THE GLUCOSE-LOWERING THERAPY STRUCTURE IN SPECIAL GROUPS OF TYPE 2 DIABETES MELLITUS PATIENTS BASED ON DATA FROM THE MOSCOW REGION REGISTER

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BACKGROUND: Data of real clinical practice in diabetes mellitus (DM) register allow to evaluate features and trends in structure of glucose-lowering therapy (GLT).

AIM: To analyze of structure of GLT received by patients with type 2 diabetes mellitus (T2DM) in Moscow region for 2018 and to evaluate its dynamics over 15 years.

METHODS: Analysis of GLT structure was carried out on basis of data from register of patients with DM in Moscow region, which is part of National register of diabetes mellitus in Russian Federation. In March 2018 it contained data on 211,792 T2DM patients of Moscow region. Structure of GLT administration was evaluated according T2DM duration, patient's age and presence of cardiovascular diseases (CVD). Dynamics of GLT is analyzed from 2004 to 2018 yrs.

RESULTS: In 2018 non-insulin glucose-lowering drugs (NIGD) prescription prevailed (78.3%), insulin therapy was prescribed in 18.5% of patients, 3.2% of patients did not receive drug therapy. Most commonly prescribed NIGD were metformin (69.3%) and sulfonylurea (51.3%). Older patients more often than younger did not use GLT at all and less frequently received insulin therapy and iDPP-4. Insulin therapy was prescribed twice as often in patients with CVD compared with patients without CVD (29.6% and 15.5%). NIGD monotherapy has been less commonly used in patients with CVD (67.3% and 81.2%). Glucagon-like peptide-1 receptor agonists (GLP-1 RA) were prescribed to patients with CVD GLP-1 RA – in 0.1% of cases, without CVD in 0.3% of cases, and sodium-glucose cotransporter 2 (SGLT2) inhibitors in 1.1% and 0.6%. correspondently.

CONCLUSION: Metformin was most commonly prescribed drug in GLT structure for T2DM patients in the Moscow region in 2018 yr. Percentage of new drugs in the structure of GLT increased mainly due to iDPP-4, and secondly due to SGLT2 inhibitors. New classes of GLT were more often prescribed to patients of younger age, with diabetes duration up to 10 years, overweight or obese. Administration of NIGD with proven cardiovascular protection in presence of CVD is almost two times less than for those without CVD.

KEYWORDS: type 2 diabetes mellitus; the structure of glucose-lowering therapy; the diabetes mellitus register

СТРУКТУРА САХАРОСНИЖАЮЩЕЙ ТЕРАПИИ В ОСОБЫХ ГРУППАХ ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ 2 ТИПА НА ОСНОВАНИИ ДАННЫХ РЕГИСТРА МОСКОВСКОЙ ОБЛАСТИ

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ОБОСНОВАНИЕ. Данные реальной клинической практики, отраженные в регистре больных сахарным диабетом (СД), позволяют оценить особенности и тенденции в структуре сахароснижающей терапии (ССТ).

ЦЕЛЬ. Анализ структуры ССТ, получаемой больными СД 2 типа (СД2) в Московской области на 2018 г., и оценка ее динамики за 15 лет.

МЕТОДЫ. Анализ особенностей ССТ проведен на основании данных регистра больных СД Московской области, являющего частью Федерального регистра РФ, в котором на март 2018 г. содержались данные о 211 792 больных СД2. Оценена структура назначений в первый год после установления диагноза СД2, а также в зависимости от возраста больных и наличия у них сердечно-сосудистых заболеваний (ССЗ). Динамика ССТ проанализирована с 2004 по 2018 гг.

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РЕЗУЛЬТАТЫ. В структуре ССТ у больных СД2 в 2018 г. преобладали препараты неинсулинового ряда (ПНИР) – 78,3%, инсулинотерапия использовалась у 18,5% больных, медикаментозную терапию не получали 3,2% пациентов. Наиболее часто применялись метформин (n=146 820 (69,3%)) и препараты сульфонилмочевины (ПСМ) (n=108 536 (51,3%)). У пациентов старшего возраста чаще, чем у молодых, не использовалась медикаментозная сахароснижающая терапия и реже применялись инсулинотерапия и ингибиторы дипептидилпептидазы 4 типа (иДПП-4). При наличии ССЗ в два раза чаще применялась инсулинотерапия (29,6% и 15,5%). Реже использовалась монотерапия ПНИР (67,3% и 81,2%). Препараты класса агонистов рецепторов глюкагоноподобного пептида-1 (АР ГПП-1) у больных без ССЗ использовались в терапии в 0,3% случаев, ингибиторы натрий-глюкозного котранспортера 2 типа (иНГКТ2) – в 1,1%. При наличии ССЗ АР ГПП-1 – в 0,1% случаев, иНГКТ2 – в 0,6%.

ЗАКЛЮЧЕНИЕ. В общей структуре ССТ больных СД2 в Московской области за период 2004–2018 годов наиболее часто применяемым препаратом являлся метформин. Доля новых препаратов в структуре ССТ увеличилась преимущественно за счет иДПП-4, во вторую очередь – иНГКТ2. Новые классы сахароснижающих препаратов чаще применялись у пациентов более молодого возраста, с длительностью СД до 10 лет, с избыточной массой тела или ожирением. ПНИР с доказанной кардиоваскулярной протекцией при наличии ССЗ применялись практически в два раза реже, чем у лиц без ССЗ.

