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Research Article

Risk management strategy for preventing the reduced treatment effectiveness from the position of drug interactions and polypharmacy in patients with coronary heart disease

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Abstract

Introduction: In modern clinical practice, various drug combinations are widely used, especially in cardiological patients. The existing clinical recommendations necessitate using organ protective agents, especially with a patient having a comorbid pathology and with an ineffective monotherapy. In some cases, drug interaction decreases the effectiveness of pharmacotherapy and increases the risk of developing adverse events (AE).

The purpose of the study was to analyze the modern pharmacotherapy of patients with coronary heart disease (CHD), identify polypharmacy of treatment, evaluate its significance for the treatment process, and determine ways to solve the problem of using a multi-component system of pharmacotherapy risk management.

Materials and methods: The study involved 156 patients with CHD, among whom 39 received more than 8 drugs at a time.

Results and discussion: In these patients, the evaluation of drug interactions revealed 580 variants (48 were dangerous, 428 – significant, 104 – insignificant). The administration of a therapy to comorbid patients, taking into account possible changes in the activity of cytochrome P450 isoenzymes, is one of the promising ways to improve the safety of a combined pharmacotherapy.

Conclusion: It was revealed that with a mutated cytochrome P450 most of processes of drug biotransformation occurs. And there is a greater risk of developing AE against the background of polypragmasia in polymorbid patients, which makes it possible to individually adjust the dose of beta-blockers, thus affecting the frequency of their development. The choice of management measures should be determined considering all the areas of personalized medicine, including pharmacogenetic predictors, pharmacoepidemiological data, pharmacoeconomic effectiveness, the development of adverse reactions, polypragmasia, and medical and social risk factors.

Keywords

polypharmacy, drug interaction, cardiovascular therapy, complication.

Introduction

The choice of management measures at the individual level at each stage of the formation of the quality of medical care should be determined by taking into account all the areas of personalized medicine, including pharmacogenetic predictors, pharmacoepidemiological data, the pharmacoeconomic effectiveness of the selected therapy, the development of adverse reactions and polypharmacy, as well as medical and social risk factors. The end of the 20th – beginning of the 21st centuries directed the vector of the treatment of cardiological patients to organoprotection, and the evidence-based medicine gave rise to the creation of clinical recommendations and the introduction of standards on the basis of which the effectiveness of therapy and the quality of care are assessed.

An increase in the average life expectancy has led to the emergence of a problem of a comorbid pathology, requiring an enhanced therapy. At the same time, new problems arise related to the assessment of drug interactions and the need to implement a personalized approach. According to the literary data, more than 40.0% of people over 70 years of age daily take 4–6 medicines, and 12.0% – more than 9 medicines. One of the largest studies on this problem was conducted in Sweden and revealed that the average assignment of drugs per patient is 6.2 ± 3.7. The most commonly prescrined drugs were antithrombotic, β-adrenoblockers, loop diuretics, sedative medicines, and non-narcotic analgesics. In 26.0% of the patients, potentially dangerous clinical drug interactions (DIs) were recorded, in 5.0%, potentially serious DIs were detected (Jyrkkä et al. 2009; Onder et al. 2010; Khokhlov 2011; Patterson et al. 2012; Moroz and Ryzhova 2015; Khokhlov et al. 2016; Martsevich et al. 2016; Rostova and Goodilina 2016; Sychev et al. 2016).

Decree of the President of the Russian Federation of December 1, 2016 No. 642 "On the Strategy for the Scientific and Technological Development of the Russian Federation" identified "the introduction of personalized medicine and high-tech healthcare" among the priority areas of the scientific and technological development for the next 10–15 years. The creation of a modern system of control of the rational clinical and economic drug supply, taking into account drug interaction, polypharmacy, system of control of development of side effects to drugs, is among the priority areas of scientific and technological development of Russia within the framework of this decree (Dyachenko et al. 2015; Kirshchina and Gabdrafikova 2015; Gilyarevsky and Holschmid 2016; Boytsov et al. 2019; Gruzdeva et al. 2020). In this regard, it is very important to study the problem of polypharmacy in the Russian population. To solve a number of problems, which are defined by the Procedures for providing medical care in clinical pharmacology, a developed multi-component system of managing pharmacotherapy risks should be used (Khokhlov and Lisenkova 2003; Rakov et al. 2003; Magro et al. 2012; Starodubov et al. 2012; Dalin et al. 2020).

