Research Article

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Analysis of changes in pharmacotherapy of stable angina over the five-year period at specialized out-patient level of medical care (pharmacoepidemiological study)

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Abstract

Introduction: Ischemic heart disease (IHD) remains the leading cause of death both in Europe and in Russia. The most common form of IHD is stable angina. There is compelling evidence that strict adherence to clinical guidelines greatly contributes to mortality reduction. However, the gap between modern knowledge and use of guideline-recommended medications remains significant. As shown by Western practice, one of the possible solutions of this problem is regular conduction of pharmacoepidemiological studies.

Objective: Investigate the dynamics of drug prescription rates in patients with stable angina over the five-year period on the example of routine clinical practice of outpatient cardiology institution of Moscow for the purpose of further eliminating the prescribing gap for guideline recommended pharmacological strategies.

Materials and methods: Our research work was performed as a retrospective pharmacoepidemiological study including two stages with five-year interval using cross-section method.

Results and discussion: We found a significant increase in use of antiplatelets (82.7 vs. 56.2%, p<0.05) and statins (45.6 vs. 16.1%, p<0.05). Despite the unchanged use of ACE inhibitors, the prescription rate of angiotensin receptor blockers II increased (14.7 vs. 9.7%, p<0.05). Analysis of anti-ischemic pharmacotherapy revealed an increase in beta-adrenoblockers use (74.3 vs. 63.6%, p<0.05) and a decrease in use of long-acting nitrates (26.3 vs. 31.1%, p<0.05) and calcium channel blockers (35.7 vs. 39.6%, p<0.05). Significant changes were found in prescription rates and dosage regimens of single medications in each pharmacological group. The study results demonstrated an increase in frequency of capturing data on lipid profile and diet recommendations in patient records.

Conclusion: Such type of pharmacoepidemiological study carried out for the first time made it possible to investigate the dynamics of specialists' adherence to guidelines of stable angina pharmacotherapy in routine outpatient clinical practice.

Keywords

antianginal therapy, antiplatelets, ACE inhibitors, beta-adrenoblockers, guideline adherence, guideline implementation, modifiable risk factors , pharmacoepidemiology, prescription rates, routine outpatient practice, secondary prevention, stable angina, statins.

Introduction

Cardiovascular disease (CVD) remains the most common cause of death in Europe, accounting for 45% of all deaths (49% of all deaths in women and 40% of all deaths in men). In Europe more than 4 million people die from CVD across the continent every year (Townsend et al. 2016). The contribution of CVD to total mortality in Russia is 57% (Volkova et al. 2015).

Taking into account the fact that ischemic heart disease (IHD) still represents the most common cause of death worldwide producing inestimable invaluable social and economic costs, improving prevention measures is crucial (Chapman et al. 2016). At present there is compelling evidence of the effectiveness of secondary prevention in reducing CVD morbidity and mortality (Pogosova 2014).

The most common form of IHD is stable angina. Onset of this form occurs much earlier in younger Russian patients than in patients from other countries (Shalnova and Deev 2011). This feature emphasizes the importance of preventive pharmacotherapy aimed at prophylaxis of serious complications. It is also important to study pharmacological correction of angina pectoris because it reflects the quality of therapy of the main symptom of stable angina and makes it possible to indirectly form an opinion about the general trend of the "real" clinical practice in the treatment of IHD (Solyanik et al. 2011).

Despite the wide implementation and regular updates of treatment guidelines, the gap in the use of guideline recommended medications remains significant as shown in many previous studies and registries of different patient populations with CVD. This problem exists not only in Russia, but also in other countries (Oganov et al. 2007, Tolpygina and Martsevich 2016, Abtan et al. 2016, Eastaugh et al. 2005 , Kotseva et al. 2017 , Ferrari et al. 2015, Olomu et al. 2014, Wilkins et al. 2017).

One of the possible solutions as shown by Western practice is the regular conduct of pharmacoepidemiological studies and registries. Such studies serve as the main source of feedback on prescription rate of guideline recommended medication. The results of such studies allow not only assess the status of the problem in dynamics, but can also be used to develop various administrative measures and educational programs for healthcare professionals and patients.

Only a limited number of pharmacoepidemiological studies focused on the population of stable angina patients have been done by now. Most of the studies were aimed at patients with history of myocardial infarction (MI) and revascularization procedures. A possible reason could be that prognosis of a patient with stable IHD is considered to be relatively favorable.

