

## РЕЗУЛЬТАТЫ ПИЛОТНОЙ ЧАСТИ ГОСПИТАЛЬНОГО РЕГИСТРА ПЕРЕДОЗИРОВОК КАРДИОЛОГИЧЕСКИХ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ (ГРОЗА): ФОКУС НА МЕДИКАМЕНТОЗНО ОБУСЛОВЛЕННУЮ БРАДИКАРДИЮ

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**Цель.** Анализ актуальности медикаментозно обусловленной брадикардии (МОБ) как медико-социальной проблемы, ее основных закономерностей и определение необходимости дальнейшего изучения данного вопроса.

**Материалы и методы.** Регистровое исследование выполнено 01.01.2017-30.06.2018 (18 месяцев) на клинической базе Государственного бюджетного учреждения Рязанской области Областной клинической кардиологической диспансер. Критерии включения: 1) синдром брадикардии/брадиаритмии на фоне приема хотя бы одного лекарственного (ЛП) с брадикардитическим действием (БКД), 2) подписание Информированного согласия. Никаких дополнительных вмешательств в диагностику или лечение пациентов в рамках регистра не проводилось.

**Результаты.** За 18 месяцев был госпитализирован 191 пациент (возраст 77,0 [69,0;82,0] лет, 26,7% мужчин) с верифицированным диагнозом МОБ, что составило 52,6% от всех случаев госпитализаций по поводу передозировки ЛП. За анализируемый период зарегистрирован рост числа госпитализаций по причине передозировки кардиологических ЛП в целом (в 1,7 раза,  $p < 0,001$ ) и ЛП с БКД в частности (в 1,8 раза,  $p < 0,001$ ). Основные клинические проявления МОБ: снижение частоты сердечных сокращений ( $< 50$  ударов/мин – 80,0%,  $< 40$  ударов/мин – 51,1%), синоатриальная (30,4%) и атриовентрикулярная (1-ой степени – 8,2%, 2-ой степени – 10,4%, 3-ей степени – 14,1%) блокады, синкопе (32,6%), сердечные паузы  $> 3$  с (7,4%). 94,8% пациентов были госпитализированы по скорой медицинской помощи, 40,7% – в отделение анестезиологии-реанимации; в 17,8% случаев требовалась имплантация электрокардиостимулятора; госпитальная летальность составила 5,2%. Более половины (54,5%) госпитализированных принимали  $\geq 2$  ЛП с БКД, 15,7% –  $\geq 3$ -х и 3,14% –  $\geq 4$ -х (как в монотерапии, так и в составе комбинации), в т.ч. бета-блокаторы – 68,4%, антиаритмические препараты – 38,9%, дигоксин – 25,8%, недигидропиридиновые антагонисты кальция – 10,5%, агонист  $H_1$ -имидазолиновых рецепторов – 9,5%, другие ЛП с БКД – 7,4%. Для анализа причины МОБ были использованы клинические данные 135 пациентов (возраст 77,0 [69,0;82,0] лет, 20,7% мужчин), которые могли точно назвать принятую дозу ЛП с БКД. Среди них в 14,1% случаев зарегистрировано абсолютное превышение рекомендуемой дозы, в 85,9% – суммирование/потенцирование эффекта нескольких ЛП с БКД, каждый из которых был принят в терапевтической дозе.

**Вывод.** Исследование подтвердило высокую медико-социальную значимость проблемы МОБ, что требует привлечения внимания к ней практических врачей, фармакологов и клинических фармакологов, организаторов здравоохранения, а также продолжение ее изучения.

**Ключевые слова:** регистр; ГРОЗА; передозировка; нежелательная лекарственная реакция; пульсурежающее действие; брадикардитическое действие; брадикардия.



## RESULTS OF THE PILOT PART OF THE CARDIAC DRUG OVERDOSES HOSPITAL REGISTRY (STORM): FOCUS ON DRUG-INDUCED BRADYCARDIA

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**Aim.** Analysis of the relevance of drug-induced bradycardia (DIB) as a medical and social problem, its main regularities and determination of the need for further study of this issue.