The purposes of the study are to analyze the modern therapy of patients with CHD, to identify the presence of polypharmacy in the selection of a therapy, to evaluate its significance for the treatment process and to determine ways to solve the problem as an integral part of the concept of personalized treatment.

Materials and methods

The information and procedural basis of the study was made up by clinical observations and specially conducted studies in 1,400 patients aged 18 to 80 years with established diagnoses of arterial hypertension, CHD (stable angina, acute coronary syndrome (according to the WHO/ISAG classification 2004)), who sought medical care from medical organizations of the city of Kostroma and Kostroma region. The study included the patients who had signed informed consent to participate.

Based on the conducted study (2012–2016), the risks of reduced performance, quality of medical care and organization of work of the clinical pharmacology service were assesses using a monitoring method, based on the automated platform "Management of Performance Factors in Cardiological Care" (Gruzdeva et al., Management of performance factors in cardiological care. Software // Patent of Russia No. 2018612060. 2018. Bul. No. 2.). In the prospective group, 156 patients with stable angina treated in the cardiology department were randomised. The average age was 61.7 ± 9.2 years; the prescription of medicines per patient was 7.1 ± 2.7. When analyzing the hospital records, it was found that 39 (25.0%) of them were receiving more than 8 drugs at a time. Pharmacotherapy was analyzed in all the included patients, and a genetic analysis of the CYP2D6 gene was performed.

The analysis of cardiac care effectiveness at different stages was carried out. Effectiveness assessment was performed according to the criteria of clinical recommendations. These data allowed to distinguish 2 cohorts of cases with suboptimal performance (338 cases) and optimal performance (1,062 cases) and to identify 10 options for achieving the adequacy of treatment. The data of the pharmacoeconomic analysis inextricably linked with clinical and pharmacological aspects (effica, safety of drug therapy, organization of drug care, etc.) from the point of view of cost-effectiveness and medical effectiveness according to the Industry Standard "Pharmacoeconomic Research" (OST 91500 14.0001 – 2002). The procedure of determining the level of average (standard) costs is based on the Diagnostic-Related Group (DRG) methodology.

All trade names of medicines from the medication administration records were translated into International Generic Names. Each medication administration record was then validated with Drug Interaction Checker, an online drug interaction assessment service at www.drugs.com, created by Cerner Multum based on FDA recommendations. Potential drug interactions analyzed were then di-

vided into 3 classes: Major, Moderate, and Minor. Major (dangerous) – dangerous drug interactions, combinations of these drugs need to be avoided, since the risk of their joint use exceeds the benefit of the medicines (Gnjidic et al. 2012; Somers et al. 2012; Hanlon and Schmader 2013; Guthrie et al. 2015; Sizova et al. 2015). Moderate (significant) – significant drug interactions should be avoided if possible, as they require enhanced security monitoring. Minor (insignificant) – interactions with minimal clinical significance, characterized by the lowest risk of adverse reactions or ineffective therapy.

Results and discussion

The choice of management measures at the individual level at each stage of the formation of the quality of medical care should be determined taking into account all the areas of personalized medicine, including pharmacogenetic predictors, pharmacoepidemiological data, the pharmacoeconomic effectiveness of the selected therapy, the development of adverse reactions and polypharmacy, as well as medical and social risk factors. The risk of polypharmacy is potentially present in every patient with CHD. For instance, in accordance with the clinical guidelines for the diagnosis and treatment of chronic coronary syndrome (CCS) (2019, ESC; 2016, The National Clinical Recommendations), the following groups of drugs are recommended in drug therapy: antiischemic drugs (nitrates, β-adrenoblockers, calcium channel blockers, ivabradine, nicorandil, ranolazine, trimetazidine), antiplatelet agents (aspirin, oral P2Y12 inhibitors, anticoagulants, proton pump inhibitors, statins, renin blockers). Thus, a patient with CCS will have to take 4–10 drugs. In the presence of a comorbidity, such as diabetes mellitus (DM), 1–5 medicines will be added to the therapy (2019, National Clinical Recommendations).

In the course of the study, an analysis of the effectiveness of cardiological care at different stages of its delivery was carried out, and it was found that the optimal result in the whole array of the analyzed cases reached 75.9% (1,062 cases), that is, every fourth case of care did not achieve the optimal result.