КЛЮЧЕВЫЕ СЛОВА: сахарный диабет 2 типа; структура сахароснижающей терапии; регистр больных СД

In recent years, significant changes have occurred in treating patients with type 2 diabetes mellitus (DM2), which has been triggered by the emergence of new classes of antihyperglycemic drugs (AHGD), as well as new data on the efficacy and safety of both novel and well-known drugs to treat this disease. Currently, the primary aim of DM2 treatment is reducing cardiovascular risks, but not just in terms improving certain glycemia and glycated haemoglobin (HbA1c) indicators. According to principal Russian and foreign guidelines, managing patients with DM2 depends on a number of factors, namely variations in beginning therapy related to the onset of the disease and its intensification during patient monitoring. These factors include age, comorbidities - including cardiovascular diseases that worsen long-term prognosis - risk of hypoglycaemia, and baseline glycemic control as measured by HbA1c.

Data collection from actual clinical practice enables us to assess changes occurring during antihyperglycemic therapy (AHGT), and identify current trends or particular aspects of prescribing various drugs in certain groups of patients.

AIM

We aimed to analyse the AHGT structure of patients with DM2 within the Moscow Region (MR) in 2018, based on age, time of DM diagnosis establishment and the presence of cardiovascular disease (CVD), as well as an assessment of treatment dynamics over a 15-year period (from 2004 to 2018) based on the DM registry data of the MR.

METHODS

AHGT's structure for patients with DM2 is estimated based on data from the registry of patients with DM2 in the MR, which is part of the Federal Registry of DM of the Russian Federation. There, the patient with DM2 registry was created in 2003, and an online version has been available since 2014. The registry contains information about patients who are monitored in medical institutions of the MR. We used data that included the following information: patients' ages, treatment obtained, presence of macro- and microvascular complications, laboratory parameter data and HbA1c levels over time. This information helps us to determine the AHGD structure used and study the extent to which the current situation corresponds to the contemporary guidelines for managing patients with DM2.

At the beginning of 2018, the DM registry of the MR contained data on 211,792 patients with DM2. Analysis of the AHGT characteristics as of March 16th, 2018, was performed, and changes in the AHGT from 2004 to 2018 were assessed. The structure of noninsulin agents (NIA) as a whole was evaluated as a percentage of the total number of patients with DM and the total number of prescriptions. NIA usage for patients without insulin therapy, and in combination with insulin therapy, was determined separately. Administration of NIA prescriptions in patients during the first year after diagnosis of DM2 was analysed.

To assess AHGT characteristics, depending on age and CVD presence, sample groups of patients were formed. There were groups under 65 and over 65, as well as groups with and without CVD. Nonfatal infarction, nonfatal cerebrovascular disease, ischaemic heart disease and chronic cardiovascular insufficiency were classified as CVDs.

Another sample group of patients with DM2 was analysed separately, including those that received drugs. Some patients were prescribed drugs with a cardioprotective effect, namely glucagon-like peptide-1 receptor agonists (GLP1RA) and type 2 sodium-glucose linked transporter inhibitors (SGT2i). Certain group characteristics were analysed based on anamnestic data (e.g. age, DM duration, presence of macrovascular complications), physical characteristics (e.g. body mass index (BMI)) and laboratory (i.e. HbA1c) examinations.

Sample data were taken from the Federal Registry of Patients with DM2, which was developed by the Endocrinology Research Centre, with technical support from the Aston Consulting Company. Quantitative variables are presented as mean value, standard deviation and 95% confidence interval (CI). For qualitative variables, absolute and relative frequencies (%) with two-sided 95% CIs are given. To determine the statistical significance of differences in independent groups for quantitative variables, a Student t-test was used; for qualitative variables, the Pearson chi-squared test was used. P-values <0.05 were considered statistically significant. Calculations were performed with the programme Statistica 13.2 (Dell Inc., USA).

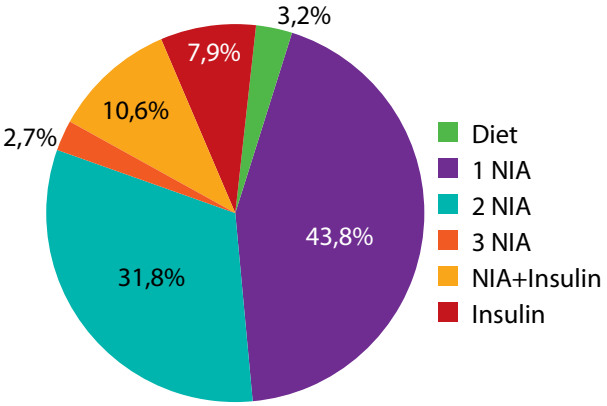

Fig. 1. The antihyperglycemic therapy structure in the Moscow region in 2018. NIA–noninsulin agents.

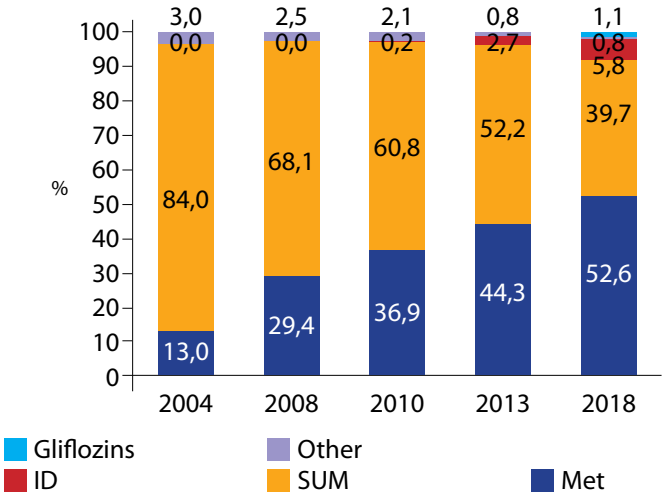

Fig. 2. Changes in the use of noninsulin agents without insulin in patients with DM2 from 2004 to 2018 (100% being total number of prescriptions). ID - incretin drugs; SUM–sulfonylurea medications; Met–metformin.