**Materials and Methods.** The register study was performed on 01 Jan 2017-30 Jun 2018 (18 months) at the clinical base of the Ryazan Regional Clinical Cardiology Dispensary. Inclusion criteria were: 1) bradycardia/bradyarrhythmia syndrome with intake of at least one drug with a bradycardic effect (BCE), 2) signing Informed consent to the processing of personal and clinical data. No additional interventions were performed in the diagnosis or treatment of patients within the registry.

**Results.** During 18 months, 191 patients (age 77.0 [69.0;82.0] years, 26.7% of men) were hospitalized with a verified diagnosis of DIB, which accounted for 52.6% of all cases of hospitalization for drug overdose. During the analyzed period, there was an increase in both the total number of drug overdoses (1.7 times,  $p<0.001$ ) and overdoses of drugs with BCE (1.8 times,  $p<0.001$ ). Main clinical manifestations of DIB: reduced heart rate ( $<50$  beats/min – 80.0%,  $<40$  beats/min – 51.1%), sinoatrial (30.4%) and atrioventricular blocks (1<sup>st</sup> degree – 8.2%, 2<sup>nd</sup> degree – 10.4%, 3<sup>rd</sup> degree – 14.1%), syncope (32.6%) and cardiac pauses  $>3$  s (7.4%). Almost all (94.8%) the patients were hospitalized by ambulance, 40.7% – to the intensive care unit; 17.8% required pacemaker implantation; hospital mortality was 5.2%. More than half (54.5%) of hospitalized patients took  $\geq 2$  drugs with BCE, 15.7% –  $\geq 3$  and 3.14% –  $\geq 4$  (both in monotherapy and as a part of a combination): beta-blockers – 68.4%, antiarrhythmic preparations – 38.9%, digoxin – 25.8%, non-dihydropyridine calcium antagonists – 10.5%, I1-imidazoline receptor agonist – 9.5%, and other drugs with BCE – 7.4%. To analyze the cause of DIB, we used clinical data of 135 patients (age 77.0 [69.0;82.0] years, 20.7% of men), who could indicate the exact dose of a taken drug with BCE. Among them, the absolute exceedance of the recommended dose of drugs with BCE was found in 14.1% of cases, while in 85.9% of cases summation/potential effect of several drugs with BCE was observed, with intake of each in a therapeutic dose.

**Conclusion.** The study confirmed high medical and social significance of the problem of DIB, which requires attention of practitioners, pharmacologists and clinical pharmacologists, health care providers, and also continuation of its study.

**Keywords:** register; STORM; overdose; adverse drug reaction; pulse-reducing effect; bradycardic effect; bradycardia.

At present cardiovascular diseases (CVD) are the leading cause of mortality of the population both worldwide (17.3 million deaths annually, or 31.5% of all deaths on the planet) [1], and in the Russian Federation (RF) as well. According to the data of 2014, half of deaths were caused by CVD with 80% of them resulting from ischemic heart disease and cerebral strokes [2].

Despite a significant reduction of the mortality in some European countries [3], experts predict further growth of socio-economic burden of CVD due to continuing urbanization, increase in the life duration and ageing of the population [4].

In connection with the above, prophylaxis of cardiovascular diseases, both primary and secondary, is one of the leading directions

of the modern healthcare [4]. Despite high efficiency of non-medicinal correction of risk factors [5-7], the leading role of medicinal therapy/prophylaxis is undeniable [8-12]. Moreover, a characteristic treatment for CVD is a *combined* medicinal therapy [4,6,8-12], and, taking into account the fact that cardiovascular diseases usually run in the form of *comorbidity* including multiple comorbidity [13,14], a routine clinical practice nowadays is *multi-component* medicinal therapy of CVD.

Obviously, even with full justification of all the administered drugs which is far not always so, the risk of drug interactions and undesired drug reactions increases with expansion of the composition of medicinal prophylaxis/treatment [15]. Thus, recently in our practice we faced with a problem of growth of hospitalizations for medical drug-induced bradycardia (DIB).

Therefore, the *aim* of our pilot study is analysis of actuality of drug-induced bradycardia as a medical and social problem, of its main regularities and determination of the necessity for further study of this matter.

### Materials and Methods

The work was performed in the period 01.01.2017-30.06.2018 (18 months) on the clinical base of Ryazan Regional Clinical Cardiologic Dispensary (RRCCD, functioning as Regional Cardiovascular Center of the Ryazan region) within Hospital Registry of Overdoses of Cardiologic Medical Drugs (HROCD). The protocol of study was approved by Local ethic committee at RRCCD (Protocol №12A of 21.12.2016).