Among the major international studies and registries with Russian participation, it is necessary to mention ATP (Oganov et al. 2003) and CLARIFY (Shalnova et al. 2013). The results showed that in the Russian population dominating were the patients with more severe functional classes of stable angina. These studies also revealed problems with controlling the target level of blood pressure (BP), blood lipids and adequate lipid lowering therapy, frequent use of clinically insignificant dosages and the high prevalence of risk factors (RF), such as smoking, overweight and diabetes mellitus (DM). At the same time, Russian clinics involved were mainly institutions with a high level of medical care so the obtained data could be a bit "distorted" in a better way. Thus, the results of national registry "PROGNOZ IHD" demonstrated low prescription rate of drugs recommended by secondary prevention guidelines before admission of patients to cardiology settings and a significant increase in their prescription rate during in-house period (Tolpygina and Martsevich 2016).

Despite the persisting need in the results of this type of pharmacoepidemiological analysis and its relevance to Russian healthcare, recently there has been a tendency to reduce the number of major studies in this field (Petrov 2006). Taking into account regular updates of foreign and national guidelines of secondary prevention and pharmacotherapy of CVD, it seems essential to carry out such pharmacoepidemiological studies at intervals of four to six years on a regular basis, including separate studies at regional level and in individual medical institutions.

Objective

To investigate the dynamics of drug prescription rates in patients with stable angina over the five-year period on the example of routine clinical practice of outpatient cardiology institution of Moscow for the purpose of further eliminating the prescribing gap for guideline recommended pharmacological strategies in treating patients with IHD (pharmacoepidemiological study).

Materials and methods

Our research was designed as a retrospective pharmacoepidemiological study, including two stages with a five-year interval using cross-section method at every stage. The object of the research was source medical documentation – outpatient records. The study was approved by the Ethical Committee of Cardiology Dispensary #2 of Healthcare Department of Moscow". The scheme of the study is shown in Figure 1.

At the first stage, a retrospective analysis of medical records of patients with stable angina who primarily visited cardiology clinic in Moscow in 2006 was conducted. The main variables of interest were the prescription rates of medications assigned by cardiologists and the degree of specialists' attention to modifiable risk factors of IHD. The obtained results revealed a significant prescribing gap for guideline recommended medications and low adherence of cardiologists to national IHD management guidelines. On basis of the results of the first stage, some practical activities (use of reminder templates, series of lectures, administrative incentives) were introduced within the institution to increase compliance of specialists
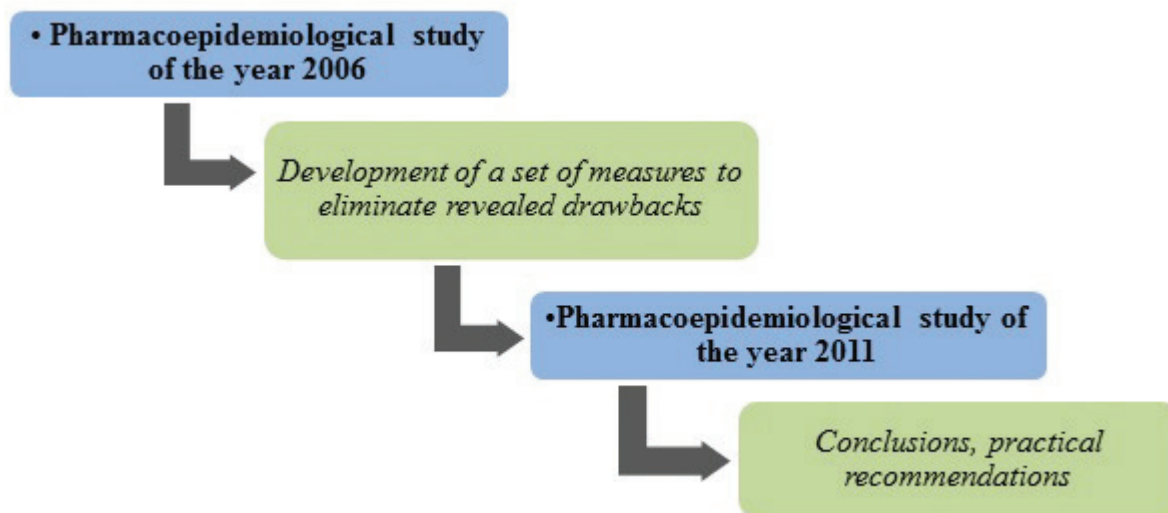
Figure 1. Scheme of retrospective two-stage pharmacoepidemiological study conducted in a specialized outpatient institution.

with clinical guidelines. The second stage was conducted basically in the same methodological way and aimed to assess the degree of success of complex practical activities carried out over the five-year period.

The inclusion of patient medical records into each of the samples was carried out by randomization from records of patients who primarily visited the institution during the analyzed period. The comparative analysis included the data of 2915 outpatient medical records at the first stage and 1633 at the second stage.

Information from patient records was transferred to a specially designed case report form (CRF). CRF included the following sections: patient's social status and demographic data, medical history, instrumental and laboratory tests results, non-pharmacological correction of RF and drug therapy.