The impact of care needs to be analysed in close connection with patient satisfaction, lack of adverse reactions and economic costs of the treatment. In this regard, a comparative analysis was carried out in patient groups depending on the effectiveness of care and an implementation rate of the standard of its provision, patient satisfaction, and resource savings (Table 1).

Table 1. Standard Performance

Parameters	Positive result	Negative result
Implementation of the standard		
- implemented completely	342–32.2%	37–11%
- there are deviations with an increased volume	531–50.0%	139–32%
- with a decreased volume	189–17.8%	262–57%
Patient satisfaction		
- completely satisfied	886–83.4%	2–0.6%
- not satisfied	176–17.9%	336–99.4%
Saving resources		
- optimal consumption	877–82.5%	242–71.6%
- resource overrun	185–17.5%	96–28.4%
Total	1062–100%	338–100%

Table 1 shows that in 682 cases (48.7%) a positive result was obtained with optimal use of resources and patient satisfaction with medical care in the presence of deviations from the standards (420 with an increase and 262 with a decrease in the standard), versus 52 cases (3.7%), when the standard of patient management was met, but the result was negative.

Thus, 10 groups of options for the effectiveness of cardiac care can be distinguished (Table 2). Extreme groups are 1 and 10, the rest are intermediate, which are currently not taken into account in clinical and economic assessments of the quality of care.

This grouping can be used by experts of the quality of health care in solving issues of imposing penalties on medical organizations, and by the management to run medical organizations for a differentiated approach to the promotion and the punishment of health care providers. Deviation from the standard should not be considered as an absolute criterion for assessing the provision of cardiac care.

Table 2. Options for Achieving the Impact of Medical Services and Clinical and Pharmacological Care

Options	Implementation of standard	Clinical outcome	Patient satisfaction	Saving resources	Quantification	Expert solution	Expert recommendations
1	+	+	+	+	4	+	Encourage the doctor. Use his experience in mentoring
2	+	+	+	–	3	–	Doctors' professional competence (PC) on pharmacoeconomics
3	+	+	–	+	3	–	Doctors' PC on interpersonal communications, patients' rights
4	+	–	–	+	2	–	Doctors' PC on clinical issues, patients' rights
5	+	–	–	–	1	–	Comprehensive PC of a doctor: clinical, legal psychological, and pharmacoeconomic
6	–	+	+	+	3	–	Doctors' clinical PC
7	–	+	+	–	2	–	Doctors'' clinical PC
8	–	+	–	+	2	–	Doctors comprehensive PC
9	–	–	–	+	1	–	Doctors' comprehensive PC
10	–	–	–	–	0	–	Comprehensive PC of a doctor: clinical, legal psychological, pharmacoeconomic. Incomplete official compliance of a doctor

Due to the low adherence to the treatment of cardiovascular pathology, it is necessary to carry out in full the measures aimed at improving the effectiveness of therapy by increasing compliance, including by using the personalized medicine (assessment of drug interaction using specialized software, genetic testing).

The insufficient number of spontaneous reports of adverse reactions makes it difficult to assess the safety of therapy, including for widely used generics, so it is advisable to encourage the population and doctors to submit such reports. The analysis revealed that in the framework of monitoring the safety of adverse reactions to drugs and through the automated information system of the Federal Health Care Supervision Service in Kostroma region, only a small number of spontaneous calls were registered in 2016–2019 (Fig. 1). The group of cardiovascular drugs which had been reported on included ticagrelor (Brilinta), metoprolol (Betalock ZOK), dabigatran (Pradaxa), clopidogrel (Plavix), and propranolol (Anaprilin). According to the WHO recommendation, 600 reports of adverse reactions to medicines per 1 million people are considered an indicator of the effectiveness of the method. Thus, for Kostroma region, 410 spontaneous calls per year will be considered an effective indicator.

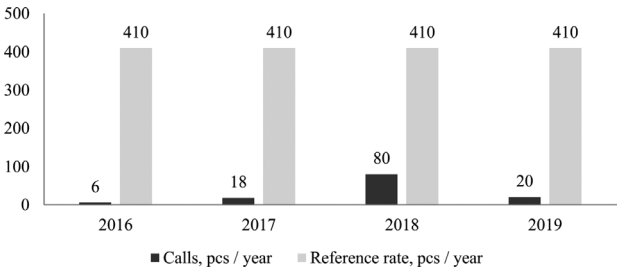

Figure 1. Number of complaints about adverse events per year.

