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Original Article

Effectiveness of patient-oriented intervention in primary prevention of cardiovascular diseases with statins: Open-label randomized study

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Abstract

Background: Poor adherence to treatment is an obstacle to reach the target level of lipids. The purpose of the study was to investigate the impact of patient-oriented intervention with primary focus on patients' adherence to lipid-lowering therapy on low-density lipoprotein cholesterol (LDL-C) in patients with dyslipidemia and receiving statins for primary prevention of cardiovascular diseases (CVD).

Methods: A prospective, open-label, randomized, multicenter study in parallel groups. Data was collected from 11 study sites. 2,912 patients were recruited between June 2018 and August 2019. Test Intervention: extended consultation on drug compliance, patient-oriented printed materials about CVD prevention, SMS- and phone reminders. The primary endpoint was LDL-C. Chi-square test or Fisher's exact test was used for qualitative variables. Paired Wilcoxon test was used to compare the variables between patient visits. The odds ratio (OR) at 95% confidence interval (CI) was defined as the ratio of the chance of fulfilling the criterion in the group or subgroup (subpopulation).

Results: At 12 month, the number of patients achieving target levels of LDL-C, total cholesterol (TC) and blood pressure (BP) was significantly higher in the intervention group vs control (LDL-C: 80% vs. 70%, OR: 1.68, 95% CI: 1.40 to 2.01, p<0.001; TC: 80% vs. 67%, OR: 1.92, 95% CI: 1.60 to 2.29, p<0.001; BP: 85% vs 79%, OR: 1.49, 95% CI:1.22 to 1.83, p=0.0001).

Conclusion: Proposed patient-oriented intervention helps to achieve the target level of LDL-C, TC and supports better control of BP in patients receiving statins for primary prevention of CVD.

Keywords: Cholesterol, Drug compliance, Dyslipidemia, Patient-oriented preventive intervention, Primary cardiovascular prevention, Statins.

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Cardiovascular diseases (CVD) are the major cause of death (1). Administration of statins is well-established approach to reduce the prevalence and mortality from CVD, both in individuals with already identified CVD (2-5) and in those without diagnosed cardiovascular (CV) pathology (6-8). Effectiveness of statins in primary prevention of CVD was demonstrated for the groups of patients with moderate risk (MR) and high risk (HR) of CVD (6, 9, 10). According to the Epidemiology of Cardiovascular Diseases and their Risk Factors in Regions of Russian Federation (ESSE-RF) trial, 57.6% of the population (aged 25-64 years) have elevated total cholesterol (TC) (11). Only 7-17% of the patients with HR and very high risk (VHR) take statins (11, 12) and no more than 30% of patients are compliant to prescribed treatment regimen of statins (13, 14). The Dyslipidemia International Study in Russia (DYSIS) demonstrated that only 12.2% VHR patients and 30.3% HR patients treated with statins achieved target level of low-density lipoprotein cholesterol (LDL-C) (15).

Poor adherence to treatment (early self-discontinuation, missing doses) could be a primary obstacle to reach the target level of lipids. Adherence to therapies for chronic conditions averages 50% in developed countries. These rates are even lower in developing countries (16). If risk factors (RF) are present, clinical recommendations require a physician to provide standard preventive counseling (lifestyle changes, diet correction, physical activity, body weight correction) and, if indicated, to prescribe appropriate therapy, for instance, statins in dyslipidemia (17, 18). At the same time, standard preventive counseling in addition to statin treatment does not always help enough to reach the target levels of lipids (11, 14, 15). The patient-oriented preventive intervention program, with primary focus on patients' adherence to lipid-lowering therapy, was developed. We intended to investigate the impact of proposed patient-oriented intervention on LDL-C levels and to improve the quality of medical care in individuals with dyslipidemia and receiving statins for primary prevention of CVD.

Methods

The research question was whether the patient-oriented intervention helps to achieve the LDL-C goal in individuals with dyslipidemia and receiving statins for primary prevention of CVD?