Ethical considerations

The study protocol was approved by the local independent ethical committee under the M. Vladimirsky Moscow Regional Research Clinical Institute (protocol No. 3; March 6, 2018).

RESULTS

In 2018, NIA accounted for 78.3% of AHGT for patients with DM2; 3.2% of patients did not receive drug therapy. Insulin therapy was used for 18.5% of patients.

The AHGT breakdown is presented in Fig. 1.

Over the course of 15 years, the proportion of patients not using drug therapy decreased significantly, from 10.7% in 2004 to 3.2% in 2018. The proportion of patients using insulin increased from 10.8% to 18.5% within this same period due to a significant increase in the combination of insulin with NIA (4.6% in 2004 and 10.6% in 2018). At the same time, the proportion of patients receiving NIA did not change over 15 years, 78.5% (2004) and 78.3% (2018).

In 2018, among the various classes of NIA, metformin (n=146,820; 69.3%) and sulfonylurea medications (SUM) (n=108,536; 51.3%) were most often used. In total 15,379 (7.3%) patients received dipeptidyl peptidase-4 inhibitors (DPP4i), 3,278 (1.6%) patients received SGT2i and 805 (0.4%) patients received GLP1RA; 2241 patients (1.1%) received preparations of other drug classes (e.g. alpha-glucosidase inhibitors, thiazolidinediones, glinides). The percentages were calculated based on the total number of patients with DM2.

Among the NIAs that were used without insulin therapy in 2018, metformin (n=128,659; 52.6%) and SUM (n=97,208; 39.7%) were most often prescribed. In 2018, there was an increase in the proportion of metformin used within NIA and a decrease within SUM compared to previous years, as well as more active use of incretin drugs (ID) within therapy, and the appearance of SGT2i usage (Fig. 2).

GLP1RA was used most often - as liraglutide (55.2%) and exenatide (43.7 %) - while the proportion of other GLP1RA drugs (e.g. dulaglutide, lixisenatide) accounted for only 1.1% (Fig. 3).

SGT2i drugs were prescribed as dapagliflozin in 49.2% of cases, as well as canagliflozin (25.6%) and empagliflozin (25.2 %), which were prescribed with approximately the same frequency (see Fig. 3).

Most often, these classes of drugs were administered to relatively young patients (the average age of patients receiving GLP1RA was 55.6±9.9 years, while those who received SGT2i were 59.9±9.6 years old), with a duration of diabetes lasting up to 10 years among those being overweight or obese (Table 1).

In NIA administration (i.e. no insulin), a single drug was used for therapy in 56.1% of patients. Within this group,

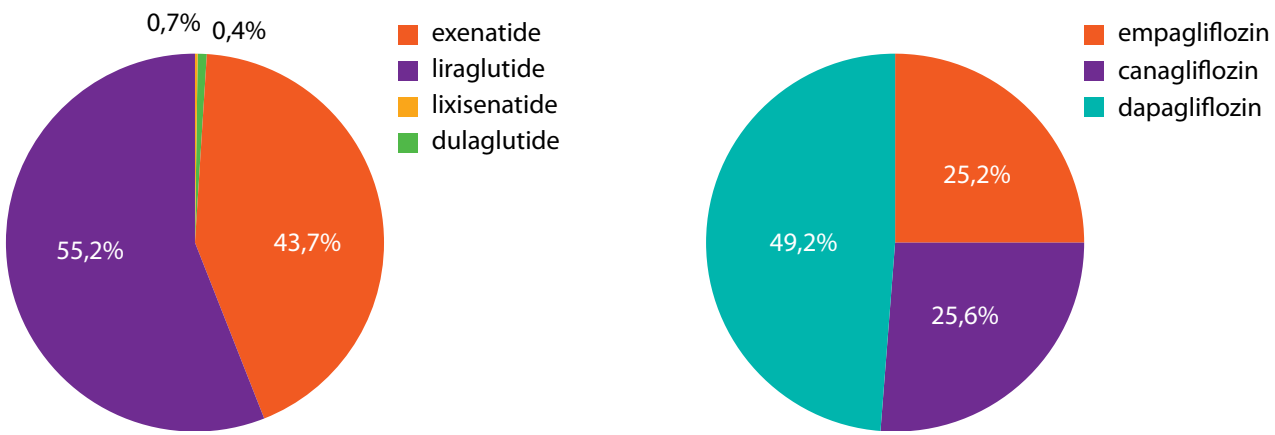

Fig. 3. The proportions of various drugs of the class of glucagon-like peptide-1 receptor agonists (n=835) and SGT2i (n=3476) within the treatment of patients with DM2 in 2018.

Table 1. Characteristics of patients receiving novel class antihyperglycemic drugs.

NIA name	Average age of DM diagnostics	Average duration of DM	Mean age	Average BMI
GLP1RA	47.6±9.3	8.6±5.4	55.6±9.9	38.5±7.9
SGT2I	52.8±9.5	7.7±5.9	59.9±9.6	33.8±6.4

Abbreviations: DM–diabetes mellitus; BMI–body mass index; NIA - noninsulin agents; GLP1RA - glucagon-like peptide-1 receptor agonists; SGT2i - type 2 sodium-glucose linked transporter inhibitors.

