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“Possibilities of early prevention of chronic kidney disease in patients with type 2 diabetes mellitus based on clinical and anamnestic data”

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Annotation
Purpose of the study :to study the possibilities of early prevention of CKD in patients with type 2 diabetes based on clinical and anamnestic data.
Materials and methods. Total durationThe study duration was 3 months. A retrospective analysis of 290 medical records of patients with type 2 diabetes hospitalized at the City Clinical Hospital named after. V.P. Demikhov for the period 2021-2022. Among the patients, 2 groups were divided: patients with type 2 diabetes with CKD and without concomitant severe comorbid pathology and patients with type 2 diabetes without CKD. All patients underwent standard clinical, laboratory and instrumental examination according to algorithms for the management of patients with type 2 diabetes.
Research results. According to the results of our study, the most significant non-modulated risk factors for the development of CKD were: age (>60 years) and length of diabetes (>10 years). Of all 290 patients, 173 (59.65%) were over 60 years of age and of these, 120 (41.38%) had CKD of varying severity. Of the 165 patients, 91 patients (55.15%) had more than 10 years of experience.
Significant modulated factors in the development of CKD were: hypertension, obesity, high fasting glycemia, taking PSM and BB insulin therapy. Especially patients with obesity and taking PSM and BB insulin therapy had a large number of other factors.
Conclusions. Based on the results of the study, despite the absence of severe comorbid pathology, there was a high prevalence of traditional risk factors (RFs) for the development of cardiovascular accidents, regardless of the length of diabetes mellitus, gender and age of the patients. The leading risk factors for the development of CKD were: age over 60 years, GN, hypertension, obesity. Treatment of PSM and BB with insulin therapy was also associated with renal dysfunction. However, metformin and NGLT-2 intake, on the contrary, were associated with a reduced risk of developing CKD. Factors such as gender, HbA1c level and taking drugs from incretin groups had a neutral effect.
Keywords: type 2 diabetes mellitus, chronic kidney disease, risk factors

Introduction. Diabetic nephropathy (DN) is one of the leading causes of chronic kidney disease (CKD) in patients with type 2 diabetes mellitus (T2DM). In many countries
Most diabetic patients starting renal replacement therapy now have type 2 rather than type 1 diabetes. The classic definition of diabetic nephropathy is a progressive increase in urinary albumin excretion combined with an increase in blood pressure, resulting in decreased glomerular function.
filtration and ultimately to end-stage renal disease (Box 1). The development of pathology in the kidneys in type 2 diabetes occurs in stages: from preclinical structural changes in kidney tissue in the first years of the disease to diffuse or nodular glomerulosclerosis after 15-20 years of diabetes, however, according to the results of recent global studies, there are some factors that enhance the development of DN . These two major medical problems are closely interrelated, since type 2 diabetes increases the risk of developing CKD, and the presence of CKD, in turn, aggravates the course of type 2 diabetes and affects the selection of therapy.

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Many studies over the past 10 years have emphasized the strong association between diabetic nephropathy and cardiovascular disease (Box 2). According to the latest meta-analyses, in type 2 diabetes without CKD, the risk of CVD increases 2-3 times [1], and in patients with type 2 diabetes with CKD, the risk of CVD increases 10 times [2]. According to the United Kingdom Prospective Diabetes Study (UKPDS), annual mortality rates of all deaths from CVD are 0.7% in people with type 2 diabetes with normoalbuminuria, 2.0% in people with type 2 diabetes with microalbuminuria, 3.5% in people with type 2 diabetes and 12.1% in patients with type 2 diabetes with elevated serum creatinine levels or on RRT [3].

Вставка 1. Клиническое определение диабетической нефропатии.

1) Прогрессирующее повышение экскреции альбумина с мочой.
2) Прогрессирующее повышение кровяного давления.
3) Возможное снижение скорости клубочковой фильтрации и терминальная стадия почечной недостаточности.
4) При наличии диабетической ретинопатии.
5) Сопровождается прогрессирующим повышением сердечно-сосудистого риска.