Study design and setting: This prospective, multicenter, randomized, open-label, study in parallel groups was conducted between June 2018 and December 2020 at 11 study sites (preventive care facilities) with 31 investigators in 5 cities of the Russian Federation. Patients were enrolled in the study from June 2018 till August 2019. Subjects were randomly assigned to the intervention or standard treatment group (allocation ratio 1:1) considering the CV risk type according to the Systematic Coronary Risk Evaluation Scale (SCORE) (central randomization with allocation concealment, CRSTAT system: after entering the data of the next eligible patient, the system sent to the investigator the information about study group which the patient should be allocated via e-mail and Short Message Service (SMS)). The total study period was 12 months, with four scheduled patient visits at Day 0 (M0), Month 3, Month 6, Month 12 (M12). The last patient visit was in August 2020.

Study objectives: The primary objective was to investigate the impact of proposed patient-oriented intervention with primary focus on patients' adherence to lipid-lowering therapy on low-density lipoprotein cholesterol (LDL-C) in patients with dyslipidemia and receiving statins for primary CVD prevention. The secondary objectives were (1) to investigate the impact of proposed patient-oriented intervention with primary focus on patients' adherence to lipid-lowering therapy, (2) to evaluate risk factors of CVD in patients receiving statins for primary CVD prevention in the MR, HR and VHR subpopulations.

Ethics statement: This research project obtained the approval from the Independent Ethics Committee, 125468, Moscow, 51 Leningradskiy ave. (Meeting #08, May 18, 2018; code 08.2018.05.18; regulated by Federal Law #61-FZ 12.04.2010 "On Circulation of Medicines". Registration number ClinTrials.gov NCT03927196). All methods were carried out in accordance with relevant guidelines and regulations. The trial was conducted in accordance with the ethical principles of the Declaration of Helsinki. The informed consent was obtained from all study subjects before the randomization to the treatment.

Selection of study subjects: Patients aged 40-65 years without CVD of atherosclerotic genesis, with TC level ≥5 mmol/L and with one or more RFs were pre-selected by review of medical records and invited for medical examination. All patients were examined according to the standards of care of the regular medical settings, including blood pressure (BP), anthropometry, and electrocardiography. Blood lipids were determined by a rapid lipid test. Risk of CVD was calculated according to SCORE for countries with high risk (17). Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were calculated, to assess possible risk of statin administration. Patients matching inclusion and exclusion criteria and providing their informed consent were invited to the first study visit (M0).

Eligibility criteria: Patients with MR, HR, or VHR, who had no clinical manifestations of the atherosclerotic disease and not taking atorvastatin at study entry, were included in the study. Patients with a history of myocardial infarction, transient ischemic attack and stroke were not enrolled. Further details are presented in figure 1.

Sample size calculation: The number of subjects achieving LDL-C goal among the total enrolled patients with dyslipidemia, RF and treated with statins was considered for sample size calculation (11, 15). Also, data on the effectiveness of the measures to increase the adherence to statins in primary care was considered (19-21). Considering the possible drop out, sample size was calculated as 2,912 patients and were randomized in equal proportions between the intervention and control groups. Target subpopulation were MR: 1,242 patients, HR: 1,044 patients and VHR: 626 patients, which corresponds with the distribution of RF in total population (11, 15). Risk of CVD was defined, and patients were allocated to one of the study subpopulations

(MR, HR or VHR) based on their CVD risk. Patients were equally randomized (1:1) to the intervention or control group within each RF subpopulation using central randomization (CRSTAT). Enrollment to RF subpopulation was terminated after reaching the target size of subpopulation.

Test intervention: All patients received atorvastatin for primary prevention of CVD. Selection of the initial dose of atorvastatin and dose adjustment or discontinuation during the study were carried out by a physician according to regular practice of the medical institution. Atorvastatin was chosen as the standard statin treatment as it is the most prescribed statin in the Russian Federation (15). Atorvastatin is included in the clinical recommendations for prevention of CVD and the Russian List of Vital and Essential Drugs (22), which ensured availability of the drug from regular medical settings during the study. In the large Russian epidemiological study (DYSIS-Russia) (15), the atorvastatin group was the most representative and this allowed to calculate sample size for this study appropriately. The proposed patient-oriented intervention (5-min extended consultation on drug compliance during the visit, providing the patient with printed materials about CVD prevention, once-in-two-week SMS reminders about the need to take the drug regularly, phone reminders to visit a physician as scheduled) was provided to the intervention group in addition to standard medical counselling of patients with dyslipidemia (lifestyle changes, diet correction, physical activity, body weight correction, personalized recommendations for correcting risk factors). The control group received standard medical counselling only.