Criteria of inclusion:

1) development of bradycardia/bradyarrhythmia syndrome with the underlying intake of at least one medical drug (MD) of bradycardic effect (BCE) irrespective of whether the drug was administered by a treating physician or taken by a patient on his own initiative. Here, BCE could be both a direct pharmacological effect of MD (for which the drug was administered), and a side effect;

2) signing by a patient or (in case of his death) by his relatives of Informed consent to processing of personal and clinical data;

3) age  $\geq 18$  years.

Criteria of exclusion: acute coronary syndrome, etc., as a cause for bradyarrhythmia.

No additional interventions into the diagnostics or treatment of patients within the frame of the register were performed.

The results were statistically processed using application program packages Excel 2010 (Microsoft Corporation, USA) and Statistica 10.0 (Stat Soft Inc., USA). Correspondence of a variable to normal distribution was determined using Shapiro-Wilk test. Trait/event frequency was presented in the form of absolute and relative values (n and %); quantitative values that do not satisfy the normal distribution criteria were presented in the form of median and interquartile range: Me [Q25;Q75]. For comparison of two relative parameters in two independent groups by the qualitative characteristics, Pearson's chi-square test or Fisher's exact test in case of the least value  $< 5$  of the expected characteristics, were used. Comparison of the groups on the basis of the quantitative characteristics was conducted using Mann-Whitney test. The critical level of significance in verification of the statistical hypotheses was taken to be  $p < 0.05$ .

### Results and Discussion

During 18 months 191 patients were hospitalized to RRCCD (age 77.0 [69.0;82.0] years, 26.7% of men) with verified diagnosis of DIB which accounted for 52.6% of all cases of hospitalization to this hospital for cardiologic MD overdose (Figure 1). Attention is caught by the fact that within a short period of time – 18 months – the total amount of both cases of MD overdose requiring hospitalization and cases of overdose of MD with BCE increased (1.7-fold,  $p < 0.001$  and 1.8-fold,  $p < 0.001$ , respectively, Figure 2). In the following analysis only cases were included (n=135, age 77.0 [69.0;82.0] years, 20.7% of men) with the known dose of taken MD with BCE that was important for studying regularities of DIB.

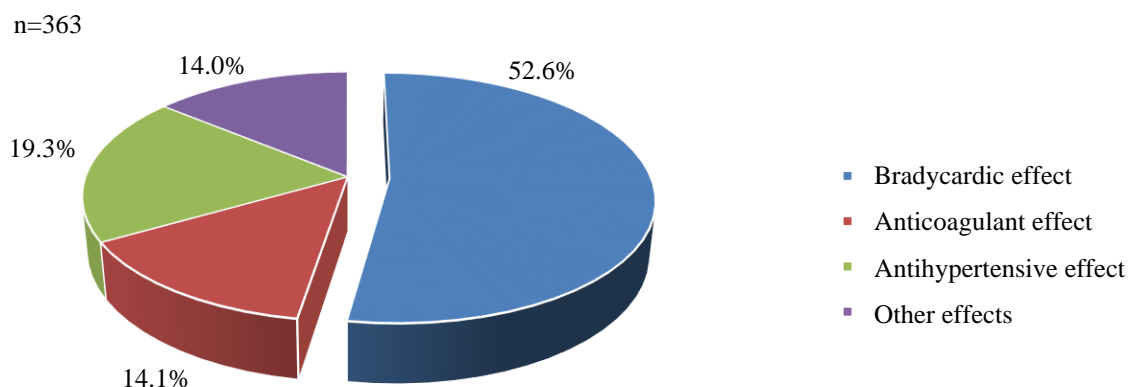


Fig. 1. Structure of clinical manifestations of MD overdose as a cause of hospitalization to RRCCD within 18 months of 2017-2018