Table 2. Structure of the use of different classes of noninsulin agents in combination with insulin and without it.

Variants of NIA prescription		NIA (no insulin) n; % (CI)	NIA+insulin n; % (CI)
1 NIA	1 NIA in total	92 694; 56.1 (55.9-56.3)	10 330; 53.6 (52.9-54.3)
	Metformin	56 613; 61.2 (60.9-61.5)	9 438; 91.4 (90.9-91.9)
	SUM	33 347; 36.1 (35.8-36.4)	477; 4.6 (4.2-5.0)
	DPP4i	1 597; 1.7 (1.6-1.8)	187; 1.8 (1.5-2.1)
	SGT2i	282; 0.3 (0.3-0.3)	134; 1.3 (1.1-1.5)
	GLP1RA	65; 0.1 (0.1-0.1)	33; 0.3 (0.2-0.4)
	other drugs	790; 0.9 (0.8-1.0)	61; 0.6 (0.5-0.7)
Combination of 2 NIAs	2 NIAs in total	66 925; 40.5 (40.3-40.7)	8 132; 42.2 (41.5-42.9)
	Metformin+SUM	57 406; 85.8 (85.5-86.1)	6 669; 82.0; (81.2-82.8)
	Metformin+DPP4i	6 965; 10.4 (10.2-10.6)	765; 9.4 (8.8-10.0)
	SUM+DPP4i	749; 1.1 (1.0-1.2)	141; 1.7 (1.4-2.0)
	SUM+SGT2i	106; 0.2 (0.2-0.2)	38; 0.5 (0.3-0.7)
	Metformin+SGT2i	1 058; 1.6 (1.5-1.7)	325; 4.0 (3.6-4.4)
	Metformin+GLP1RA	312; 0.5 (0.4-0.6)	80; 1.0 (0.8-1.2)
	DPP4i+SGT2i	29; 0.04 (0-0.04)	7; 0.1 (0-0.2)
	other drugs	300; 0.4 (0.4-0.4)	107; 1.3 (1.1-1.5)
Combination of 3 NIAs	3 NIAs in total	5 570; 3.4 (3.3-3.5)	799; 4.1 (3.8-4.4)
	Metformin+SUM+SGT2i	833; 15.0 (14.1-15.9)	138; 17.3 (14.7-19.9)
	Metformin+SUM+DPP4i	3 997; 71.8 (70.6-73.0)	532; 66.6 (63.3-69.9)
	Metformin+SUM+GLP1RA	170; 3.1 (2.6-3.6)	35; 4.4 (3.0-5.8)
	Metformin+SUM+glinides	270; 4.8 (4.2-5.4)	32; 4.0 (2.6-5.4)
	Metformin+DPP4i+SGT2i	151; 2.7 (2.3-3.1)	27; 3.4 (2.1-4.7)
	other drugs	149; 2.7 (2.3-3.1)	35; 4.4 (3.0-5.8)
	Total	165 189 (100%)	19 261 (100%)

Notes: The percentage of prescriptions is calculated depending on the number of combined NIAs.

metformin was used most often, followed by SUM and DPP4i (Table 2). A combination of two NIAs was administered in 40.5% of cases; within this group, the most common drug combinations were metformin and SUM, and metformin and DPP4i, and, less often, metformin and SGT2i. The use of three or more NIAs was recorded in 3.4% of cases; within this group, the most frequently used combinations were metformin, SUM and DPP4i, as well as metformin, SUM and SGT2i. A combination of four drugs was used in rare cases (data not shown).

NIA administration, combined with insulin, shows significant differences compared to therapy without insulin, a single NIA is applied less often, and double or triple combinations of NIA are applied more often. A single NIA, combined with insulin, was used much more commonly with metformin and much less often with SUM. The frequency of using DPP4i as a single NIA does not differ significantly between patients, whether they were simultaneously using insulin therapy or not. At the same time, the frequency of use of SGT2i as a single NIA is significantly higher for patients receiving insulin therapy versus those who do not use insulin. SGT2i is used as the sole drug in combination with metformin with almost the same frequency as DPP4i. Dual combinations of metformin+SUM or metformin+DPP4i are administered more often for patients not using insulin therapy, and the combinations of SUM+DPP4i, SUM+SGT2i, metformin+SGT2i, metformin+GLP1RA and DPP4i+SGT2i are more often prescribed for patients

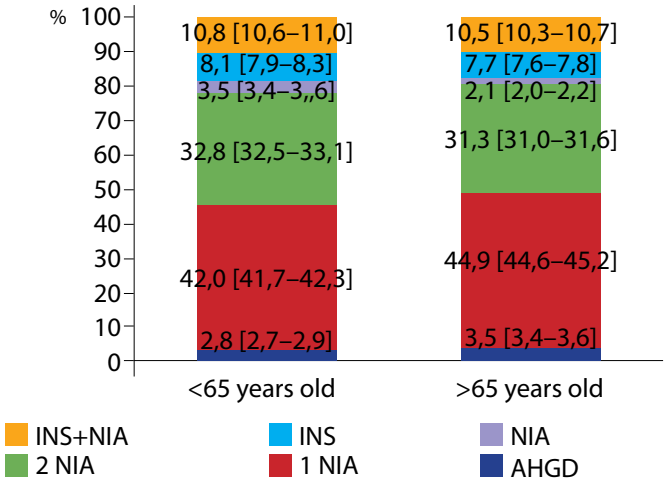

Fig. 4. The structure of antihyperglycemic therapy in DM2 patients in general and depending on age (2018). INS - insulin; NIA - noninsulin agents.

receiving insulin. Among the triple combinations of NIAs prescribed to patients receiving insulin, the combination of metformin+SUM+DPP4i is the least used. In isolated cases, the registry noted simultaneous use of insulin with four NIAs.