Pharmacotherapy (both preventive and anti-ischemic) was analyzed for prescription rates of main groups of drugs and single medications, as well as for dosage regimens. Prescribed pharmacotherapy was compared to the recommendations of national guidelines for secondary prevention and pharmacotherapy of IHD available at the period of study stages (Chazov et al. 2004, Akchurin et al. 2008). The prevalence and correction of modifiable RF were identified by capture degree of this information in patient medical records.

Data from CRFs was transferred to MS Excel database. All statistical tests were performed using SPSS PASW Statistics 22. Continuous variables were expressed as mean and standard deviation, median and 25th and 75th percentiles, minimum and maximum values. Categorical variables were expressed as frequencies and percentages. Student's t-test was used to compare normally distributed continuous data from two independent samples. Mann-Whitney U test was used in case of different distribution and for ordinal scale parameters. Chi square tests were used for nominal variables. In case of restrictions for Chi square test, Fisher's exact test was used. Multi-

ple comparisons of ordinal data were performed using Mann-Whitney U test. In case of significant differences, pairwise comparisons were performed using the Fisher's exact test. Statistical significance was assessed between the data from the first and the second stage of the study. A p-value <0.05 was considered significant.

Results and discussion

Comparative analysis of patients' population

The main demographic and medical history data is presented in Table 1. Women continue to dominate in the gender structure of the analyzed population. However, the analysis of the data revealed a decrease in the number of female patients and an increase in the number of male subjects at the second stage of the study.

Over the period of five years, the mean age of a patient with stable angina remained almost the same: 65.73±9.10 years and 66.78±9.46 years, respectively. The analysis of the dynamics of patient age distribution revealed that the majority of subjects belonged to the age group over 60 years. At both stages of the study, there were less than 30% of patients under 60 years of age. Patients with stable angina class II and class III according to the Canadian Cardiovascular Society (CCS) classification continued to dominate within the study population at each stage.

High frequency of cardiovascular concomitant diseases was revealed in addition to the history of stable angina, according to the patients' medical records. At the second stage of the study, the following conditions were detected significantly more often: hypertension, chronic heart failure (CHF), diabetes mellitus, and various heart rhythm disturbances. The number of patients with prior MI increased more than 1.5 times, which can be explained by lack of secondary prevention measures.

Table 1. Demographics and clinical characteristics of the patient populations under study

Variables	2006 (n=2915)	2011 (n=1633)
Gender:		
Male, n (%)	977 (33.5)	693 (42.4)*
Female, n (%)	1936 (66.4)	940 (57.6)*
Age (y), mean±SD	65,73±9,10	66,78±9,46*
Angina CCS Class:		
I, n (%)	91 (3.1)	40 (2.4)
II, n (%)	2458 (84.3)	1420 (87.0)*
III, n (%)	305 (10.5)	154 (9.4)
IV, n (%)	3 (0.1)	2 (0.1)
Prior myocardial infarction, n (%)	640 (22,0)	624 (38.2)*
Arterial hypertension, n (%):	2674 (91.7)	1526 (93.4)*
Grade 1	108 (4.0)	52 (3.4)
Grade 2	689 (25.8)	345 (22.6) *
Grade 3	1826 (68.3)	1104(72.3)*
Chronic heart failure, n (%)	1562 (53.6)	1254 (76.8)*
Prior stroke, n (%)	152 (5.2)	119 (7.3)*
Diabetes mellitus, n (%)	398 (13.7)	357 (21.9)*
Different types of arrhythmias, n (%)	650 (22.3)	439 (26.9)*

Note: *p<0.05 in comparison with the year of 2006; CCS – Canadian Cardiovascular Society.

Analysis of the prescription rates dynamics of secondary prevention drugs in patients with stable angina

For patients with stable angina, an integral part of preventing CVDs and their complications, according to the Russian and international clinical guidelines, is the prescription of drugs with a proven ability to prevent the risk of cardiovascular events – antiplatelet agents, statins, beta-adrenoblockers (BBs) (history of MI or CHF) and angiotensin-converting enzyme (ACE) inhibitors (if intolerable or contraindicated – angiotensin II receptor blockers (ARBs)). Despite the fact that BBs are important for improving the prognosis in patients with stable angina, the data obtained on prescription rates and dosage regimen of BBs is presented within the analysis of anti-ischemic pharmacotherapy. Furthermore, BBs are the first line drugs to relieve angina symptoms, according to guidelines.

Dynamics of prescription rates of secondary prevention drugs recommended to patients with stable angina is presented in Table 2. It should be noted that significant changes were revealed in comparison with the first stage of the study: a higher frequency of recommendations for antiplatelets and an almost threefold increase in the frequency of prescribing statins. The use of ACE inhibitors remained at the same level, whereas the frequency of ARBs increased significantly.

At the same time, antiplatelet agents and statins (must be prescribed to all patients with stable angina) were recommended only to 665 patients at the second stage of the study (40.7%). Significant changes were also detected in prescription rates of single medications and their dosage regimens in each pharmacological group.