Inclusion criteria
Men and women with no CVD of atherosclerotic genesis, not taking statins or other lipid-lowering drugs, and with the presence of: • MR (≥1% and <5%) and LDL-C ≥3.0 mmol/L who have not achieved target LDL-C level with lifestyle changes, or • HR (≥5% and <10%) and LDL-C ≥2.5 mmol/L, or • VHR (≥10%) and LDL-C ≥1.8 mmol/L, or • Carotid stenosis >50% in the absence of cerebrovascular diseases and LDL-C ≥ 1.8 mmol/L • Diabetes mellitus (with LDL-C above target level depending on CV risk) who can be prescribed atorvastatin in accordance with the practice of the medical institution, and who signed informed consent
Exclusion criteria
• Coronary heart disease • Heart failure • Atherosclerotic peripheral arterial disease • Carotid atherosclerosis with underlying cerebrovascular disease • Chronic kidney disease, creatinine clearance <30 ml/min • Hepatic disorders, AST and ALT >3 times upper limit of normal • History of muscle injury or other neuromuscular disorders with increased creatine kinase • Alcohol dependence, cancer, mental and other severe comorbidities • History of intolerance to statins • Other lipid-lowering drug therapy

Figure 1. Criteria for inclusion and exclusion in the study

Primary endpoint: The primary endpoint was proportion of participants reached the target LDL-C level, calculated automatically according to Friedwald after determination of lipid profile. Target levels: MR <3.0 mmol/L; HR<2.5 mmol/L; VHR<1.8 mmol/L (17, 18).

Secondary endpoints: The secondary endpoints were proportion of participants reached the target level of:

- Total cholesterol (TC). Target level: <5 mmol/L (17, 18).
- High-density lipoprotein cholesterol (HDL-C). Target levels: males >1.0 mmol/L, females >1.2 mmol/L (17,18)
- Triglycerides (TG). Target level in "non-fasting" blood: <2.0 mmol/L, corresponds to <1.7 mmol/L in "fasting" blood sample (23). All study sites used standard analyzer (CardioCheck PA) and standard test strips (PTS Lipid Panel, Polymer Technology Systems)
- Blood pressure (BP). Target level: <140/90 mm Hg
- Body mass index (BMI). Target level: <25 kg/m^2
- Abdominal obesity. Target levels of waist circumference: males <102 cm, females <88 cm.

This study also evaluated the patient reported outcomes, which included balanced diet and physical activity (>30 min/day). As part of the safety evaluation, AST and ALT were evaluated.

Statistical analysis: The actual data were checked using the Shapiro-Wilk test. The hypothesis of the normality of the distribution was rejected for all variables, and the estimate

of the p-value (p-normal) was not displayed in the tables as not informative. Nonparametric criteria were selected to assess calculated probability in the statistical analysis. Quantitative variables were presented with number of observations (n), mean and standard deviation (Mean±SD), median (Me), interquartile range (Q1-Q3), minimum (min) and maximum (max) values. Qualitative variables were described using the number of observations (n), and absolute and relative frequencies. Chi-square test or Fisher's exact test was applied for qualitative variables, if at least one value in the contingency table of binary data was less than five. Comparisons between visits were made using paired Wilcoxon test. The odds ratio (OR) at 95% confidence interval (CI) was calculated as the ratio of the chance of fulfilling the criterion in the group or subgroup (subpopulation) with tested intervention versus the control. The chance of fulfilling the criterion was calculated as the ratio of number of subjects for whom the criterion was met versus the number of subjects for whom the criterion was not met.

Results

A total of 2,912 subjects were included in the study. Subjects (n=129) who did not come for any follow-up visit or did not take at least one dose of atorvastatin were excluded from all analyses. For the safety analysis (Intent-to-Treat (ITT) population), 2,783 subjects were considered. Seven subjects who did not meet the inclusion criteria were excluded and finally 2,776 subjects were included in the efficacy analysis (Per Protocol (PP) population, table 1). The patient disposition is shown in figure 2.

Primary endpoint: At M12, number of participants achieving LDL-C goal was significantly higher in the intervention group compared with the control group for the overall population: 80% vs.70% (OR, 1.68; 95% CI, 1.40 to 2.01; p<0.001), MR subpopulation: 93% vs. 84% (OR, 2.75; 95% CI, 1.84 to 4.10; p<0.001), HR subpopulation: 81% vs. 71% (OR, 1.68; 95% CI, 1.24 to 2.29; p<0.001), and VHR subpopulation: 52% vs. 39% (OR, 1.68; 95% CI, 1.20 to 2.36; p<0.001) (table 2).