Identifying diabetic nephropathy as early as possible in the disease process currently offers the best chance of delaying or possibly preventing progression to terminal disease. Last yearsDue to advances in diabetes treatment and therapy, the prevalence of kidney disease among patients with diabetes has stabilized at about 35% [4], and the incidence of acute cardiovascular disease among patients with diabetes has decreased by more than 50% [5]. However, the absolute number of patients with diabetes is increasing, and the global prevalence is expected to be 7.7% by 2030 [6]. The looming burden of diabetes in the context of the obesity epidemic is likely to affect younger people developing kidney disease and its complications [7]. In this review, we describe the early prevention and management of patients with type 2 diabetes in CKD, highlight important aspects of clinical guidelines, and discuss the evidence supporting currentpractice [8,9].

Вставка 2: Сердечно-сосудистый риск и диабетическая нефропатия
1) Сердечно-сосудистый риск возрастает по мере прогрессирования нефропатии при сахарном диабете 2 типа.
2) Увеличивается в 2-3 раза у пациентов с микроальбуминурией по сравнению с пациентами с нормоальбуминурией.
3) Увеличивается в 10 раз при протеинурии по сравнению с пациентами с нормоальбуминурией.
4) Средняя продолжительность жизни на диализе составляет два года, а основной причиной смерти являются сердечно-сосудистые заболевания.

The above provided the basis for this study.

Purpose of the study :to study the possibilities of early prevention of CKD in patients with type 2 diabetes based on clinical and anamnestic data.

Materials and methods.A retrospective analysis of 290 medical records of patients with type 2 diabetes hospitalized at the City Clinical Hospital named after. V.P. Demikhov (Moscow) for the period 2021-2022. The total duration of the study was 3 months. Among the patients, 2 groups were divided: patients with type 2 diabetes with CKD and without concomitant severe comorbid pathology and patients with type 2 diabetes without CKD. All patients underwent standard clinical, laboratory and instrumental examination according to algorithms for the management of patients with type 2 diabetes. Laboratory parameters were assessed based on the level of glycated hemoglobin (HbA1c), fasting glycemia (FG), cholesterol (CH), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), TSH, GFR, BMI. The Jamovi program (version 2.3.21) was used for statistical analyses. To systematize the initial information and visualize the obtained data, we used Microsoft Office Excel 2013 tables.

Results and discussion. The average age of the studied patients was 62.6±11.5 [95% CI 61.3-64.0] years, the median BMI was 30.2 [26.5; 35.0] kg/m2. The average HbA1c level was 8.9 [7.6; 10.5], of which 90.34% of patients had HbA1c >7%. The median fasting blood glucose was 6.95 [5.7; 8.67] mmol/l. 68% of participants had dyslipidemia, and 74.83% had arterial hypertension (AH). Of all patients with type 2 diabetes: 30% received basal-bolus (BB) insulin therapy, 34.83% - long-acting insulin (LAI) and oral hypoglycemic drugs (ALADs), 62.07% - metformin, 27.93% - dipeptidyl peptidase-4 inhibitors (DPP-4), 11.72% - glucagon-like peptide-1 receptor agonists (arGLP-1), 12.07% - sulfonylureas (SMU) and 21.03% - sodium-glucose cotransporter-2 inhibitors (iNGLT-2).