In patients within the older age group, AHGT structure exhibited a number of significant differences compared to younger patients (Fig. 4). Monotherapy was more often used for older patients, with a combination of 2 and 3 NIAs applied less often; AHGD was not used for a larger proportion of patients, and insulin therapy was also used less often. The percentage of use of NIA treatment was the same for the different age groups.

Over the past 15 years, metformin has become more frequently used both for young and older age groups, whereas for older patients with DM2, SUM were previously used more often. Nevertheless, a higher percentage of SUM application is still used for patients greater than 65 years of age compared to younger patients, both with and without insulin (Table 3). Drugs belonging to the novel classes of antihyperglycemic drugs (e.g. GLP1RA, SGT2i, DPP4i) are less frequently used by patients over 65 years compared to younger patients, regardless of whether insulin therapy is used simultaneously or not (Table 3).

In the first year following DM2 diagnosis, the administration of NIA prescriptions is similar to the average treatment strategy and corresponds to the trend that was observed over previous years. During the past 15 years, the percentage of metformin prescriptions increased significantly; in 2004, it was the drug of choice for commencing DM2 treatment in 18.8% of cases, and in 2018 the percentages of prescriptions given for this drug increased to 52.7% and 67.0% with and without insulin therapy, respectively. At the same time, in terms of disease onset, metformin without insulin therapy was prescribed more often regardless of age, while SUM was prescribed less frequently in general. Moreover, the likelihood of metformin being prescribed was significantly lower if insulin was given during the year of the original DM2 diagnosis. DPP4i and SGT2i were prescribed significantly more often for DM2 in general, regardless of age or use of insulin therapy in the year of established diagnosis, and glinides and GLP1RA were prescribed less commonly (Table 4).

In patients with CVD history, AHGT structure was different compared to those without CVD. The former used insulin therapy almost twice as often compared to those without CVD (29.6% versus 15.5%, respectively), and NIA monotherapy was applied less often (67.3% vs. 81.2%, respectively) (Table 5). In patients with CVD, therapy with a single NIA was less frequently used, as well as triple combination of NIAs. Double combinations of NIAs were used significantly more often than for patients without CVD.

Compared to the group without CVDs, patients with CVD received metformin, GLP1RA, DPP4i and SGT2i less often, while they received SUM more often (Table 6).

GLP1RA and SGT2i are currently highlighted among the NIA classes, which, in clinical studies, have shown a protective effect on the cardiovascular system. GLP1RA drugs in patients without CVD were used in 0.3% of cases, and in 0.1% of cases in patients with CVD. SGT2i use is similar: in patients without CVD, these drugs are used in 1.1% of cases, but in the case of CVD, that number decreases to 0.6% (Table 6).

Table 3. The structure of noninsulin agents for patients with DM2 depending on age, n (%).

	NIA (no insulin)			NIA+insulin		
	Total	**<65 years old**	**≥65 years old**	**Total**	**<65 years old**	**≥65 years old**
Metformin	128659/52.56	57989/57.87	70670/48.88	18161/56.29	7892/58.76	10269/54.53
SUM	97208/39.71	31694/31.63	65514/45.31	11328/35.11	3946/29.38	7382/39.20
DPP4i	13691/5.59	7636/7.62	6055/4.19	1688/5.23	925/6.89	763/4.05
SGT2i	2582/1.05	1756/1.75	826/0.57	696/2.16	471/3.50	225/1.19
Glinides	1949/0.80	571/0.57	1378/0.95	193/0.61	60/0.45	133/0.71
GLP1RA	624/0.25	531/0.53	93/0.06	181/0.56	133/0.99	48/0.26
Thiazolidinediones	49/0.02	21/0.02	28/0.02	10/0.03	1/0.01	9/0.05
Alpha-glucosidase inhibitors	36/0.01	12/0.01	24/0.02	4/0.01	2/0.02	2/0.01
Total (100%)	244 798	100 210	144 588	32 261	13 430	18 831

Abbreviations: NIA - noninsulin agents; SUM–sulfonylurea medications; DPP4i–dipeptidyl peptidase-4 inhibitors; GLP1RA - glucagon-like peptide-1 receptor agonists; SGT2i - type 2 sodium-glucose linked transporter inhibitors.

Table 4. The structure of noninsulin agents in patients with DM2 within the onset of disease.

AHGD type		DM2 in total*	NIA (without insulin)			NIA+insulin		
			Total	<65 years old	≥65 years old	Total	<65 years old	≥65 years old
Metformin	n	11 887	11 599	7112	4487	288	195	93
	%	66.5	67.0	66.9-	67.0	52.7	52.3	53.8
SUM	n	4042	3855	2200	1655	187	124	63
	%	22.6	22.3	20.7	24.	34.2	33.2	36.4
DPP4i	n	1442	1398	950	448	44	31	13
	%	8.1	8.1	8.9	6.7%	8.1	8.3	7.5
SGT2i	n	425	401	319	82	24	21	3
	%	2.4	2.3	3.0	1.2	4.4	5.6	1.7
Glinides	n	53	51	23	28	2	2	0
	%	0.3	0.3	0.2	0.4	0.4	0.5	0.0
GLP1RA	n	21	20	19	1	1	0	1
	%	0.1	0.1	0.2	0.0	0.2	0.0	0.6
Thiazolidinediones	n	0	0	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Alpha-glucosidase inhibitors	n	0	0	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total	n	17870	17324	10623	6701	546	373	173
	%	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Notes and abbreviations: The structure of NIA for patients with DM2 regarding onset of disease, regardless of AHGD and age. AHGD–antihyperglycemic drugs; NIA - noninsulin agents; SUM–sulfonylurea medications; DPP4i–dipeptidyl peptidase-4 inhibitors; GLP1RA - glucagon-like peptide-1 receptor agonists; SGT2i - type 2 sodium-glucose linked transporter inhibitors.