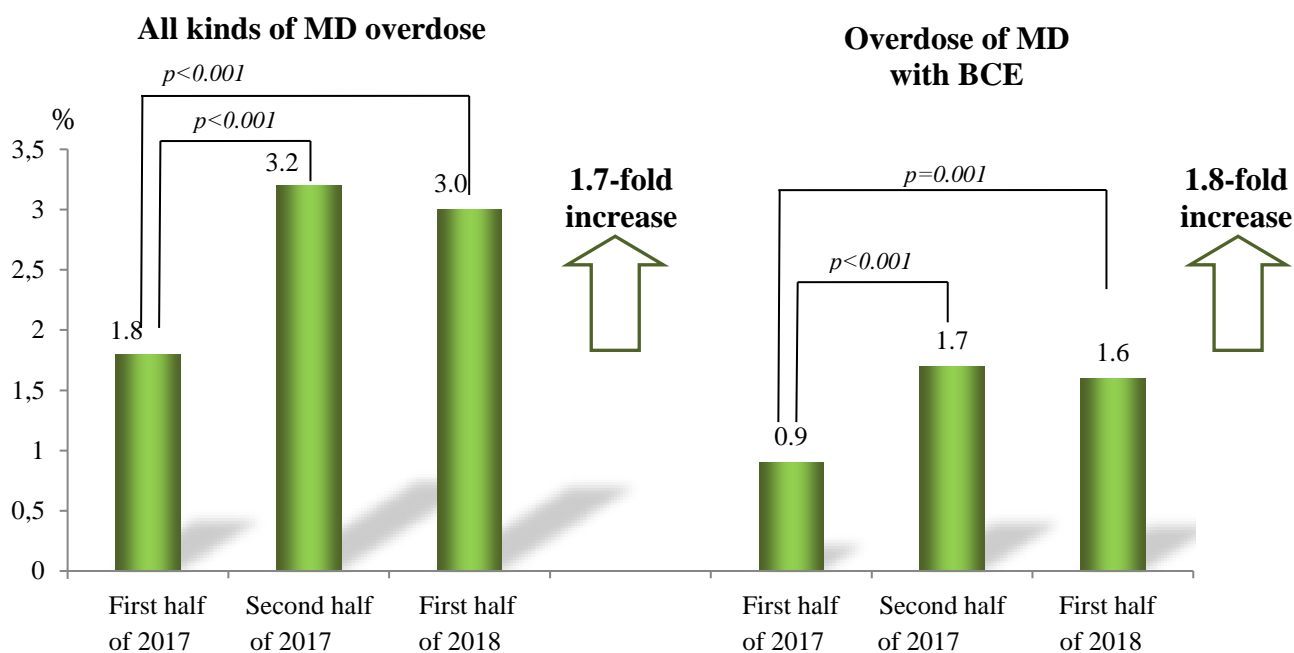


Fig. 2. Increase in the share of MD overdose in the structure of causes for hospitalizations to RRCCD for 18 months of 2017-2018

As it is presented in Table 1, the condition of the analyzed cohort of patients was rather severe: 94.8% of patients were hospitalized by ambulance; 40.7% – to the anesthesiology and resuscitation department (ARD); in 17.8% of patients, implantation of the temporary (in case of pronounced severity of

symptoms) or permanent (if DIB developed with the underlying sick sinus syndrome) electrocardiostimulator (ECS) was required; 5.2% of cases ended lethally.

The leading clinical manifestations of DIB were: sinus bradycardia, sinoatrial (SA) and atrioventricular (AV) blocks, syncopal

conditions/attacks of Morgagni-Adams-Stokes syndrome (MASS), Frederick syndrome and cardiac pauses (Table 1).

Table 1

*Clinical and Demographic Characteristics of Groups of Patients with Absolute and Relative Overdose of MD with BCE*