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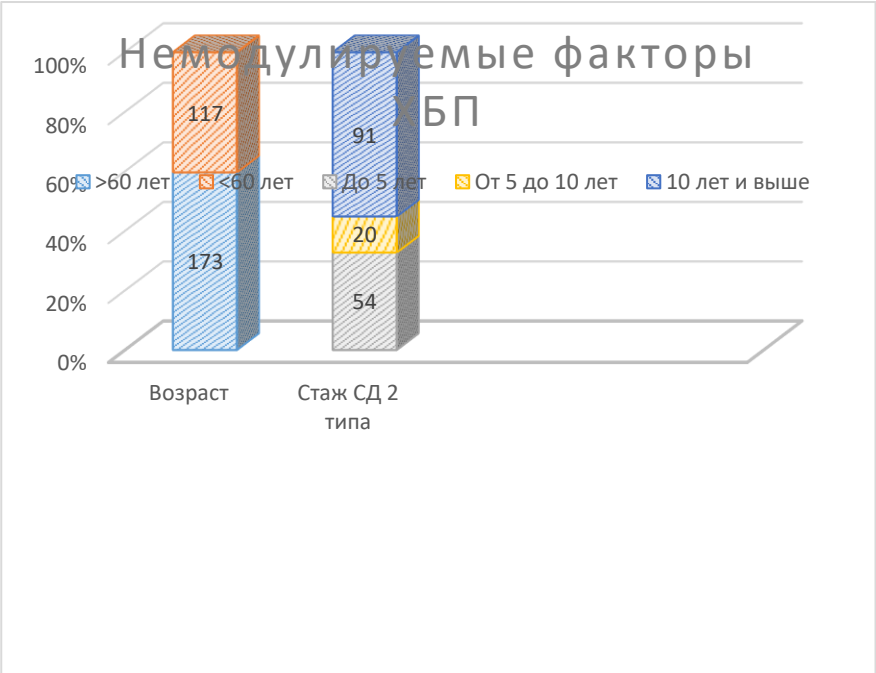
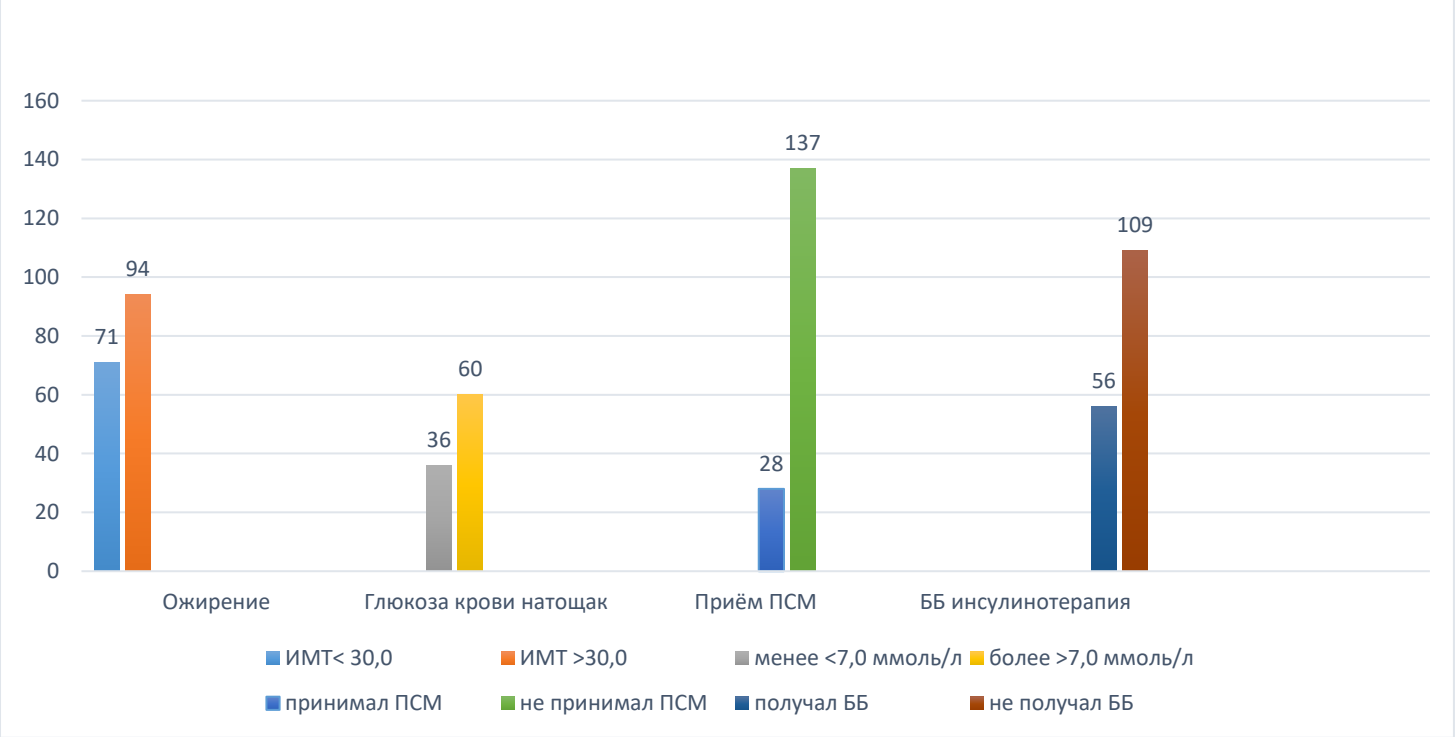


According to the results of our study, the most significant non-modulated risk factors for the development of CKD were: age (>60 years) and length of diabetes (>10 years). Of all 290 patients, 173 (59.65%) were over 60 years of age and of these, 120 (41.38%) had CKD of varying severity. Of the 165 patients, 91 patients (55.15%) had more than 10 years of experience.