A well-functioning health care supervision system is essential for the timely prevention of adverse reactions. In this regard, special attention should be paid to the prevention of polypharmacy. In our study, in CCS patients receiving over 8 drugs at the inpatient stage, an evaluation of drug interactions revealed 580 variants, of which 48 were major, 428 moderate, and 104 minor (Fig. 2). Some drugs were not recognized by the Drug Interaction Checker service, including bromodihydrochlorophenylbenzodiazepine, moxonidine, glyclaside, molsidomine, and vildagliptin.

During the study, the following dangerous drug-drug interactions were identified (Fig. 3). The data are presented as: an interaction group – frequency of occurrence

– Clopidsogrel with dabigatran – 6, clopidogrel with apixaban – 3, aspirin with apixaban – 3, increasing the risk of bleeding, including severe. Since the formation of the active metabolite of clopidogrel occurs with the help of enzymes of the cytochrome P450 system, some of which may differ in polymorphism or be inhibited by other drugs, not all patients can adequately suppress platelet aggregation. In patients over 65 years of age with impaired liver and kidney function, metabolic disorders and a slow elimination are possible. Therefore, dual antithrombotic therapy increases the risk of developing adverse reactions.
– Amiodarone with furosemide – 13, which increases the risk of heart rhythm disturbances, including serious ones, which requires regular monitoring of electrolytes;
– Amiodarone with warfarin – 6, increasing the risk of bleeding, requiring more careful monitoring of INR (international normalized ratio);
– Spironolactone with perindopril – 10, spironolactone with enalapril – 3, increasing the level of potassium, the risk of hyperkalemia, especially in case of water imbalance, kidney disease, diabetes mellitus, in the elderly;
– Metoprolol with digoxin – 3, bisoprolol with digoxin – 1, increasing the risk of developing bradycardia and proarrhythmic effect.

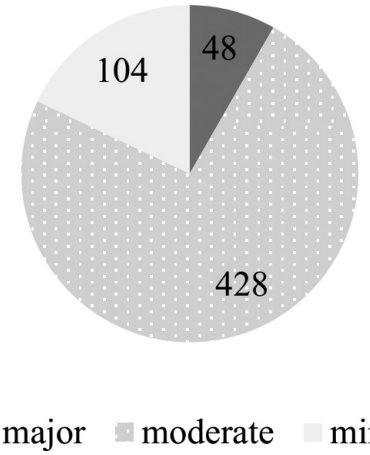

Figure 2. Identified variants of drug interactions.

Thus, major complications occur among antiarrhythmics (amiodarone (29)), antithrombotic drugs (24), and diuretics (16).

Moderate drug-drug interactions identified in patients with CHD are shown in Figure 4. The following combinations were most common:

– Amiodarone with atorvastatin – 32, amiodarone can increase blood levels of atorvastatin, which can increase the risk of side effects and the risk of liver damage, as well as cause rhabdomyolysis, a rare but serious complication. In some cases, rhabdomyolysis can lead to kidney damage and death. Dose adjustment or more frequent monitoring by a doctor is required to use both drugs safely;
– bisoprolol with amlodipine – 31, may have additive effects in lowering blood pressure;
– amiodarone with bisoprolol – 25, amiodarone with metoprolol – 8, can lead to increased bradycardia, hypotension, and prolongation of the QT interval.