Secondary endpoints: At M12, the percentage of participants achieving the recommended TC targets was significantly higher in the intervention group compared with the control group, for the overall population (80% vs. 67%; OR 1.92, 95% CI 1.60 to 2.29, p <0.001) and for all RF subpopulations (table 2). There was no clinically significant difference in the proportion of patients achieving target level of HDL-C between the intervention and standard treatment groups at M12, for overall population (82% vs. 85%; OR 0.78, 95% CI 0.64 to 0.97, p=0.02, table 2) and for all RF subpopulations. Also, there was no significant difference in the proportion of subjects achieving target level of TG between the two groups at M12, for overall population (85% vs. 86%; OR 1.04, 95% CI 0.93 to 1.29, p=0.8, table 2) and for all RF subpopulations. Compared with the baseline (M0 vs M12), the proportions of patients with the target levels of TC, HDL-C and TG at M12 visit were higher in both groups, for the overall population, and as well as for the RF subpopulations, as effect of atorvastatin treatment. At M12, the percentage of participants reached the target level of BP was higher in the intervention group compared with the standard treatment group (85% vs. 79%; OR, 1.49; 95% CI,1.22 to 1.83; p=0.0001) for the overall population and as well as for the HR subpopulation (84% vs. 76%; OR, 1.70; 95% CI, 1.22 to 2.35; p=0.0014) and VHR subpopulation (82% vs. 72%; OR, 1.74; 95% CI, 1.17 to 2.61; p=0.0063). There was no difference between the groups for the proportion of participants with BMI $\geq$25.0 kg/m^2 at M0 and M12. Also, there was no difference between the groups in the proportion of participants with abdominal obesity (figure 3). Patient reported outcomes showed that the proportion of patients following a balanced diet increased during the study (M0 vs. M12) in both the intervention group (21% vs. 69%; p<0.001) and the control group (24% vs. 65%; p<0.001). At M12, the proportion of patients following a balanced diet was higher in the intervention group in comparison with the standard treatment group (69% vs 65%; OR, 1.20; 95% CI, 1.02 to 1.41; p=0.029) (figure 3). The proportion of patients with sufficient physical activity also increased during the study (M0 vs M12) in both the intervention group (48% vs.73%; p<0.001) and the control group (48% vs. 72%; p<0.001). Nevertheless, at M12 there was no difference between the groups.

Administration of atorvastatin (PP): In the MR subpopulation, the difference in daily dose of atorvastatin between groups at M0 and M12 was not statistically significant. In the HR subpopulation, there were some differences (more than 5%) between groups in the proportion of individuals receiving 10 mg (44.3% vs. 51.1%) and 40 mg (5.0% vs 10.1%) of atorvastatin at M0 and (10 mg: 45.3% vs. 52.8%; 40 mg: 14.8% vs. 7.0%) at M12. In the VHR subpopulation, at M0 there was no statistically significant difference in the atorvastatin dose, but by M12 the percentage of patients receiving 40 mg was lower in the intervention group than in the control group (34.0% vs. 39.1%). Drop-out rate was lower in the intervention group (3.4%, n=48) compared with the control group (8.5%, n=116).