Analysis of the prescription rates dynamics of antiplatelet agents

A significant increase in antiplatelets use (up to 83.0%) was found. However, the same value was 90% or more in Russian population of patients, looking at the results of studies PROGNOZ IHD (Tolpygina and Martsevich 2016), EUROASPIRE IV (Pogosova et al. 2016), CLARIFY (Shalnova and Deev 2011).

Prescription rates of acetylsalicylic acid (ASA) as monotherapy decreased significantly. This was partially due to an increase in use of ASA in combination with clopidogrel. Dual antiplatelet therapy (DAPT) was implemented into clinical practice at the time of the second stage of the study (Table 3). At the same time, the proportion of patients with indications for DAPT (one-year history of MI and/or interventional procedure) was 14.8%.

Prescription rates of daily ASA doses also changed over the five-year period. The number of patients receiving ASA at adequate doses of 100 mg and 75 mg increased significantly (Table 4). ASA 50 mg was also prescribed frequently in spite of the fact that the guidelines instruct to use ASA at doses of 75-150 mg. As a positive aspect, it should be noted that physicians almost stopped to use the dose of 125 mg which was prescribed as "aspirin ¼" and gave favor to ASA drugs in form of tablets coated with an intestinal membrane or ASA with antacids (magnesium hydroxide).

In general, the changes which had happened over the five-year period in antiplatelet pharmacotherapy can be assessed positively. But still significant reserves remain for further optimization of DAPT as well as for prescriptions rates and adequate dosage regimens.

Table 2. Dynamics of prescription rates of secondary prevention drugs

Pharmacological groups	First stage (n=2915)		Second stage (n=1633)		Statistical significance
	Number of patients	%	Number of patients	%	
Antiplatelet agents	1639	56.2	1351	82.7	p<0.05
Statins	469	16.1	745	45.6	p<0.05
ACE inhibitors (including combination medications)	2028	69.6	1104	67.6	p>0.05
ARBs (including combination medications)	282	9.7	240	14.7	p<0.05

Note: ACE – angiotensin-converting enzyme; ARB – angiotensin II receptor blockers.

Table 3. Dynamics of prescription rates of antiplatelet agents

Antiplatelets	First stage		Second stage		Statistical significance
	Number of patients	%	Number of patients	%	
ASA (including combination medications)	1627	99.3	1256	93.0	p<0.05
Dual antiplatelet therapy (ASA + Clopidogrel)	3	0.2	73	5.4	p<0.05
Clopidogrel	5	0.3	21	1.6	p<0.05
Ticlopidine	4	0.2	1	0.1	p>0.05
Total:	1639	100	1351	100	

Note: ASA – acetylsalicylic acid.

Table 4. Dynamics of prescription rates of daily ASA doses

Daily ASA doses (mg)	First stage		Second stage		Statistical significance
	Number of patients	%	Number of patients	%	
500	1	0.1	–	–	–
250	7	0.4	–	–	–
150	14	0.9	13	1.0	p>0.05
125	614	37.7	6	0.5	p<0.05
100	782	48.0	945	71.1	p<0.05
75	28	1.7	150	11.3	p<0.05
50	117	7.2	194	14.6	p<0.05
No data	67	4.1	21	1.6	p<0.05
Total	1630	100	1329	100	

Note: ASA – acetylsalicylic acid.

Analysis of the prescription rates dynamics of statins

The number of important changes were revealed in statin therapy along with a significant increase in statin use frequency on the whole. Cardiologists significantly more often recommended atorvastatin at the second stage of the study, but simvastatin prescription rate comparably reduced. Rosuvastatin prescriptions were very rare at both stages, possibly due to its high cost and availability of only one analogue drug. Such medications as fluvastatin and lovastatin were not used at the second stage (Table 5).

The analysis of dosage regimens of statins demonstrated an increased use of leading statins in higher doses. Thus, simvastatin 20 mg was prescribed significantly more often and simvastatin 10 mg – almost twice as rarely at the second stage of the study. The dose of 40 mg was prescribed only in a few cases at both stages (Table 6).

More than 50% of patients received atorvastatin 10 mg at both stages of the study despite the significant increase in its use of 20 mg dose. Atorvastatin 40 mg was prescribed only in a few cases at the second stage (Table 7).

On one hand, the above results look promising and can contribute to improving the efficacy of lipid-lowering pharmacotherapy and to achieving target levels for total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C). But on the other hand, more than 50% of patients have not received statins as part of secondary prevention therapy.