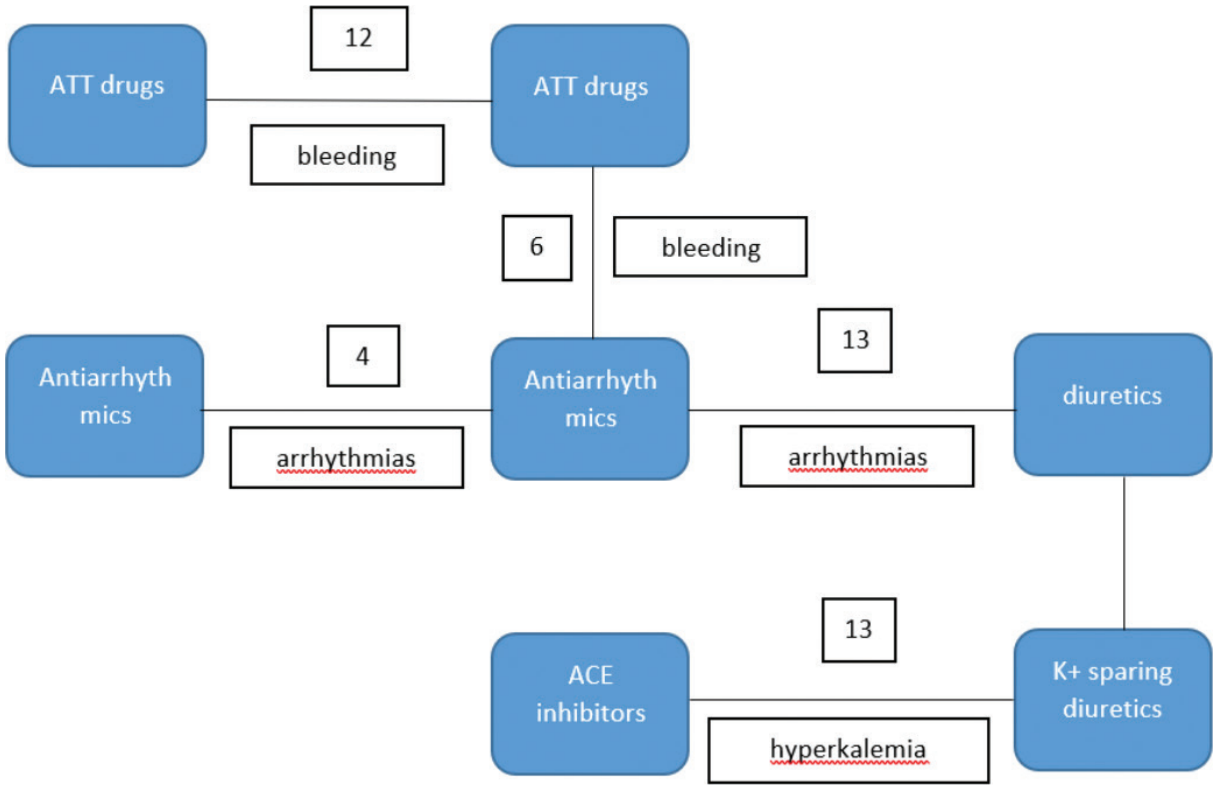

Figure 3. Dangerous drug interactions.

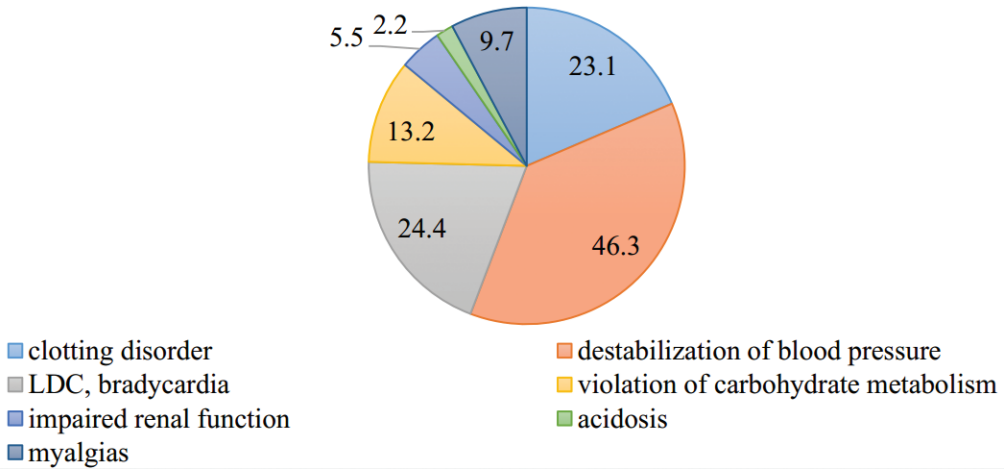

Figure 4. Moderate drug-drug interactions (in shares).