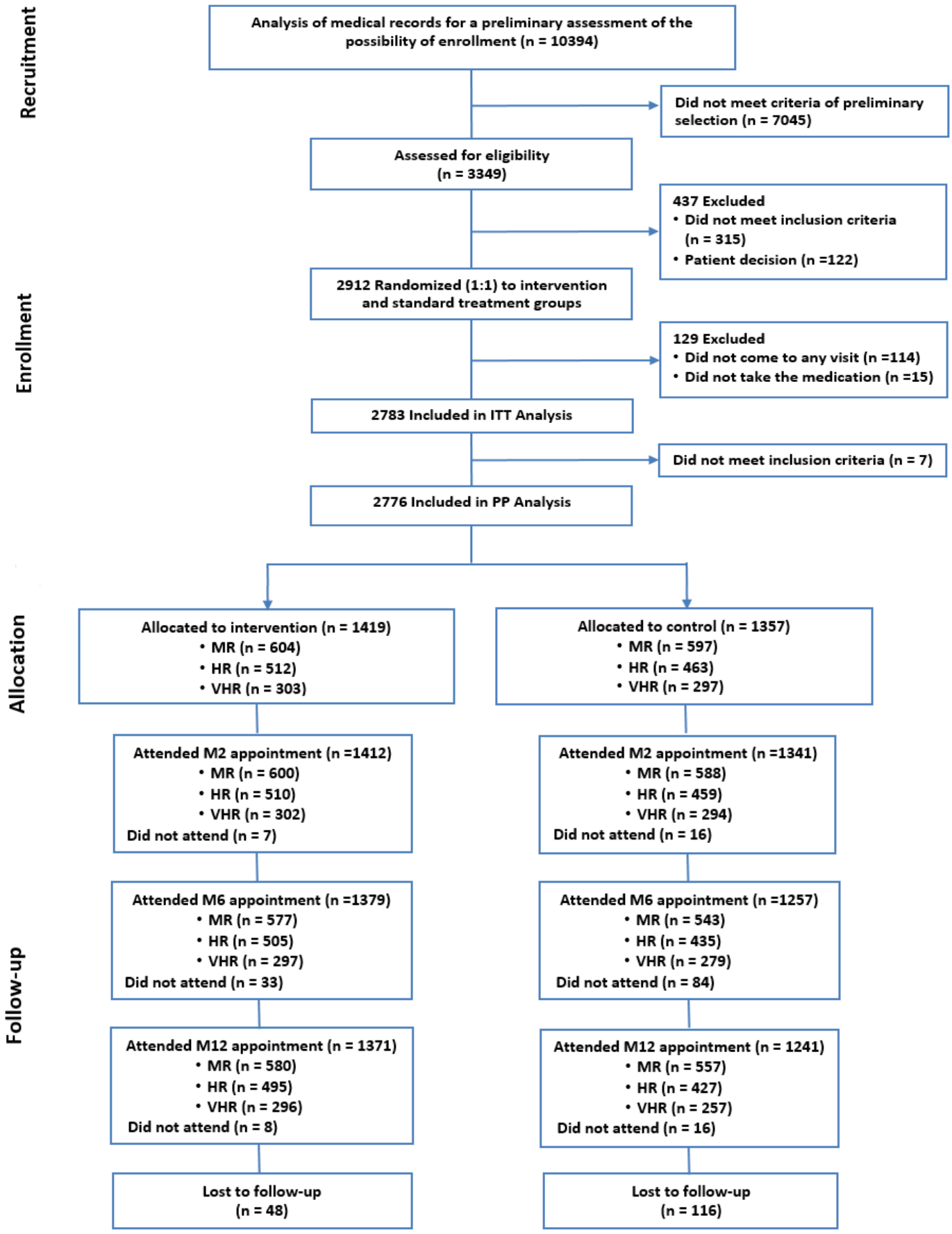

Figure 2. Patient disposition

Table 1. Baseline characteristics of PP population

Parameter n (%)	Intervention n=1419	Control n=1357
Female patients	975 (68.7)	928 (68.4)
Male patients	444 (31.3)	429 (31.6)
Age, years		
• **40-49**	278 (19.6)	289 (21.3)
• **50-59**	721 (50.8)	660 (48.6)
• **60-65**	420 (29.6)	408 (30.0)
Cardiovascular risk factors		
• **Inherited predisposition to CVD**	683 (48.1)	634 (46.7)
• **Arterial hypertension**	822 (57.9)	769 (56.7)
• **Overweight ≥ 25.0 kg/m²**	1121 (79.0)	1050 (77.4)
• **Abdominal obesity (WC: males ≥102 cm, females ≥88 cm)**	708 (49.9)	661 (48.7)
• **TG ≥2 mmol/L**	542 (38.2)	523 (38.5)
• **Total cholesterol ≥5 mmol/L**	1394 (98.3)	1326 (97.8)
• **Imbalanced diet**	1114 (78.5)	1026 (75.6)
SCORE risk		
• **Moderate (≥1% and <5%)**	604 (42.5)	597 (44.0)
• **High (≥5% and <10%)**	512 (36.1)	463 (34.1)
• **Very high (≥10%)**	303 (21.4)	297 (21.9)
Initial dose of atorvastatin, mg		
• **10**	657 (46.3)	670 (49.4)
• **20**	652 (45.9)	606 (44.7)
• **30**	11 (0.8)	14 (1.0)
• **40**	99 (7.0)	67 (4.9)

