INFLUENCE OF TYPE 2 SODIUM-GLUCOSE CO-TRANSPORTER INHIBITORS (DAPAGLIFLOZIN) ON THE INDICATORS OF TOTAL MORTALITY IN PATIENTS WITH TYPE 2 DIABETES (CARDIA-MOS STUDY, MOSCOW)

© Mikhail B. Antsiferov[1], Nikolay A. Demidov[2]*, Maria A. Balberova[3], Olga V. Lobanova[2], Irina G. Mudrikova[4], Dinara G. Gusenbekova[5]

[1]Endocrinological Dispensary, Moscow
[2]Shcherbinsk City Hospital, Moscow
[3]Kuznechiki Hospital, Moscow
[4]Hospital of Moscovskiy city, Moscow
[5]City Polyclinic No. 219, Moscow

BACKGROUND: The widespread use in clinical practice of drugs with cardio- and nephroprotective properties, in particular, sodium-glucose cotransporter type 2 inhibitors (SGLT2i), is based on the results of large-scale international randomized trials. Meanwhile, there are no data demonstrating the possibility of the influence of these drugs on mortality rates in real clinical practice in Russian patients. To study this issue, a CARDIA-MOS study was conducted on a population of patients with type 2 diabetes (T2DM) in Moscow.

AIM: To study the effect of SGLT2i on the total mortality of patients with T2DM in Moscow.

MATERIALS AND METHODS: To assess the frequency of different outcomes, two samples of patients were formed according to predetermined criteria: 1) patients who started therapy with SGLT2i (dapagliflozin) in 2017; 2) a control group of patients corresponding to the main group in terms of key indicators: age, duration of T2DM, presence of cardiovascular diseases, use of insulin therapy, HbA_{1c} level.

RESULTS: Firstly, an analysis of the data of 499 patients who started treatment with dapagliflozin in 2017, as well as 499 patients in the control group (n = 998) was made. The baseline characteristics of the patients were generally comparable. Pre-study SBP and HbA_{1c} were worse in the dapagliflozin group. The use of dapagliflozin was associated with a 39% reduction in the relative risk of death from all causes (RR 0.614, 95% CI 0.417–0.903, p = 0.013), led to a decrease in HbA_{1c} levels by 0.8% (from 8.5 to 7.7%, p<0.001) for 48 months. observations. The safety profile of dapagliflozin was comparable to that of the control group

CONCLUSION: The use of dapagliflozin in the treatment of patients with T2DM can reduce overall mortality and improve glycemic control.

KEYWORDS: type 2 diabetes mellitus; dapagliflozin; SGLT2i; relative risk of death; CVD; CHF; CKD

ВЛИЯНИЕ ИНГИБИТОРОВ НАТРИЙ-ГЛЮКОЗНОГО КОТРАНСПОРТЕРА 2 ТИПА ДАПАГЛИФЛОЗИНА НА ПОКАЗАТЕЛИ ОБЩЕЙ СМЕРТНОСТИ БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ 2 ТИПА (ИССЛЕДОВАНИЕ CARDIA-MOS, МОСКВА)

© М.Б. Анциферов[1], Н.А. Демидов[2]*, М.А. Балберова[3], О.В. Лобанова[2], И.Г. Мудрикова[4], Д.Г. Гусенбекова[5]

[1]Эндокринологический диспансер, Москва
[2]Щербинская городская больница, Москва
[3]Больница «Кузнечики», Москва
[4]Городская больница г. Московский, Москва
[5]Городская поликлиника №219, Москва

ОБОСНОВАНИЕ. Широкое применение в клинической практике препаратов с кардио- и нефропротективными свойствами, в частности ингибиторов натрий-глюкозного котранспортера 2 типа (иНГЛТ-2), базируется на результатах крупномасштабных международных рандомизированных исследований. Между тем отсутствуют данные, демонстрирующие возможности влияния данных препаратов на показатели смертности в реальной клинической практике у российских пациентов. Для изучения данного вопроса было проведено исследование CARDIA-MOS на популяции больных сахарным диабетом 2 типа (СД2) г. Москвы.

ЦЕЛЬ. Изучить влияние иНГЛТ-2 на показатели общей смертности больных СД2 Москвы.

МАТЕРИАЛЫ И МЕТОДЫ. Для оценки частоты различных исходов были сформированы две выборки пациентов по заранее определенным критериям: 1) пациенты, начавшие терапию иНГЛТ-2 (дапаглифлозином) в 2017 г. и получавшие его в течение 48 мес; 2) контрольная группа пациентов (не получавших иНГЛТ-2), соответствующая основной группе по ключевым показателям: возраст, длительность СД, наличие сердечно-сосудистых заболеваний, использование инсулинотерапии, уровень гликированного гемоглобина (HbA_{1c}).

Received: 06.06.2022. Accepted: 15.09.2022

РЕЗУЛЬТАТЫ. На 1-м этапе работы был проведен анализ данных 499 пациентов, начавших лечение дапаглифлозином в 2017 г., а также 499 пациентов контрольной группы (n=998). Исходные характеристики пациентов в основном были сопоставимыми. Показатели систолического артериального давления и уровня HbA_{1c} до исследования были хуже в группе дапаглифлозина. Применение дапаглифлозина ассоциировалось со снижением относительного риска (ОР) смерти от всех причин на 39% (ОР 0,614; 95% ДИ 0,417–0,903; p=0,013), приводило к снижению уровня HbA_{1c} на 0,8% (с 8,5 до 7,7%, p<0,001) на протяжении 48 мес наблюдения.

ЗАКЛЮЧЕНИЕ. Использование дапаглифлозина в терапии больных СД2 позволяет снизить показатели общей смертности и улучшить показатели гликемического контроля.