Parameter	Absolute Overdose	Relative Overdose	Total	p
n (% of all cases of pulse-decreasing MD overdose)	19 (14.1)	116 (85.9)	135* (100)	–
Men, % of n	15.8	21.6	20.74	0.566
Age, Me [Q1; Q3], years	79.0 [74.0;84.0]	77.0 [68.5;82.0]	77.0 [69.0;82.0]	0.133
<b>GFR on Admission to Hospital</b>				
<60 ml/min*1,73 m <sup>2</sup> , % of n	77.9	83.9	83.2	0.052
<45 ml/min*1,73 m <sup>2</sup> , % of n	62.1	55.3	56.5	0.925
<30 ml/min*1,73 m <sup>2</sup> , % of n	25.3	34.8	33.6	0.468
<15 ml/min*1,73 m <sup>2</sup> , % of n	15.8	11.6	12.2	0.607
<b>Clinical Manifestations</b>				
Bradycardia <50 beat/min, % of n	84.2	79.3	80.0	0.621
Bradycardia <40 beat/min, % of n	<b>84.2</b>	<b>45.7</b>	<b>51.1</b>	<b>0.002</b>
SA-block, % of n	31.6	30.1	30.4	0.896
Frederick syndrome, % of n	10.5	11.3	11.1	0.921
Pauses >3 s, % of n	10.5	6.9	7.4	0.576
Syncope, MASS attacks, % of n	47.4	30.2	32.6	0.139
I degree AV block, % of n	10.5	7.8	8.2	0.683
II degree AV block, % of n	5.3	11.2	10.4	0.431
III degree AV block, % of n	15.8	13.8	14.1	0.817
<b>Medical Care and Outcomes</b>				
Hospitalization by ambulance, % of n	94.7	94.8	94.8	0.993
Management in ARD, % of n	<b>68.4</b>	<b>36.2</b>	<b>40.7</b>	<b>0.008</b>
Temporary ECS, % of n	15.8	11.2	11.9	0.567
Implantation of permanent ECS, % of n	0	6.9	5.9	0.238
Lethal outcome, % of n	0	6.0	5.2	0.272

*Note:* \* – calculation was conducted only for cases (n=135) when MD dose was verified, GFR – glomerular filtration rate

In analysis of the results obtained we met with an interesting phenomenon which is not described in classic textbooks on clinical pharmacology. Thus, according to traditional understanding, undesired reactions to medical drugs (*adverse drug reactions*) are harmful

threatening reactions that develop unintentionally after intake of medical drugs *in doses used for prophylaxis, diagnostics and/or treatment of diseases, and also for correction and modification of physiological functions*, whereas toxic effects of MD are associated



with absolute MD overdose [15] that exceed the doses stated above. In the analyzed cohort of patients, absolute MD overdose was observed only in 14.1% with exceedance of recommendations for one-time and daily doses stated in the Instruction to this drug. In most cases (85.9%) there was no infringement of instructions for each of the administered MD with BCE. However, taking into account the fact of using several MD with alike pharmacodynamics effect (suppression of the conducting system of the heart), the resultant effect was similar to absolute overdose of one MD of analogous action. Contrary to a widely accepted term «absolute overdose», these cases are considered by us as «relative overdose».

It is interesting that phenomenon of «relative overdose» combines the characteristics of adverse drug reaction (harmful dangerous reaction that develops in use of a particular MD in a recommended dose) and of toxic effect/absolute overdose (exceedance of the required pharmacological effect to the extent of toxicity). In our opinion, the main cause of appearance and further increase in the frequency of the phenomenon of relative overdose is a wide spread of polypragmasy in the clinical practice. We think that in the conditions of multicomponent medicinal therapy it is necessary to thoroughly control MD with a unidirectional pharmacological effect summation/potentialiation of which may lead to threatening conditions.

Comparative analysis of clinical and demographic characteristics of cases of absolute and relative overdose did not reveal significant differences. An exception was a higher frequency of bradycardia with heart rate (HR) <40 beat-minute and indications to management in conditions of ARD in case of absolute overdose. It should be noted that in relative overdose *hospital* lethality was 6.0% while in absolute overdose it was 0%. This phenomenon may be explained, on the one hand, by error of low statistical power of the study which requires continuation of the research

with increased number of observations, and on the other hand – by a probability for development of lethal outcomes in most severe cases in the prehospital stage (accordingly, these cases were not included into the analysis). We think that *routine* postmortem verification of MD overdose as a cause of lethal outcome is rather difficult in the conditions of modern healthcare [16]; it is likely that in these cases the registered cause of death is some disease that previously existed in the patient [17-18].

Thus, the obtained results demonstrated that for the clinical presentation of DIB and severity of patient's condition it is not principally important in what way the conducting system of the heart was suppressed – by exceedance of the dose of one MD or by a combination of several MD with BCE taken in therapeutic doses. Besides, a high role of reduction of the filtrating capacity of kidney was found (Table 1) as a factor potentiating a pharmacological effect of MD both in cases of using it in formal therapeutic doses (relative overdoses), and in evident exceedance of recommended doses (absolute overdoses).