Table 5. The structure of antihyperglycemic therapy in DM2 patients with and without cardiovascular diseases.

AHGD type		CVD		No CVD		p
		n	% (CI)	n	% (CI)	
Diet		1356	3.1 (2.9-3.3)	5386	3.2 (3.1-3.3)	0.24
NIA (total)	29 481	67.3 (66.9-67.7)	136 387	81.2 (81.0-81.4)	<0.01	
	15 415	35.2 (34.8-35.6)	77 279	46.0 (45.8-46.2)	<0.01	
	13 029	29.7 (29.3-30.1)	54 482	32.4 (32.2-32.6)	<0.01	
	1037	2.4 (2.3-2.5)	4626	2.8 (2.7-2.9)	<0.01	
INS		5493	12.5 (12.2-12.8)	11 194	6.6 (6.5-6.7)	<0.01
INS+NIA		7483	17.1 (16.7-17.5)	15 012	8.9 (8.8-9.0)	<0.01
Total		43 813	100	167 979	100	

Notes and abbreviations: The total number of prescriptions for groups with and without CVDs was taken as 100%; the percentage for the NIA group was additionally calculated. AHGD–antihyperglycemic drugs; CVD–cardiovascular diseases; NIA - noninsulin agents; INS–insulin; CI–confidence interval.

DISCUSSION

Significant changes within the AHGT structure of DM2 patients began just over 10 years ago, after publication of the International Diabetes Federation's recommendations for prescribing metformin as a first-line drug [1]. In most countries, this led to a significant increase in metformin prescriptions and a decrease in SUM administration within the general NIA structure. By 2012 in the USA, metformin accounted for approximately 50% of AHGDs; 72.3% of DM2 patients not undergoing insulin therapy received this treatment, while the proportion of SUM administration decreased from 36.3% to 26.7% [2]. This was largely due to data on the cardioprotective effect of metformin becoming available, which was revealed in the UKPDS study [3], as well as to the proven feasibility of continuing metformin therapy after adding insulin to the treatment plan [4, 5]. In the Moscow region, the proportion of metformin administration to patients with DM2 increased four-fold from 2004 to 2018. In 2018, 69.3% of DM2 patients received metformin. This reflects global trends in the use of metformin as a first-line drug for treating DM2. Metformin was used more often

Table 6. The structure of noninsulin agents in DM patients with and without cardiovascular diseases.

	CVD		No CVD		p
	n	% (CI)	n	% (CI)	
Metformin	20282	45.5 (45.0-46.0)	108377	54.1 (53.9-54.3)	<0.01
SUM	21498	48.2 (47.7-48.7)	75710	37.8 (37.6-38.0)	<0.01
DPP4i	2021	4.5 (4.3-4.7)	11670	5.8 (5.7-5.9)	<0.01
SGT2i	288	0.6 (0.5-0.7)	2294	1.1 (1.1-1.1)	<0.01
Glinides	427	1.0 (0.9-1.1)	1522	0.8 (0.8-0.8)	<0.01
GLP1RA	60	0.1 (0.1-0.1)	564	0.3 (0.3-0.3)	<0.01
Thiazolidinediones	20	0.04 (0.04-0.04)	29	0.01 (0.01-0.01)	<0.01
Alpha-glucosidase inhibitors	8	0.02 (0.02-0.02)	28	0.01 (0.01-0.01)	0.53
Total	44604	100	200194	100	

Notes: CVDs–cardiovascular diseases; SUM–sulfonylurea medications; DPP4i - dipeptidyl peptidase-4 inhibitors; GLP1RA - glucagon-like peptide-1 receptor agonists; SGT2i- type 2 sodium-glucose linked transporter inhibitors; CI–confidence interval.

than other drugs by patients undergoing NIA monotherapy (61.5%). The analysis of a cohort of patients with DM2 in the Look AHEAD (Action for Health in Diabetes) study showed that 81.0% of patients continued to take metformin after being prescribed insulin [6]. In 2018, at the same time in the MR, only 56.3% of patients using insulin therapy received metformin. A limitation for the use of metformin may be related to decreased renal function. However, additional analyses of the reasons for non-prescription of metformin to more than half of patients using insulin therapy is needed, since adding metformin to insulin therapy could potentially improve glycemic control in these patients.