Analysis of the prescription rates dynamics of ACE inhibitors and angiotensin II receptor antagonists

Both monotherapy and combination drugs (fixed combinations with diuretics or calcium antagonists) were taken

Table 5. Dynamics of prescription rates of statins

Statins	First stage		Second stage		Statistical significance
	Number of patients	%	Number of patients	%	
Atorvastatin	216	46.1	394	52.9	p<0.05
Simvastatin	248	52.9	339	45.5	p<0.05
Rosuvastatin	1	0.2	12	1.6	p<0.05
Lovastatin	3	0.6	–	–	–
Fluvastatin	1	0.2	–	–	–
Total:	469	100	745	100	

Table 6. Dynamics of prescription rates of daily Simvastatin doses

Daily Simvastatin doses (mg)	First stage		Second stage		Statistical significance
	Number of patients	%	Number of patients	%	
5	1	0.4	2	0.6	p>0.05
10	149	60.1	122	36.0	p<0.05
20	85	34.3	205	60.5	p<0.05
40	8	3.2	8	2.4	p>0.05
No data	5	2.0	2	0.6	p>0.05
Total	248	100	339	100	

Table 7. Dynamics of prescription rates of daily Atorvastatin doses

Daily Atorvastatin doses (mg)	First stage		Second stage		Statistical significance
	Number of patients	%	Number of patients	%	
5	1	0.5	–	–	–
10	150	69.4	212	53.8	p<0.05
20	64	29.6	165	41.9	p<0.05
40	–	–	14	3.6	–
No data	1	0.5	3	0.8	p>0.05
Total	216	100	394	100	

into account when analyzing the use of ACE inhibitors and ARBs.

The prescription rate of ACE inhibitors as a whole group remained at the level of 70% throughout the five-year period. The most frequently prescribed drugs remained enalapril, perindopril and fosinopril. At the same time, the enalapril prescription rate increased significantly at the second stage of the study. Perhaps this happened due to its proven efficacy in patients with CHF and MI, whose number was higher at the second stage of the study. The prescription rates of perindopril and lisinopril also increased; however, the rate of fosinopril prescription decreased. The proportion of other ACE inhibitors (captopril, ramipril, quinapril) decreased significantly. Especially strange was the reduction in the use of ramipril because, according to the guidelines, ramipril is a preferred ACE inhibitor for patients with stable angina (Table 8).

The dosage regimen analysis revealed significant changes only for enalapril. A significant decrease in use of enalapril at higher daily doses of 20 mg and 40 mg was accompanied by an increased use of minimal and average doses – 2.5 mg, 5 mg and 10 mg (Table 9).

It was necessary to take into account that at the time of the first stage of the study, perindopril was marketed as perindopril tretbutylamine form and at the time of the second stage – as perindopril arginine form. The doses

of tertbutylamine perindopril – 2 mg, 4 mg and 8 mg – correspond to the doses of 2.5 mg, 5 mg and 10 mg of perindopril arginine. Dosage regimen of perindopril was similar at both stages of the study. Perindopril at the dose of 5 mg was recommended to 184 patients (47.8%) at the first stage and to 134 patients (50.4%) at the second stage. Perindopril at the dose of 2.5 mg was recommended to 140 patients (36.2%) at the first stage and to 79 patients (29.7%) at the second stage. Perindopril was prescribed to 50 patients (12.9%) at the first stage and 43 patients (16.2%) at the second stage (p>0.05) at the maximal daily dose of 10 mg.

Due to the fact that according to the guidelines ACE inhibitors should be replaced by ARBs in cases of intolerance or contraindication, it seemed important to analyze prescription rates of ARBs (Table 10). Losartan remained the most commonly used drug among ARBs (p.>0.05). The frequency of valsartan prescriptions was about 10% at each stage of the study. Telmisartan, candesartan, eprosartan, olmesartan were recommended in a few cases.

Despite a significant increase in prescription rates of losartan at the dose of 100 mg, the dose of 50 mg was still prescribed in more than 50% cases at both stages of the study. The dose of 12.5 mg was not recommended at the second stage, while the prescription frequency of the dose of 25 mg increased significantly (Table 11).

Table 8. Dynamics of prescription rates of ACE inhibitors

ACE inhibitors	First stage		Second stage		Statistical significance
	Number of patients	%	Number of patients	%	
Enalapril	883	43.5	558	50.5	p<0.05
Perindopril	386	19.0	266	24.1	p<0.05
Fosinopril	413	20.4	156	14.1	p<0.05
Lisinopril	91	4.5	95	8.6	p<0.05
Ramipril	48	2.4	11	1.0	p<0.05
Captopril	94	4.6	9	0.8	p<0.05
Quinapril	108	5.3	7	0.6	p<0.05
Trandolapril	–	–	1	0.1	–
Zofenopril	–	–	1	0.1	–
Moexipril	1	0.1	–	–	–
Cilazapril	1	0.1	–	–	–
Spirapril	3	0.2	–	–	–
Total:	2028	100	1104	100	

Note: ACE – angiotensin–converting enzyme.