CVD: cardiovascular diseases; WC: waist circumference; TG: triglycerides; SCORE: Systematic Coronary Risk Evaluation Scale

Safety analysis: Subjects who took at least one dose of atorvastatin (ITT population, n=2,783) were included in the safety analysis. The safety profile of atorvastatin was consistent with the approved label of the drug. A total of 260 cases of adverse events (AEs) were reported in the intervention (130) and the control groups (130). Most-commonly reported AEs (ICD-10) included acute upper respiratory infections of multiple and unspecified sites (n=75, J06), acute nasopharyngitis (common cold; n=67, J00), gastritis and duodenitis (n=35, K29). Serious adverse events were reported in 15 (0.5%) subjects (4 and 11 in the intervention and control groups, respectively). No serious, unexpected, or suspected adverse drug reactions related to atorvastatin were reported.

Discussion

Several studies of patient-oriented preventive interventions (single- and multi-component) aimed to improve the compliance to the lipid-lowering drug regimen have been reported (24).

However, only 3 out of 32 studies present data on target LDL-C levels (25-27), and 2 of them (26, 27) did not report difference in target LDL-C level between the intervention and the control groups. This study demonstrated that the proposed patient-oriented intervention in primary prevention of cardiovascular disease with statins may help to reach LDL-C goals and stimulate positive changes of other laboratory and clinical parameters (TC, HDL-C, TG, BP).

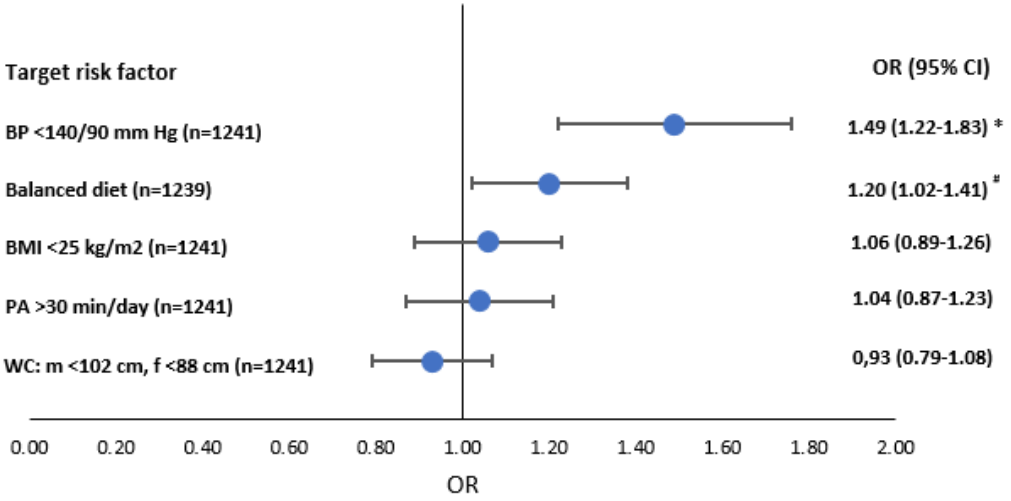

Figure 3. Risk factors at month 12 (OR to achieve target level, intervention vs control). BP: blood pressure, BMI: body mass index, PA: physical activity, WC: waist circumference, *: p <0.001, #: p <0.05.