A large proportion of the currently available studies on DM2 treatment are devoted to new classes of AHGD. Thus, an analysis of the OLDW medical database, containing data from 1,657,610 patients with DM living in different geographic regions of the USA, showed that using DPP4i within therapy increased from 0.5% to 14.9% from 2006 to 2013 ($p<0.001$) [7]. In the UK in 2016, DPP4i was used more often than SUM as a second drug, in addition to metformin, with DPP4i being used in 40% of cases and SUM in only 34% [8]. The analysis of the Adelphi Real World Diabetes Disease Specific Programmes cohort of patients with DM2 from the USA and Europe showed that the proportion of patients using monotherapy with metformin began to decrease since 2012 and amounted to 36% in 2015 due to an increase in the proportion of AHGD combinations [9]. In addition, the total share of new drugs (i.e. DPP4i, GLP1RA, SGT2i) increased from 1% to 43% from 2000 to 2015. In the MR, the proportion of new drugs used has also steadily increased, reaching 9.3% by 2018. DPP4i was the most frequently used, followed by SGT2i. The proportion of GLP1RA used remained low; in the cohort analysed, GLP1RA was used primarily in patients of relatively young age (55.6±9.9 years), with a sufficiently long duration of DM (8.6±5.4 years) and a high BMI (38.5±7.9 kg/m^2). A similar analysis conducted among 403 patients with DM2 in Spain showed that GLP1RA was used more commonly in patients of slightly older age (58.3±10.4 years), with a slightly longer duration of DM (9.9±7 years) and lower BMI (36.2±5.5) as compared to our cohort [10]. Interestingly, in Spain, as in a number of other EU states, there is a law that financial compensation for the purchase of the drug GLP1RA is paid only to DM2 patients with a BMI of more than 30 kg/m^2 (majority of Spain) or more than 35 kg/m^2 (fewer areas). SGT2I was used in patients aged 59.9±9.6 years with an average DM duration of 7.7±5.9 years and am BMI of 33.8±6.4 kg/m^2. Incretins and SGT2i are included in most international and national algorithms for treating DM2 [11, 12], which determines increased prescriptions within AHGD administration.

The choice of AHGD and treatment regimen in DM2 onset can largely determine the prognosis of late complications and the risk of premature death. Despite recommendations for prescribing metformin as a first-line drug in disease onset, patients only 66.5% of patients in our sample used metformin in the first year after diagnosis. At that, 22.6% of patients received SUM at the onset of DM2 [11]. In 2010, among the cohort of 97,350 patients with newly diagnosed DM2 living in the USA, 75.2% used metformin as the starting drug [13]. However, within some countries, approximately 40% of AHGD prescriptions as a starting drug do not include biguanides. Fujihara et al. determined that the choice of metformin as a starting drug was associated with younger age, higher BMI and shorter DM2 duration, while prescription of SUM was correlated with older age, decreased glycemic control and lower BMI [14]. In the UK in 2016, in cases of DM2 onset DPP4i, GLP1RA or SGT2i was prescribed in 10%, 2% and 2% of cases, respectively. In the MR, new classes of AHGD were used less frequently at DM2 onset; incretins

were prescribed in 8.2% of cases, and SGT2i was used in 2.4% of cases. The decreased proportion of novel classes of drug prescriptions as initial treatment for patients with DM2 is likely due to the fact that many endocrinologists still consider these drugs to be rescue medication, prescribed when therapy with more traditional AHGD (i.e. metformin and SUM) does not lead to achievement of glycemic target values. Undoubtedly, the lower availability of novel drugs for prescription and their high cost relative to more traditional drugs are also significant limiting factors for their widespread use.

Older patients with DM2 need particular approaches for choice of AHGT, as caused by an increased risk of CVD in the case of hypoglycaemia, as well as a large spread of comorbid conditions which limit the choice of AHGD. Some drugs have age limits, which also affects the overall administration of AHGT in older DM2 patients. The previously existing upper age limit of 65 years significantly limited the possibility of prescribing metformin. Currently, the drug is not recommended for patients over 60 years of age who perform heavy physical work due to an increased risk of lactic acidosis. Therefore, this drug has the potential to be prescribed for most patients of older ages as long as there are no other contraindications. This allowed doctors in the MR to actively prescribe metformin (67.0% and 53.8% in combination with insulin) or continue treatment using this drug (48.9% and 54.5% in combination with insulin) to many patients over 65.

Due to the high safety profile and the small number of complicating factors in many countries, incretins are widely used in older people. DPP4i has no upper age limit for use. Analysis of AHGD prescriptions among Japanese patients aged 65 and older in 2013 showed that patients most often received drugs of the DPP4i group (49.1%), while in people under 65, this group of drugs was used somewhat less frequently (45.4% of cases) [15]. The high percentage of DPP4i use in Japanese patients can be explained not only by the general advantages of this class of drugs (e.g. low risk of hypoglycaemia, good tolerability), but also by a more pronounced hypoglycaemic effect in East Asians compared to other groups [16]. In our sample of patients, those over 65 received DPP4i less often (3.1%) than younger patients (4.6%). Among NIA use in 2013, SUM (37.8%) ranked second among Japanese people over 75 years old, although their share decreased significantly in this age group compared to 2005, in which it was > 55%. In 2013, SUM was prescribed less frequently to patients under 65 compared to the older age group (30%).

The rationale for the choice of a second drug to be administered to older DM2 patients receiving metformin may be due to the potential benefits of various combinations for reducing cardiovascular risks. Data from the Clinical Practice Research Datalink patient database in the UK showed that adding DPP4i to metformin was associated with a 48% reduction in the incidence of myocardial infarction, as well as a 39% reduction in the risk of total severe cardiovascular events compared to the addition of SUM to metformin. In this retrospective study, which included 10,484 patients, SUM was added to metformin for 42% of older patients, and DPP4i was added in 28% of cases [17].