After that the analysis of MD with BCE taken before hospitalization, was conducted. Here, both the preparations administered by the doctor and those taken by the patient on his own initiative (routinely and/or for elimination of an acute clinical situation) were taken into account. More than 2/3 of patients were found to take beta-blockers (Figure 3).

Can the group of beta-blockers be held «guilty» of increase in the cases of DIB? In the authors' opinion, the problem is not in beta-blockers, but rather in administration of other groups of MD «above» beta-blockers possessing not that evident bradycardic effect, but an ability for summation or potentialiation of their effects in a combination, especially in individuals of advanced and old age and in patients with disorders in filtration function of kidney. Thus, it was found that more than half of patients were taking at least 2 MD with BCE, 15.7% – at least three MD with BCE and

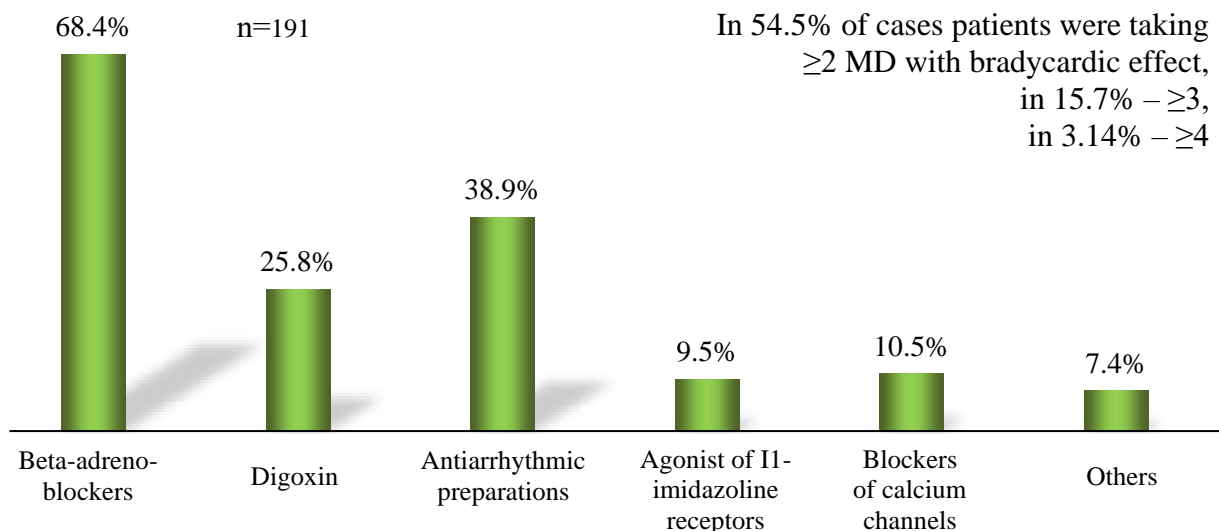


Fig. 3. Frequency of intake of MD with BCE by patients before hospitalization

3.14% – minimum four analogous MD. Here, the following drugs were taken both as monotherapy and in a combination: antiarrhythmic drugs with BCE, digoxin, non-dihydropyridine calcium antagonists (verapamil, diltiazem), agonist of II-imidazoline receptors (moxonidine) and other MD with BCE (ivabradine and ticagrelor, and so on, Fig.3). This regularity is alerting given that the analyzed sample, as it was said above, was represented by patients of older age groups where the given MD should be administered with great care.

Thus, STOPP-criteria (STOPP-criterion is a MD not recommended for patients of advanced age, and also a clinical situation when risk associated with intake of MD at the advanced age, reliably overweighs their usefulness; the criterion was proposed in Ireland in 2008 for audit of administration of medical drugs; revised in 2015) include:

- digoxin for treatment of heart insufficiency with preserved systolic function (cause: usefulness not proven; introduced in 2015);
- antihypertensive MD of central action (including moxonidine) except cases of intolerance to or insufficient effectiveness of antihypertensive drugs of other classes (cause:

antihypertensive drugs of central action are in general less tolerated by aged individuals than by young patients; introduced in 2015);

- beta-adrenoblockers in a combination with verapamil (cause: risk of development of heart block; introduced in 2008; preserved in 2015);

- beta-adrenoblockers in stable angina (2008 and 2015);

- acetylcholine esterase inhibitors in patients with persistent bradycardia in history (<60 beat/min.), heart block or recurrent syncope of unclear genesis or with intake of HR-reducing MD, such as beta-adrenoblockers, digoxin, diltiazem, verapamil (cause: risk of frustration of cardiac conduction and development of syncope and traumas; introduced in 2015) [19].