Table 2. Target lipid levels at month 12

Parameter	Control group		Intervention group		Odds ratio (95% CI)	p
	n	Achieved target level n (%)	n	Achieved target level n (%)		
Target LDL-C level*						
Overall population	1241	872 (70)	1371	1095 (80)	1.68 (1.40-2.01)	<0.001
Moderate risk	557	467 (84)	580	542 (93)	2.75 (1.84-4.10)	<0.001
High risk	427	305 (71)	495	400 (81)	1.68 (1.24-2.29)	<0.001
Very high risk	257	100 (39)	296	153 (52)	1.68 (1.20-2.36)	0.004
Target level of other blood lipids						
Total cholesterol <5 mmol/L						
Overall population	1240	835 (67)	1371	1094 (80)	1.92 (1.60-2.29)	<0.001
Moderate risk	557	346 (62)	580	451/580 (78)	2.13 (1.64-2.77)	<0.001
High risk	426	293/426 (69)	495	388/495 (78)	1.65 (1.22-2.21)	<0.001
Very high risk	257	196/257 (76)	296	255/296 (86)	1.94 (1.25-3.00)	0.004
HDL-C (males >1.0 mmol/L, females >1.2 mmol/L), overall population	1239	1056 (85)	1370	1122 (82)	0.78 (0.64-0.97)	0.0221
Triglycerides <2.0 mmol/L#	1239	1058 (85)	1370	1176 (86)	1.04 (0.83-1.29)	0.8

LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, *: according to cardiovascular risk, #: corresponds to 1.7 mmol/L in fasting blood test.

Proportion of patients adhering to the prescribed treatment regimen of atorvastatin was significantly higher in the intervention group, and this is probably a main reason for clinically and statistically significant difference in laboratory and clinical variables. At the end of 12-months, the dropout rate (lost for follow up) was lower in the intervention group than in the control group (n=48 vs. n=116), like the results reported from other real-world

studies (27-31). Although some differences in the atorvastatin doses, between the intervention and control groups in two subpopulations (MR and VHR) were observed, they were insignificant (not more than 5-7% of the individuals receiving same dose of atorvastatin), and most important, was multidirectional (proportion of patients receiving higher doses of atorvastatin was higher in the intervention group than in the standard treatment group for the HR subpopulation and lower for the VHR subpopulation). In total population, patients with MR are the most prominent group with significant proportion of young people and women (11).

Women still have significant mortality from coronary heart disease and there is a tendency towards increasing prevalence of myocardial infarction at the age of less than 55 years (32). Importance of preventive measures in MR subpopulation is underestimated when compared with HR and VHR subpopulations, although primary CVD prevention in MR patients may significantly reduce social consequences of CVD. In this study, among the MR patients, 93% and 84% achieved target LDL-C level of <3.0 mmol/L ($p<0.001$) in the intervention and control group, respectively.

Strengths and limitations: Strengths of the study are large sample size, prospective study design, randomization and standard method of primary endpoint testing.

Limitations of this study are: Open-label design. Some outcomes, such as adherence to a balanced diet and physical activity, rely on self-reporting, which may lead to recall or reporting bias. At the same time the fact that participants and investigators knew which group they were in (intervention or control) could not influence primary and most of secondary efficacy endpoints which are the objective variables (laboratory measurements).

Limited generalizability: The study was conducted in the Russian Federation, and some findings (changes in balanced diet and physical activity) may not be directly applicable to other populations with different healthcare systems and socioeconomic backgrounds. At the same time this limitation could not influence the primary and most of the secondary efficacy endpoints which are the objective variables (laboratory measurements). Proposed patient-oriented intervention (5-min extended consultation on drug compliance during the visit, providing the patient with printed materials about CVD prevention, once-in-two-week SMS reminders about the need to take the drug regularly, phone reminders to visit a physician as scheduled) helps to achieve the target level of LDL-C in individuals with dyslipidemia and receiving statins for primary prevention of CVD. The intervention helps to reach target level of TC and supports better control of BP. The cost-effectiveness of these measures should be assessed in real health care settings.

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Ethics approval: The study was approved by The Independent Interdisciplinary Ethics Committee on Ethical Review for Clinical Studies, 125468, Moscow, 51 Leningradskiy ave. (Meeting #08, May 18, 2018; code 08.2018.05.18; regulated by Federal Law #61-FZ 12.04.2010 “On Circulation of Medicines”).

Conflict of interests: The authors have no conflicts of interest associated with the material presented in this paper.

Authors’ contribution: EVB, SAB, OMD, OGM, EKB and IVK contributed to the conception, design, acquisition, analysis, and interpretation of the data. EVB, SAB, OGM, EKB and IVK drafted the manuscript and OMD contributed to critically revising it. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Consent for publication: Manuscript does not contain any individual person’s data in any form.

Availability of data and materials: Data are available upon reasonable request. Original data are available on request. Please contact the corresponding author for further information (ivkimivkim@gmail.com).

Trial registration: Registered at ClinicalTrials.gov 25.04.2019. Registration number NCT03927196.

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