Current research data on the effect of various NIAs on CVD, which are reflected in the national algorithms for DM2 treatment [11], could potentially influence administration of AHGD prescriptions, especially for patients with CVD history. Studies on the cardiovascular safety of DPP4i (alogliptin, saxagliptin and sitagliptin) demonstrated these drugs had no effect on major adverse cardiac events (MACE) [18–20]. In 2018, the CARMELINA study assessed cardiovascular safety and microvascular renal outcomes in DM2 patients with high vascular risk who received linagliptin therapy, compared to those who received placebo, as added to standard AHGT (CArdiovascular Safety & Renal Microvascular outcomE study with LINAgliptin). This was a multicenter, international, randomised, double-blind, placebo-controlled study conducted in parallel groups in 27 countries. The results of the CARMELINA study were presented at the 54th European Association for the Study of Diabetes (EASD) in Berlin, Germany. The study evaluated a three-component primary endpoint, which was defined as the time elapsed before the development of one of the outcomes, including: death due to a cardiovascular event, nonfatal infarction and nonfatal stroke. As a result of this study, which included 6979 patients with DM2, linagliptin, as well as other DPP4i drugs, demonstrated long-term cardiovascular safety in this category of patients without the need for dose adjustment and regardless of renal function. Linagliptin showed no increase in the risk of a three-component primary endpoint of HR 1.02 (95% CI 0.89, 1.17), with a p=0.0002 for non-inferiority, and p=0.7398* for superiority, as well as hospitalisation due to chronic heart failure (CHF), including for patients with a high risk of CHF of HR 0.90 (95% CI 0.74, 1.08), p=0.2635. In addition, linagliptin demonstrated long-term safety for kidneys, which was determined by the time of death due to kidney disease, the progression of kidney disease to the final stages or a steady decline in eGFR greater to or equal to 40% compared to placebo: HR 1.04 (95% CI 0.89–1.22), p=0.6164. Along with linagliptin intake, there was a decrease in albuminuria progression, HR 0.86 (95% CI 0.78–0.95), p=0.0034.

Studies of GLP1RA in terms of their effect(s) on cardiovascular events showed some discrepancies in the results. The effect of lixisenatide was neutral [21], and the use of liraglutide was associated with a decrease in major cardiovascular events. A decrease in MACE was also demonstrated in patients with DM2 who received empagliflozin and canagliflozin [22, 23]. The results obtained in the course of these studies resulted in the Ministry of Health of the Russian Federation's approval of a separate indication for the instruction concerning the use of empagliflozin and liraglutide to reduce the risk of cardiovascular death. This was reflected in revision 8 of the Algorithms of Specialised Medical Care for patients with DM, in which it is indicated that empagliflozin and liraglutide are priority drugs for DM2 patients with confirmed cardiovascular diseases in order to reduce potential cardiovascular mortality. In addition, empagliflozin is the drug of choice for DM2 patients with CHF to reduce the risk of hospitalisation.

Recommendations for predominant prescription of SGT2i as second-line drugs following metformin are also demonstrated in the updated consensus on the management of hyperglycemia in DM2, ADA/EASD, as presented at the EASD Congress that took place in October 2018 in Berlin. According to the consensus recommendations, SGT2i has been indicated - with empagliflozin followed by canagliflozin - as drugs exhibiting advantages in reducing the risk

of hospitalisation due to CHF, as well as increased time to adverse outcomes related to the kidneys, for patients with prevailing problem(s) of CHF or chronic kidney disease in addition to DM. Alternatively, GLP1RA can be prescribed; if CVD of atherosclerotic genesis is a predominant issue, then GLP1RA is indicated as an alternative to SGT2i [24].

Evidence from actual clinical practice, as summarised in the CVD REAL study, demonstrated that SGT2i therapy is associated with a 50% decrease in cardiovascular mortality [25]. An interim analysis of approximately 35,000 patients in the EMPRISE study showed that empagliflozin reduces the risk of hospitalisation for CHF by 44% compared to therapy with DP-P4i according to actual clinical practice [26]. Despite the clear advantages of GLP1RA and SGT2i in reducing cardiovascular outcomes in patients with CVD, within our cohort these classes of drugs were prescribed less often compared to patients lacking CVD. At the same time, the proportion of SUM in the treatment of DM2 patients with CVD remained quite high (48.2%), and increased in patients without CVD [27].

CONCLUSION

In the general AHGT administration for patients with DM2in the MR during 2004–2018, the highest proportion was represented by NIAs. Insulin therapy has become more commonly used, primarily due to its combination with NIA. A significant change in treatment occurred within NIA, as metformin was the most commonly used drug for both monotherapy and in combination with other drugs, which reflects global trends for prescribing metformin as a first-line drug for treatment of DM2. Moreover, only approximately half of DM2 patients using insulin therapy received metformin, even though its administration, in conjunction with insulin therapy, can potentially improve glycemic control.

The proportion of new drugs within AHGT use increased mainly due to DPP4i, followed by SGT2i. These drugs are more commonly prescribed to younger patients with DM duration of up to 10 years, and in overweight or obese patients. SGT2i was used more often in combination with insulin. Despite the advantages of GLP1RA and SGT2i in terms of reducing adverse cardiovascular outcomes, fewer patients with CVD used them compared to patients without CVD. In general, an insufficient share of drugs of novel classes within AHGT at DM2 onset may be due to a lower availability of preferential provision, their high cost, and the fact that this therapy is, in most cases, unnecessarily considered a rescue therapy.

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Contribution of authors. I.V. Misnikova created the concept and design of the article, analysed the literature, wrote the text and designed the drawings. Yu.A. Kovaleva analysed the registry data, wrote the text and designed the drawings. M.A. Isakov was involved in creating samples from the Federal Registry of Patients with DM, developed by the Endocrinology Research Centre, and provided technical support. A.V. Dreval edited the text.

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