Significant modulated factors in the development of CKD were: hypertension, obesity, high fasting glycemia, taking PSM and BB insulin therapy. Especially patients with obesity and taking PSM and BB insulin therapy had a large number of other factors.



Hypothyroidism, gender, HbA1c level, and use of DPP-4 inhibitors and GLP-1 antibodies were not associated with increased odds of developing CKD.

Taking metformin and SGLT-2 inhibitors were associated with a reduced risk of developing CKD, and taking drugs from these groups reduced plasma creatinine levels and accordingly increased GFR.

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Metformin is a first-line antidiabetic agent that can be safely administered to most patients with a baseline eGFR >30 mL/min/1.73 m2. Metformin has multiple mechanisms of action, including sensitization to insulin in peripheral tissues and reduction of hepatic gluconeogenesis. In the UKPDS study, patients treated with metformin had a reduction in mortality from diabetes, CVD and other causes compared with insulin and sulfonylureas [10]. Metformin is associated with a reduction in the incidence of end-stage renal disease and adverse cardiovascular outcomes in patients with DN compared with other glucose-lowering drugs [11]. Kwon et al reported lower all-cause mortality and progression of ESRD in patients with eGFR >30 mL/min/1.73 m2 who were prescribed metformin, without an increase in the incidence of all-cause lactic acidosis [12]. In separate studies, metformin was associated with a reduced risk of cardiovascular events and readmissions for heart failure in patients with DN [13,14].

In 2012, Swedish researchers conducted a study and demonstrated that metformin had a lower risk for the composite endpoint of acidosis, serious infection, and all-cause mortality compared with insulin and other oral antidiabetic agents in a subgroup of patients with an eGFR of 45–45%. 60 ml/min/1.73 m2. According to this, scientists from Sweden and the USA recommend continuing metformin in patients with eGFR ≥45 ml/min/1.73 m2, carefully titrating the dose or halving the dose if eGFR 30–44 ml/min/1.73 m2 and discontinuing use metformin with eGFR <30 ml/min/1.73 m2.

Избранные обсервационные исследования, сообщающие о риске ацидоза у принимающих метформин пациентов со сниженной функцией почек

Автор	Год публикации	Страна	N	Возраст	ОР (95% ДИ) исхода ацидоза	Основные результаты
Экстрем *и др.* [31]	2012	Шведский национальный регистр диабета (Швеция)	51 675	В среднем 65,3 года	0,85 (от 0,74 до 0,97) (рСКФ 45–60 мл/мин/1,73 м ^{2}); 0,98 (от 0,79 до 1,21) (рСКФ 30–45 мл/мин/1,73 м ^{2})	По сравнению с другими пероральными сахароснижающими препаратами и инсулином применение метформина ассоциировалось со снижением риска ацидоза и серьезных инфекций, а также смертности от всех причин у пациентов с рСКФ 45–60 мл/мин/1,73 м ^{2}. Использование метформина не было связано с повышенным риском ацидоза и серьезной инфекции, а также смертности от всех причин у пациентов с рСКФ 30–45 мл/мин/1,73 м ^{2}.
Лазарус *и др.* [29]	2018	Система здравоохранения Гейзингера (США)	75 413	В среднем 60,4 года	1,16 (от 0,95 до 1,41) (рСКФ 45–59 мл/мин/1,73 м ^{2}); 1,09 (от 0,83 до 1,44) (рСКФ 30–44 мл/мин/1,73 м ^{2}); 2,07 (от 1,33 до 3,22) (рСКФ <30 мл/мин/1,73 м ^{2})	Использование метформина не было связано с развитием ацидоза у пациентов с рСКФ >30 мл/мин/1,73 м ^{2}. Применение метформина ассоциировалось с учащением случаев ацидоза у пациентов с рСКФ <30 мл/мин/1,73 м ^{2}.
Чу *и др.* [30]	2020	Национальное управление здравоохранения ветеранов, Medicare, Medicaid, Национальный индекс смертности (США)	49 204	Медиана 70 лет	1,21 (от 0,99 до 1,50) (рСКФ <60 мл/мин/1,73 м ^{2})	Среди пациентов, у которых развилась сниженная функция почек, частота госпитализаций по поводу лактоацидоза статистически не отличалась между теми, кто принимал метформин, и теми, кто принимал производные сульфонилмочевины.