Table 9. Dynamics of prescription rates of daily Enalapril doses

Daily Enalapril doses (mg)	First stage		Second stage		Statistical significance
	Number of patients	%	Number of patients	%	
40	62	7.0	23	4.1	p<0.05
30	13	1.5	1	0.2	p<0.05
20	386	43.7	163	29.2	p<0.05
15	2	0.2	2	0.4	p>0.05
10	288	32.6	212	38.0	p<0.05
5	79	8.9	100	17.9	p<0.05
2,5	27	3.1	49	8.8	p<0.05
1,25	–	–	2	0.4	–
No data	26	2.9	6	1.1	p>0.05
Total	883	100	558	100	

Table 10. Dynamics of prescription rates of angiotensin II receptor antagonists

Angiotensin II receptor antagonists	First stage		Second stage		Statistical significance
	Number of patients	%	Number of patients	%	
Losartan	249	88.3	209	87.1	p>0.05
Valsartan	24	8.5	26	10.8	p>0.05
Telmisartan	4	1.4	1	0.4	p>0.05
Eprosartan	–	–	1	0.4	–
Candesartan	–	–	2	0.8	–
Olmesartan	–	–	1	0.4	–
Irbesartan	5	1.8	–	–	–
Total:	282	100	240	100	

Table 11. Dynamics of prescription rates of daily Losartan doses

Daily Losartan doses (mg)	First stage		Second stage		Statistical significance
	Number of patients	%	Number of patients	%	
12.5	16	6.4	–	–	–
25	6	2.4	17	8.1	p<0.05
50	192	77.1	140	67.0	p<0.05
100	26	10.4	40	19.1	p<0.05
No data	9	3.6	12	5.7	p>0.05
Total	249	100	209	100	

Summing up the results describing the dynamics of prescriptions rates of ACE inhibitors and ARBs, it should be noted that the proportion of patients with stable angina receiving these medications increased over five years. The tendency regarding the use of minimal and average doses remains.

Analysis of the prescription rates dynamics of anti-ischemic drugs in patients with stable angina

The main purpose of stable angina treatment is not only to improve prognosis (prevention of complications and mortality), but also to improve the quality of patients' life (associated with a lower frequency and intensity of angina attacks).

The Russian and international guidelines recommend the following pharmacological groups of anti-ischemic drugs: beta-blockers, calcium channel blockers (CCBs), long-acting nitrates, I_f-channel blockers (selective inhibition of the sinus node I(f) pacemaking current), K^+-channel activators (stimulation of ATP-sensitive potassium channels), myocardial cytoprotectors – trimetazidine and ranolazine. The analysis of the prescription rates dynamics of the main groups of anti-ischemic drugs revealed significant changes (Table 12).

Above all, a higher prescription rate of BBs and a lower prescription rate of long-acting nitrates should be noted. Also, the second stage results revealed significant reduction in prescription rates of CCBs and trimetazidine.

Analysis of the prescription rates dynamics of beta-adrenoblockers

The prescription rate of the group of BBs increased by 10.7% over the five-year period. That could be recognized as a positive trend. The analysis of prescription rates of different BBs identified a number of significant changes. Thus, bisoprolol was prescribed almost twice as often and took a leading position, replacing metoprolol at the second stage of the study. Specialists started prescribing nebivolol more frequently and atenolol – less. Other BBs had a very small share of prescriptions within the group (Table 13). A significant increase in the use of bisoprolol and nebivalol can be explained by a larger proportion of patients with DM and chronic obstructive pulmonary disease at the second stage of the study. It is common knowledge that these drugs are more cardioselective in comparison with other BBs. Absence of prescriptions of non-selective propranolol at the second stage is definitely a positive finding.

The analysis of dosage regimens of BBs revealed significant changes only regarding bisoprolol. Over the five-year period, the prescription rate of the dose of 5 mg decreased, while the rate of the dose 10 mg increased (Table 14). Bisoprolol at the dose of 20 mg was recommended only at the second stage of the study in individual cases. The minimal therapeutic dose of 2.5 mg started being used more often.

Along with bisoprolol, other BBs were still prescribed at minimal doses: metoprolol 50 mg – 56.3% (451 patients) and 51.5% (171 patients), atenolol 50 mg – 63.7% (116 patients) and 62.2% (23 patients) at the first and the second stage of the study, respectively. The results obtained on BB dosage regimens can be explained by high comorbidity rates (CHF, DM, COPD) requiring the use of minimal doses with gradual titration.

The study results demonstrated positive dynamics in terms of prescription rates of BBs and a more frequent choice of cardioselective medications. However, the fact that at the second stage BBs were not prescribed to approximately 25% of patients causes concern.