- amiodarone with clopidogrel – 22, which reduces the effectiveness of clopidogrel, which in some cases requires dose adjustment or drug replacement;
- atorvastatin with clopidogrel – 20, which reduces the effectiveness of antithrombotic therapy, which can lead to an increase in thrombus formation and require dose adjustment;
- aspirin with clopidogrel – 19, increasing the risk of bleeding, which may require dose adjustment, and refusal to take NSAIDs simultaneously;
- aspirin with amlodipine – 22, can lead to increased blood pressure, which may require more frequent monitoring and dose adjustment;
- enalapril with aspirin –18, lisinopril with aspirin – 4, which can affect blood pressure and renal function;
- furosemide with perindopril – 11, furosemide with enalapril – 11, having an additive effect on hypotension.

Thus, in our study, the major drug interactions as part of a complex therapy in patients with CHD can be ranked as follows: with antiarrhythmic drugs (42.6%), with antithrombotic drugs (33.3%), and with ACE inhibitors (24.1%). The moderate drug interactions can be ranked in descending order: antiarrhythmics (33.4%), antithrombotic drugs (20.8%), ACE inhibitors and sartans (14.2%), diuretics (14.0%), dihydropyridine calcium antagonists

(9.2%), and statins (8.4%). Minor drug interactions were also most common in antithrombotic drugs (28.9%), then in calcium antagonists of the dihydropyridine series (21.1%), ACE inhibitors (17.3%), diuretics (14%), β-blockers (12%), and finally in statins (6.7%).

The most studied and common mechanisms are interactions between drugs associated with changes in the activity of cytochrome P450 isoenzymes. According to the analysis of the 200 most commonly prescribed drugs in the United States, about 73.0% of drugs are metabolized, of which about 75% of drugs are metabolized by cytochrome P450 isoenzymes. The most important biotransformation enzyme is cytochrome P450, which has more than 1,000 isoenzymes, 5 of which (CYP3A4, CYP2D6, CYP2C9, CYP2C19, and CYP1A2) metabolize up to 90.0% of all drugs. The most common of the moderate complications due to drug-drug interactions are the effect on hemodynamics, rhythm and conduction disturbances, when drug metabolism occurs mainly through the CYP2D6 isoenzyme; and then – on the coagulation system, isoenzyme – CYP2C9. In patients with concomitant diabetes mellitus, hypoglycemia and hypotension are most often challenged (Lund et al. 2010; Kirshchina and Gabdrafikova 2015; Sizova et al. 2015; Sychev et al. 2016).

The analysis of the frequency of occurrence of CYP2D6*4 and CYP2D6*10 gene polymorphisms was carried out. It was revealed that in the group of polymorbid patients with a high risk of thrombotic complications, there was a tendency for a higher frequency of heterozygosity for cytochrome P450 isoenzyme, which can lead to an increase in drug-drug interactions and the development of adverse reactions against the background of polypharmacy. The patients were comparable by age and sex (Tables 3, 4).

Patients suffering from a severe cardiovascular pathology (acute myocardial infarction, CVA, Pulmonary Artery Thromboembolism, etc.), who have comorbidities (diabetes, COPD, ulcerative disease, etc.) require a greater amount of therapy. Therefore, in the presence of a mutation of cytochrome P450, on which most processes of drug biotransformation occur, there is a greater risk of the development of adverse reactions against the background of polypharmacy (Larock et al. 2014; Page et al. 2016; Dalin et al. 2020; Foley et al. 2020; Martinez et al. 2020).

Among the genes studied, (GA gene) CYP2D6*4, taking part in the metabolism of β-blockers, had a significant advantage in the frequency of occurrence in 28.2% cases in patients with polypharmacy (receiving 8 or more drugs). The determination of the polymorphism of this gene will allow personalized correction of a dose of β-blocker, thereby reducing the risks of side effects in patients taking several drugs at the same time. By introducing drug interactions more widely into clinical practice and registering them in the reporting documentation (hospital records, outpatient cards) by using drugs.com application, thereby preventing polypharmacy, which is possible when strictly applying the standards without much thought, we will be able to obtain both clinical and economic effects from preventing the development of complications, measures to correct them, saving on dangerous combinations of drugs in these situations.