- **рСКФ, расчетная скорость клубочковой фильтрации.**

Drugs from the SGLT-2 group have significant evidence supporting a reduction in the risk of developing end-stage renal failure, death from cardiovascular diseases and hospitalizations for heart failure. The cardiovascular and renal benefits of SGLT-2 are independent of the antihyperglycemic effect, which is attenuated by lower eGFR. iNGLT-2 improves glomerular hemodynamics, reduces oxidative stress and optimizes tissue energy.

Large cardiovascular safety studies of SGLT-2 have demonstrated favorable secondary renal outcomes in patients with type 2 diabetes and variable baseline renal function. Empagliflozin, Cardiovascular Outcomes

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and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) included patients with eGFR ≥30 ml/min/1.73 m2 and demonstrated a 46% reduction in the risk of a combined secondary renal outcome when serum creatinine doubled and reduced the number of patients with renal death [15]. In the retrospective EMPA-REG OUTCOME analysis, empagliflozin demonstrated improvement in renal function regardless of baseline eGFR or degree of albuminuria [16]. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS) enrolled patients with eGFR ≥30 mL/min/1.73 m2 and reported a 40% reduction in the combined secondary renal outcome. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes (DECLARE-TIMI 58) included patients with eGFR ≥60 ml/min/1.73 m2 and reported a 47% risk reduction for the combined secondary renal outcome [17]. . However, in the Ertugliflozin in Type 2 Diabetes Cardiovascular Outcomes Study (VERTIS CV), the reduction in the secondary composite renal outcome was not statistically significant. Both EMPA-REG OUTCOME and CANVAS demonstrated significant reductions in the primary outcome of cardiovascular safety, and DECLARE-TIMI 58 and VERTIS CV achieved noninferiority in cardiovascular safety. These data support the use of NGLT-2 drugs in patients with DN.

The Canagliflozin and Renal Outcomes in Diabetes and Type 2 Nephropathy (CREDENCE) trial was a seminal trial of SGLT2 in DN with a specific composite primary renal outcome [18]. The CREDENCE study included patients with type 2 diabetes, eGFR 30-90 ml/min/1.73 m2 and urine albumin-to-creatinine ratio 300-5000 mg/g. The prespecified strategy aimed to include at least 60% of patients with eGFR <60 mL/min/1.73 m2, a population at higher risk of developing end-stage CKD than previously studied. In this double-blind, placebo-controlled study, canagliflozin reduced the primary composite renal endpoint by 31%, with a notable benefit on secondary heart failure. The trial was terminated early after 2.6 years due to overwhelming efficacy. CREDENCE demonstrated renal benefits regardless of baseline HbA1c, degree of HbA1c reduction, and CKD stage, leading to the first indication for SGLT2 inhibitors in the US in 2019.

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Избранные клинические испытания SGLT2i и SGLT1/2i, эмпаглифлозина, канаглифлозина, дапаглифлозина, эртуглифлозина и сотаглифлозина

SGLT2i или SGLT1/2i	Пробный	вмешательство	Н	Средняя исходная рСКФ (мл/мин/1,73 м ^{2})	Медиана наблюдения (лет)	Первичный составной результат (ОР (95% ДИ))	Почечный исход (ОР (95% ДИ))
Эмпаглифлозин	РЕЗУЛЬТАТ EMPA-REG	Эмпаглифлозин 10 мг 1 раз в сутки, эмпаглифлозин 25 мг 1 раз в сутки или плацебо	7020	74	3.1	Смерть от сердечно-сосудистых причин, инфаркт миокарда без летального исхода (за исключением немого инфаркта миокарда) или инсульт без летального исхода (0,86 (от 0,74 до 0,99))	Удвоение уровня креатинина в сыворотке крови при рСКФ ≤45 мл/мин/1,73 м ^{2}, заместительная почечная терапия или почечная смерть (0,54 (от 0,40 до 0,75))
Канаглифлозин	ХОЛСТ	Канаглифлозин 100 мг 1 раз в сутки с возможным увеличением до 300 мг 1 раз в сутки или плацебо	10 142	76,5	2,4	Смерть от сердечно-сосудистых причин, инфаркт миокарда без летального исхода или инсульт без летального исхода (0,86 (от 0,75 до 0,97))	Снижение рСКФ ≥40%, заместительная почечная терапия (трансплантация, хронический диализ или устойчивая рСКФ <15 мл/мин/1,73 м ^{2}) или почечная смерть (0,53 (от 0,33 до 0,84))
	КРИДЕНС	Канаглифлозин 100 мг один раз в день или плацебо	4401	56,2	2,62	ТХПН (диализ, трансплантация или устойчивая рСКФ <15 мл/мин/1,73 м ^{2}), удвоение уровня креатинина в сыворотке или смерть от почечных или сердечно-сосудистых причин (0,70 (от 0,59 до 0,82))	См. первичный составной результат.