Analysis of prescription rates dynamics of calcium channel blockers

Calcium channel blockers are second-line agents (in accordance with the guidelines of the Russian Society of Cardiology effective at time of the second stage of the study) in patients with stable angina and recommended in cases of poor tolerance or low efficacy of BBs (Class I, Level A). The study results demonstrated the reduction in prescription rates of CCBs over the five-year period (p<0.05). Within the group, dihydropyridines CCBs were prescribed in major cases (over 80%). Non-dihydropyridine CCBs were prescribed in 18.7% of cases at the first stage and in 15.8% of cases at the second stage. High prescription rates of dihydropyridines CCBs were most likely caused by high prevalence of hypertensives (more than 90%) at both study stages. It is important to mention that amlodipine prescription rate increased and the nifedipine rate decreased (Table 15). The fact that specialists preferred amlodipine to nifedipine is undoubtedly recognized as a positive trend.

It is also very important to note the revealed changes in amlodipine dosage regimen. The dose of 5 mg was prescribed at a lower rate, but the maximal recommended therapeutic dose of 10 mg was prescribed more often at the second stage of the study (Table 16). The dose of 2.5 mg was prescribed in 6.4% and 6.5% of cases at the first and the second stage, respectively. The use of this low dose might be justified by taking into account a large proportion of elderly patients and high prevalence of CHF.

Analysis of the prescription rates dynamics of long-acting nitrates

If CCB monotherapy or combination therapy of CCB and BB is ineffective, it is necessary to replace CCB by long-acting nitrate, according to the current clinical guidelines. The results of the present study revealed a significant decrease in nitrates use that can be recognized as a positive trend. There were no significant changes in the group structure. Cardiologists continued to recommend isosorbide dinitrate in more than 50% of cases.

Analysis of the prescription rates dynamics of other anti-ischemic drugs

Following the actual classification, among the anti-ischemic medications recommended for the treatment of stable angina are also ivabradine, nicorandil, ranolazine, and trimetazidine. The present paper looked only at the prescription dynamics of ivabradine and trimetazidine. Nicorandil and ranolazine were not included into the guidelines ef-

Table 12. Dynamics of prescription rates of anti-ischemic drugs

Pharmacological groups	First stage (n=2915)		Second stage (n=1633)		Statistical significance
	Number of patients	%	Number of patients	%	
Beta–blockers (including combination medications)	1853	63.6	1213	74.3	p<0.05
Calcium channel blockers (including combination medications)	1154	39.6	583	35.7	p<0.05
Long–acting nitrates	906	31.1	429	26.3	p<0.05
Trimetazidine	724	24.8	234	14.3	p<0.05
Ivabradine	–	–	12	0.7	–

Table 13. Dynamics of prescription rates of beta–blockers

Beta–blockers	First stage		Second stage		Statistical significance
	Number of patients	%	Number of patients	%	
Bisoprolol	610	32.9	667	55.0	p<0.05
Metoprolol	801	43.2	332	27.4	p<0.05
Nebivolol	38	2.1	101	8.3	p<0.05
Carvedilol	110	5.9	74	6.1	p>0.05
Atenolol (including combination medications)	182	9.8	37	3.1	p<0.05
Betaxolol	103	5.6	2	0.2	p<0.05
Propranolol	9	0.5	–	–	–
Total:	1853	100	1213	100	

Table 14. Dynamics of prescription rates of daily bisoprolol doses

Bisoprolol daily doses (mg)	First stage		Second stage		Statistical significance
	Number of patients	%	Number of patients	%	
20	–	–	3	0.5	–
10	30	4.9	62	9.3	p<0.05
7.5	2	0.3	7	1.0	p>0.05
5	390	63.9	321	48.1	p<0.05
2.5	175	28.7	264	39.6	p<0.05
1.25	2	0.3	7	1.0	p>0.05
No data	11	1.8	3	0.5	p>0.05
Total	610	100	667	100	

Table 15. Dynamics of prescriptions rates of calcium channel blockers

Calcium channel blokers	First stage		Second stage		Statistical significance
	Number of patients	%	Number of patients	%	
Amlodipine	511	44.3	345	59.2	p<0.05
Nifedipine	354	30.7	96	16.5	p<0.05
Felodipine	72	6.2	48	8.2	p>0.05
Lercanidipine	1	0.1	2	0.3	p>0.05
Verapamil	164	14.2	71	12.2	p>0.05
Diltiazem	52	4.5	21	3.6	p>0.05
Total:	1154	100	583	100	

Table 16. Dynamics of prescription rates of daily Amlodipine doses

Daily Amlodipin doses (mg)	First stage		Second stage		Statistical significance
	Number of patients	%	Number of patients	%	
2.5	32	6.3	22	6.4	p>0.05
5	325	63.6	185	53.6	p<0.05
10	131	25.6	123	35.7	p<0.05
20	6	1.2	7	2.0	p>0.05
No data	17	3.3	8	2.3	p>0.05
In total	511	100	345	100	

fective at time of the study. Ivabradine was included into the guidelines only in 2008. The proportion of ivabradine prescriptions at the second stage of the study was extremely low. The prescription rate of trimetazidine decreased significantly over the five-year period (Table 12).

