, and changes in LDL cholesterol in patients who did not demonstrate significant changes in serum atherogenicity also point out to the role of lipid metabolism disturbances in early atherogenesis.

As garlic-based preparations are considered to possess lipid-lowering effects [5, 6, 38, 151], the direct anti-atherosclerotic action of garlic provided by the prevention of intracellular lipid deposition may be complemented by its effects on LDL and HDL cholesterol levels.

The beneficial effects of the rise in HDL cholesterol observed in the given study, especially in placebo recipients, that are clearly associated with the spontaneous regression of early atherosclerosis, are obviously of great importance and provide the promising field for further investigations. Additionally, the rather high proportion of patients in placebo group who demonstrated spontaneous regression of early atherosclerosis may witness of the wave-form character of atherogenesis, especially at early stages, and gives the reason for future studies, since the mechanisms of this phenomenon are still obscure.

The results obtained are generally in good coincidence with the data from recent double-masked placebo-controlled randomized study by Koscielny, et al. [152].

It has been demonstrated that 4-year treatment with garlic-based drug Kwai inhibited the increase in the volume of atherosclerotic plaques in carotid and femoral arteries by 5-18%. The age-dependent representation of the plaque volume has shown an increase between 50 and 80 years that was diminished under garlic treatment by 6-13% related to 4 years. So, with garlic application
the plaque volume in the whole collective remained practically constant within the age-span of 50-80 years.

There is a substantial experimental background to explain the possible mechanisms underlying a direct anti-atherosclerotic action of Allicor. The components of garlic can regulate two main intracellular enzymes responsible for cholesterol intracellular metabolism. Garlic extract stimulates cholesteryl ester hydrolase and inhibits acetyl coenzyme A : cholesterol acyl transferase, thus diminishing intracellular content of cholesteryl esters [23].

Additionally, garlic extract inhibits cellular proliferative activity and the synthesis of connective tissue matrix components [23, 46]. Allicor also possesses antioxidant activity and lowers LDL susceptibility to oxidation [46]. Allicor prevents serum-induced cholesterol accumulation in cells cultured in the presence of patient’s serum taken after single dose of Allicor administration; in other words, it reduces serum atherogenic potential [46].

In animal studies, garlic-based preparations inhibit the formation of neointimal thickening in cholesterol-fed rabbits [3].

So, it could be easily proposed that long-term Allicor treatment produced a direct antiatherosclerotic effect due to the prevention of lipid deposition and depletion of cholesterol pool already accumulated in arterial wall.

The obtained results were compared with the data from several studies, where the effects of different drugs on atherosclerosis progression were investigated [153-160], and the changes in IMT of carotid arteries have been monitored as a primary or secondary outcome (Table 7).

Obviously, the decrease in IMT achieved during AMAR study is quite comparable with the results of most successful trials. However, these studies employed potent lipid-lowering agents either calcium antagonists. So, the beneficiary effects of treatment were regarded to either significant reduction of LDL cholesterol, the major risk factor for atherosclerosis development, or the reduction in arterial wall stress.

In «Atherosclerosis Monitoring and Atherogenicity Reduction» (AMAR) study, moderate changes in lipid levels were also observed. The reduction in serum triglycerides and elevation in HDL cholesterol both in Allicor-treated and placebo patients seem to be due to good compliance with the dietary recommendations given upon the inclusion in the study. The moderate rise in total cholesterol level in placebo group is partially due to the rise in HDL cholesterol. However, LDL cholesterol in placebo patients also increased during the study, and it may be explained by the processes of aging [161, 162].

Allicor treatment obviously prevented this rise. So, Allicor possesses mild lipid-lowering activity, like other garlic-based preparations [5, 6, 38, 151, 163, 164].

It is notable that the effect on carotid atherosclerosis only in small part depended on the changes in serum lipid levels, thus enforcing the explanations quite different from convenient approaches.

Blood sera from the majority of atherosclerotic patients, unlike sera from healthy subjects, are capable of inducing lipid accumulation in cultured cells, i.e. possess atherogenic properties [16, 17]. The serum atherogenic potential is mainly due to the presence of modified low density lipoprotein [17-19], and in certain extent to non-lipid atherogenic factors [165-167].