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Дапаглифлозин	ДЕКЛАР-ТИМИ 58	Дапаглифлозин 10 мг один раз в день или плацебо	17 160	85,1	4.2	Сердечно-сосудистая смерть, инфаркт миокарда или ишемический инсульт (0,93 (от 0,84 до 1,03))	Снижение рСКФ на ≥40% до <60 мл/мин/1,73 м ^{2}, ТХПН (диализ ≥90 дней, трансплантация или устойчивая рСКФ 15 мл/мин/1,73 м ^{2}) или почечная или сердечно-сосудистая смерть (0,53 (от 0,43 до 0,66))
	ДАПА-ХЗП	Дапаглифлозин 10 мг один раз в день или плацебо	4304	43.1	2,4	Устойчивое снижение рСКФ не менее чем на 50%, тХПН или смерть от почечных или сердечно-сосудистых причин (0,61 (от 0,51 до 0,72))	См. первичный составной результат.
Эртуглифлозин	ВЕРТИС РЕЗЮМЕ	Эртуглифлозин 5 мг 1 раз в сутки, эртуглифлозин 15 мг 1 раз в сутки или плацебо	8246	76,1	3.0	Смерть от сердечно-сосудистых причин, инфаркт миокарда без летального исхода или инсульт без летального исхода (0,97 (от 0,85 до 1,11))	Смерть от почечных причин, заместительная почечная терапия или удвоение уровня креатинина в сыворотке (0,81 (от 0,63 до 1,04))
Сотаглифлозин	ЗАБИЛ	Сотаглифлозин 200 мг 1 раз в сутки с возможным увеличением до 400 мг 1 раз в сутки или плацебо	10 584	44,4	1,3	Общее количество смертей от сердечно-сосудистых причин, госпитализаций по поводу сердечной недостаточности и неотложных посещений по поводу сердечной недостаточности (0,74 (от 0,63 до 0,88))	Устойчивое снижение рСКФ на ≥50% от исходного уровня в течение ≥30 дней, длительный диализ, трансплантация почки или устойчивое снижение рСКФ <15 мл/мин/1,73 м ^{2} в течение ≥30 дней (0,71 (от 0,46 до 1,08))

- **CANVAS, Канаглифлозин и сердечно-сосудистые и почечные нарушения при диабете 2 типа; КРИДЕНС, Канаглифлозин и почечные исходы при диабете 2 типа и нефропатии; DAPA-CKD, дапаглифлозин у пациентов с хронической болезнью почек; DECLARE-TIMI 58, Дапаглифлозин и сердечно-сосудистые исходы при диабете 2 типа; рСКФ — расчетная скорость клубочковой фильтрации; РЕЗУЛЬТАТ EMPA-REG, эмпаглифлозин, сердечно-сосудистые исходы и смертность при диабете 2 типа; ESKD, терминальная стадия болезни почек; SCORED, сотаглифлозин у пациентов с диабетом и хронической болезнью почек; SGLT2i, ингибиторы натрий-глюкозного котранспортера-2; SGLT1/2i, комбинированные ингибиторы натрий-глюкозного котранспортера-1 и -2; VERTIS CV, Сердечно-сосудистые исходы с Эртуглифлозином при диабете 2 типа.**

Conclusions. Based on the results of the study, despite the absence of severe comorbid pathology, there was a high prevalence of traditional risk factors (RFs) for the development of cardiovascular accidents, regardless of the length of diabetes mellitus, gender and age of the patients. The leading risk factors for the development of CKD were: age over 60 years, GN, hypertension, obesity. Treatment of PSM and BB with insulin therapy was also associated with renal dysfunction. However, metformin and NGLT-2 intake, on the contrary, were associated with a reduced risk of developing CKD. Factors such as gender, HbA1c level and taking drugs from incretin groups had a neutral effect.

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