Analysis of dynamics of specialists' attention to modifiable risk factors

An analysis of changes in the degree of cardiologists' attention to modifiable RFs was conducted because all the IHD management guidelines recommend to pay special attention to the identification and correction of RFs. Non-pharmacological measures are considered to be very important and include smoking cessation, diet, physical activity, weight loss, etc.

A full-scale analysis of the prevalence of modifiable cardiovascular RFs in patients with stable angina failed due to insufficient capture of relevant information in their medical records. Nevertheless, information concerning modifiable RFs was captured more frequently at the second stage of the study. Thus, the data on smoking status were present in 27.6% (450 patients) of records, on the attitude to alcohol – in 21.5% (351 patients) of records, while at the first stage such information was captured only in 2.4% (70 patients) and 0.3% (9 patients) of records, respectively (p<0.05). Almost no changes were recorded regarding the capture of anthropometric parameters allowing to estimate patient's body mass index (p>0.05). This information was present in 13.6% (396 patients) of records at the first stage and in 15.7% (256 patients) of records at the second stage. None of the medical records contained such a parameter as waist circumference. The data on physical activity and diet was available in more than 95% of records at both stages of the study.

The analysis of data completeness concerning the lipid profile revealed a significant increase in the degree of cardiologists' attention to all lipid parameters over the five-year period. Almost doubled frequency of capturing data on LDL-C levels is undoubtedly a positive trend. Attention of specialists to other lipids also became higher. Thus, the frequency of capturing data on high density lipoprotein cholesterol (HDL-C), triglycerides (TG) and total cholesterol significantly increased (Table 17).

The study results demonstrated some positive dynamics regarding completeness of data on modifiable RFs in patients' medical records, but still the degree of specialists' attention to such an important aspect of preventive non-pharmacological treatment remains insufficient.

It is also necessary to point out that lack of adequate measures for non-pharmacological correction of cardiovascular RFs was revealed. Thus, recommendations to do physical activity decreased from 23.5% (686 patients) to 14.9% (244 patients). Only five smokers at the first stage and 10 smokers at the second stage received written advice to stop smoking. The positive dynamics was detected in terms of correction of such a risk factor as improper nutrition. Frequency of diet recommendations increased from 50.1% (1461 patients) to 66.6% (1087 patients).

Conclusion

Thus, the present pharmacoepidemiological study allowed to investigate the dynamics of the gap between the guidelines recommended for pharmacological strategies and prescriptions when managing patients with stable angina in routine clinical practice of a specialized outpatient institution. The results obtained demonstrated an increase in prescription rates of key pharmacological groups that improve prognosis in IHD: antiplatelets (82.7 vs. 56.2%, p<0.05), statins (45.6 vs. 16.1%, p<0.05) and ARBs (14.7 vs. 9.7%, p<0.05) as well as increasing the frequency of recommending BBs (74.3 vs. 63.6%, p<0.05) and long acting nitrates (26.3 vs. 31.1%, p<0.05) and CCBs (35.7 vs. 39,6%, p<0.05) as components of anti-ischemic therapy. The study also revealed an increase in prescription rates of individual medications at higher daily doses: ASA at the dose of 100 mg (71.1 vs. 48.0%, p<0.05), simvastatin and atorvastatin at the dose of 20 mg (60.5 vs. 34.3%, p<0.05 and 41.9 vs. 29.6%, p<0.05, respectively). However, the situation can't be regarded as satisfactory. Therefore, a number of practical recommendations were developed to further improve the compliance of specialists' recommendations with the clinical guidelines at the outpatient level of routine medical care. The present study significantly contributes to mortality reduction and life expectancy increase in patients with IHD by improving the adherence of specialists to the clinical guidelines. Yet, the problems of patients following a prescribed pharmacotherapy and interchangeability of drugs are extremely important in this context and, hence, require further study.

In conclusion, the results obtained in the present study concerning IHD pharmacotherapy and changes which occurred over the five-year period are consistent in many aspects with a number of national and foreign studies on the similar problem. This fact emphasizes their credibility and importance for practical health care.

Table 17. Dynamics of capturing information on lipid profile in patients' medical records

Lipids	First stage (n=2915)		Second stage (n=1633)		Statistical significance
	Number of patients	%	Number of patients	%	
Total cholesterol	1291	44.3	1088	66.6	p<0.05
LDL-C	495	17.0	541	33.1	p<0.05
TG	1041	35.7	808	49.5	p<0.05
HDL-C	440	15.1	445	27.3	p<0/05

Note: LDL-C – low-density lipoprotein cholesterol; TG – triglycerides; HDL–C - high density lipoprotein cholesterol.

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