### Conclusion

A pilot study performed within Hospital Resister of Overdoses of Cardiologic Medical Drugs within 18 months (2017-2018) confirmed a high medical and social significance of medical drug-related bradycardia, which requires attention of practitioners, pharmacologists and clinical pharmacologists, healthcare professionals, and also continuation of its study.

The main category of patients under risk of overdose of medical drugs with bradycardic effect is individuals of advanced and old age. This regularity, on the one hand, in general reflects the population of patients with cardiovascular diseases that are the main indications for this group of drugs, and, on the other hand, is a result of age-related changes of pharmacokinetics of drugs, and of a higher vulnerability of individuals of older age groups to medicinal treatment.

It was demonstrated that adverse effects of multicomponent medicinal treatment may be associated not only with non-observance of the instruction to a particular preparation, but also with underestimation of the cooperative pharmacodynamic effect of the drugs. The effect of some drugs to suppress the conducting system of the heart may be direct,

predicted, well studied and controlled (for example, of beta-blockers, antiarrhythmic drugs, non-dihydropyridine calcium antagonists) while in relation to other drugs, for example, moxonidine, it may be a side effect, often underestimated and uncontrolled.

In this regard, it is necessary to inform practitioners of a high risk of such combinations, which is especially relevant at the present time, given the inclusion by the European Society of Cardiology (ESC) in 2019, of a combination of a beta-blocker and a non-dihydropyridine calcium antagonist in the Clinical Recommendation for Diagnosis and Management of chronic coronary syndromes [11] without specifying clear criteria for monitoring the safety of this combination and the need for its limitation in the elderly.

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**Источник финансирования.** Бюджет ФГБОУ ВО Рязанский государственный медицинский университет им. акад. И.П. Павлова Минздрава России. [Financing of study. Budget of Ryazan State Medical University.]

**Конфликт интересов.** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, о которых необходимо сообщить в связи с публикацией данной статьи. [Conflict of interests. The authors declare no actual and potential conflict of interests which should be stated in connection with publication of the article.]

**Участие авторов.** Якушин С.С. – постановка целей и задач, концепция исследования, редактирование, Никулина Н.Н. – концепция исследования, анализ литературы, написание текста, Филиппов Е.В., Селезнев С.В., Лыгина Е.В., Чернышева М.Б. – анализ литературы, работа с пациентами, статистический анализ, оформление иллюстраций. [Participation of authors. S.S. Yakushin – setting goals and objectives, research concept, editing, N.N. Nikulina – research concept, literature analysis, writing the text, E.V. Filippov, S.V. Seleznev, E.V. Lygina, M.B. Chernysheva – literature analysis, working with patients, statistical analysis, making illustrations.]

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**Цитировать:** Якушин С.С., Никулина Н.Н., Филиппов Е.В., Селезнев С.В., Лыгина Е.В., Чернышева М.Б. Результаты пилотной части госпитального регистра передозировок кардиологических лекарственных препаратов (ГРОЗА): фокус на медикаментозно обусловленную брадикардию // Российский медико-биологический вестник имени академика И.П. Павлова. 2020. Т. 28, №2. С. 153-163. doi:10.23888/PAVLOVJ2020282153-163

**To cite this article:** Yakushin SS, Nikulina NN, Filippov EV, Seleznev SV, Lygina EV, Chernysheva MB. Results of the pilot part of the cardiac drug overdoses hospital registry (STORM): focus on drug-induced bradycardia. *I.P. Pavlov Russian Medical Biological Herald*. 2020;28(2):153-63. doi:10.23888/PAVLOVJ2020282153-163

**Поступила/Received:** 16.12.2019  
**Принята в печать/Accepted:** 01.06.2020