Since the main regulatory documents for the purpose of therapy are clinical recommendations and standards, and the clinical and economic examination of quality is carried out on the basis of the orders of the Ministry of Health of the Russian Federation for the provision of care with specific measurable standards, we carried out a pharmacoeconomic assessment of the inpatient stage therapy and determined the compliance of the therapy with the treatment standard (orders 404an, 405an dated 01.07 2015) (compliance/incompliance), effectiveness of drugs in relation to the underlying disease (proved/not proved) and a pathogenetic effect from the use of the drug (high – 1 point, average – 0.5 point, low – 0 point). The standard compliance ratio was determined as = ratio/number of drugs used x 100% = 55%. Therapy evidence ratio = cases with proven effect on a given pathology/number of drugs used x 100% = 50%. Effectiveness ratio = cases with positive effect/number of drugs used x 100% = 58%. It was found out that the modern standard of medical care does not have sufficient evidence: drugs with unproven effectiveness for this nosology are included (50.0%), which indicates the need to finalize the standards of health care.

Table 3. Frequency of Occurrence of CYP2D6 Gene Polymorphism in Patients with Polypharmacy

Group	Drugs prescribed	CYP2D6*4 n (%)	CYP2D6*10 n (%)	*p*
I	<=5 (n=29)	3 (10.3%)	5 (17.2%)	0.72
II	6–8 (n=88)	24 (27.3%)	27 (30.7%)	0.74
III	>8 (n=39)	11 (28.2%)	13 (33.3%)	0.81
Total (n=156)		38 (24.3%)	45 (28.8%)	0.44

Note: p (I-II) = 0.06; p (I-III) = 0.063 (chi-square method).

Table 4. Characterization of Polymorbidity in Patients with Polypharmacy

Drugs prescribed	Number of people	Frequency of Pathology						Age, years
		CHF	PICS	CVA	Atherosclerosis	Diabetes	COPD, BA	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
≤5	29 (18.6)	12 (41.3)	0	0	2 (6.9)	2 (6.9)	1 (3.4)	61.3 ± 8.4
6–8	88 (56.4)	72 (81.8)	31 (35.2)	5 (5.7)	36 (40.9)	18 (21.6)	7 (7.9)	61.8 ± 8.7
>8	39 (25)	32 (82.7)	25 (64.1)	9 (23.0)	13 (33.3)	8 (20.5)	2 (5.1)	62.2 ± 10.6
Total	156 (100)	116 (74.4)	56 (35.9)	14 (9.0)	51 (32.7)	28 (17.9)	10 (6.4)	61.7 ± 9.2

Note: CHF – chronic heart failure, PICS – postinfarction cardiosclerosis, CVA – cerebrovascular accident;COPD – chronic obstructive pulmonary disease; BA – bronchial asthma.

Thus, evaluation and prevention of polypharmacy is an integral part of the concept of a personalized strategy of risk management in a cardiological patient, the novelty of which is the individual assessment of the influence of various factors on each particular patient, ensuring the solution of tasks. Thereby, improving the state of health in each particular patient weill lead to an increase in the quality of cardiological care in the region and an improvement in the demographic indicators.

In conclusion, a developed and implemented multi-component system of pharmacotherapy risk management should be used in the clinical pharmacology service to solve a number of tasks that are defined by the procedures for providing medical care in clinical pharmacology.

Conclusions

1. As a result of the study, it was found that in most cases polypharmacy was detected in patients with CCS (81.4% of patients receive more than 5 medicines at a time).
2. The phenomenon of polypharmacy in patients with CCS is due to significant comorbidity and the need to comply with the standards and clinical recommendations.
3. Excess drug prescriptions determine a high percentage of major (8.3%) and moderate (73.8%) drug interactions. At the same time, the rate of spontaneous reports of adverse reactions, being one of the managed and effective markers of the quality of medical care in case of effective organization of the system, over the past three years has been 19.5% of the expected (80 calls instead of 410), which indicates insufficient pharmacological supervision.
4. Determination of the polymorphism of the CYP2D6 gene, the frequency of which in patients with polypharmacy is high (28.2%), allows individual correction of a dose of β-blockers, thereby affecting the frequency of adverse reactions.
5. In order to avoid and/or reduce the development of adverse reactions in patients forced to take more than five drugs, it is necessary to use specialized software toolboxes, for example, www.drugs.com, to correct doses of drugs that may be reasonably lower than the therapeutic (recommended) ones, which will reduce the risks of developing side effects.

Conflict of Interest

The authors have no conflict of interest to declare.

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