So, blood serum atherogenicity revealed in cell culture test may be used as the integral characteristic of intracellular lipid deposition, the primary step in atherogenesis.

The significant reduction of serum atherogenicity was the major phenomenon observed in Allicor-treated group that could help explaining the beneficiary effects of Allicor on the progression of carotid atherosclerosis. Certainly, intracellular lipid deposition occurred during atherogenesis may act as a trigger event followed by other pathologic changes in vascular wall, such as the enhanced synthesis of connective tissue matrix components, migration of hematogenic cells, development of inflammatory reactions and, possibly, cellular proliferation. The mechanisms of interaction of these quite different processes still remain obscure.

---

Table 6. The changes in lipid parameters.

<table>
<thead>
<tr>
<th>Group</th>
<th>Duration of the study, months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Total cholesterol, mMol/L</td>
<td></td>
</tr>
<tr>
<td>Allicor</td>
<td>6.14±0.12</td>
</tr>
<tr>
<td>Placebo</td>
<td>6.02±0.10</td>
</tr>
<tr>
<td>HDL cholesterol, mMol/L</td>
<td></td>
</tr>
<tr>
<td>Allicor</td>
<td>1.07±0.03</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.10±0.03</td>
</tr>
<tr>
<td>LDL cholesterol, mMol/L</td>
<td></td>
</tr>
<tr>
<td>Allicor</td>
<td>4.06±0.10</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.88±0.09</td>
</tr>
<tr>
<td>Triglycerides, mMol/L</td>
<td></td>
</tr>
<tr>
<td>Allicor</td>
<td>2.17±0.14</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.23±0.12</td>
</tr>
</tbody>
</table>

* significant difference from the baseline, paired test, P<0.05
## significant difference from placebo, independent samples test, P<0.05

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CONCLUSION

It is generally believed that dietary factors may play a significant role in the prevention of atherosclerosis, and some categories at risk, such as mildly hyperlipidemic or mildly hypertensive patients, usually are poorly motivated to take powerful drugs, but may easily put trust on the agents of natural origin possessing mild biological effect. Natural agents for atherosclerosis prevention offer the possibility for long-term intervention that is safe and inexpensive.

Allicor contains just garlic powder that is thought to retain the same biologically active ingredients as raw garlic, both water-soluble and organic-soluble. On the other hand, it possesses a prolonged mode of action, as its biological effect lasts for 12-16 h after single-dose administration. So, Allicor differs greatly from other garlic-based preparations and may have considerable benefits in medicinal use.

The results of reviewed studies revealed a reduction in atherosclerotic risk factors and direct antiatherosclerotic effect of Allicor. Blood serum atherogenicity was used as the integral characteristic of intracellular lipid deposition, the primary step in atherogenesis, and supported the use of time-released form of garlic powder tablets for the prevention and treatment of cardiovascular disease.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

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REFERENCES

Table 7. The comparative data from clinical trials on carotid atherosclerosis regression.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Medication</th>
<th>Mean annual IMT change, mm</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>placebo</td>
<td>treatment</td>
</tr>
<tr>
<td>PLAC II</td>
<td>Pravastatin</td>
<td>0.068</td>
<td>0.059</td>
</tr>
<tr>
<td>KAPS</td>
<td>Pravastatin</td>
<td>0.029</td>
<td>0.010</td>
</tr>
<tr>
<td>ASAP</td>
<td>Simvastatin</td>
<td>-</td>
<td>-0.009</td>
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<tr>
<td>PREVENT</td>
<td>Amlodipine</td>
<td>0.011</td>
<td>-0.015</td>
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<tr>
<td>ASAP</td>
<td>Atorvastatin</td>
<td>-</td>
<td>-0.020</td>
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<tr>
<td>CLAS</td>
<td>Cholestipol, niacin</td>
<td>0.010</td>
<td>-0.020</td>
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<tr>
<td>MARS</td>
<td>Lovastatin</td>
<td>0.015</td>
<td>-0.028</td>
</tr>
<tr>
<td>VHAS</td>
<td>Verapamil</td>
<td>-</td>
<td>-0.028</td>
</tr>
<tr>
<td>AMAR</td>
<td>Allicor</td>
<td>0.015</td>
<td>-0.022</td>
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