КЛЮЧЕВЫЕ СЛОВА: сахарный диабет 2 типа; дапаглифлозин; иНГЛТ-2; относительный риск смерти; СС3; ХСН; ХБП

BACKGROUND

International Diabetes Federation (IDF) estimates that by 2045, the global incidence of diabetes will rise by 50% [1]. Most of the diabetes cases are type 2 (T2D). Even though many different antihyperglycemic drugs are in use nowadays, T2D is still associated with a high risk of delayed complications and mortality attributable to cardiovascular diseases [2].

T2D therapy includes lifestyle change, pharma therapy in order to prevent complications, and continuous glycaemic control – primarily, control of glycated haemoglobin (HbA1c). The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend setting individual HbA1c targets based on the patient's condition, risks involved in the therapy, and concomitant diseases. As per the ADA/EASD consensus statement [3, 4], the HbA1c target suitable for most adult patients is $\leq$7.0%. The Russian 2021 guidelines likewise emphasise the importance of setting individual HbA1c targets as part of diagnosis and state that HbA1c$\leq$7.0% is a target suitable for most adult patients [5].

However, achieving and maintaining a target HbA1c in T2D patients cannot reliably protect them from the onset and development of cardiovascular diseases, chronic heart failure (CHF) and chronic kidney disease (CKD) [6–10]. Data held in the Federal Patient Registry show that CKD is the cause of death in about 30% of T2D patients [6]. Approximately one-third of T2D patients have CKD, and this contributes to higher rates of hospitalisations/deaths, to higher demand for kidney dialysis procedures, and to an excessive workload for the healthcare system in general [7].

Contemporary methods of diabetes therapy require an analysis of any co-morbidity. A special focus is made on antihyperglycemic drugs that also have cardioprotective/renoprotective effects. New classes of diabetes treatment drugs have been developed and successfully used, such as sodium-glucose cotransporter type 2 inhibitors (SGLT2i). This group of drugs was the first to show a reduction in risk of cardiovascular accidents and CHF hospitalisation and thus earned special recognition in the T2D therapy [8–10]. The key feature of SGLT2i use is a reduction of the rate of major cardiovascular accidents (cardiovascular lethality, non-lethal myocardial infarctions (MIs), or acute cerebral blood flow failures), as well as the rate of heart failure hospitalisations [11]. These drugs reduce the demand for kidney dialysis procedures, the rate of kidney transplantation and kidney-associated mortality; they also reduce the rate of other adverse renal outcomes [12]. On the one hand, there is a solid body of evidence conclusively demonstrating cardioprotective/renoprotective effects of SGLT2i drugs. On the other, one ought to verify the reproducibility of these effects in real clinical practice with a Russian population of patients and to evaluate the contribution of these drugs to survival of T2D patients; this was the object of the CARDIA-MOS study. At Phase 1, we added dapagliflozin to the existing T2D therapy and examined the effects of this drug on total mortality.

Dapagliflozin is a selective and manageable SGLT2i drug [13]. In randomised controlled studies it has proven highly efficient and safe, including in terms of cardiorenal outcomes [14–17].

OBJECTIVE

To study the effect of SGLT2i on total mortality in T2D patients in Moscow.

MATERIALS AND METHODS

Study sites, start and end dates

Site. Moscow Endocrinological Dispensary.

Start and end dates. Our analysis covered retrospective data from T2D patients' primary medical records for the period from 1 January 2017 to 31 December 2020.

Observed population(s)

To evaluate the rate of different outcomes in T2D patients, two sample groups were created: a target (dapagliflozin) group and a control group.

The target (dapagliflozin) group included patients meeting the following criteria.

Inclusion criteria:

- T2D
- Age 50 to 75
- Prior cardiovascular diseases or one or more factors of risk of their onset (such as arterial hypertension or dyslipidemia)
- No prior treatment with glucagon-like peptide-1 receptor agonists (GLP-1-RA) or SGLT2i drugs
- SGLT2i (dapagliflozin) therapy start in 2017.

Exclusion criteria:

- Medical records lack information on the patient's condition throughout the entire 48-month-long observation period unless the patient's death within that period has been confirmed
- Medical records show that dapagliflozin treatment was suspended for a duration of over 3 months within the observation period
- Any GLP-1-RA treatment within the observation period (up to 48 months following the start of SGLT2i treatment).

The control group included patients meeting the following criteria.

- T2D
- Age 50 to 75
- Prior cardiovascular diseases or one or more factors of risk of their onset (such as arterial hypertension or dyslipidemia)
- No prior treatment with glucagon-like peptide-1 receptor agonists (GLP-1-RA) or SGLT2i drugs.

Exclusion criteria:

- Medical records lack information on the patient's condition throughout the entire 48-month-long observation period unless the patient's death within that period has been confirmed.

Population(s) sampling method

The target (dapagliflozin) group was created by selecting T2D patients' medical records from the Federal Diabetes Patient Registry (Moscow Division) where dapagliflozin therapy was started within the period from 1 January 2017 to 31 December 2017, subject to the inclusion and exclusion criteria (n=703). Since primary medical records contain much more detailed information than the Federal Diabetes Patient Registry does, we ran an additional verification of matching the inclusion and exclusion criteria for this cohort of patients (n=703) using data held in their EMIAS electronic records. Patients found to be matching the inclusion criteria and not to be falling under the exclusion ones on the basis of their primary medical records (n=499) were included in the target group.

In order to create a control group, our target group patients were subdivided into 36 categories based on their sex, age (under 60, 60 to 70, over 70), prior cardiovascular diseases, and the use of insulin therapy.

The control group of patients was created by random selection of T2D patients' medical records from the Federal Diabetes Patient Registry (Moscow Division) where these were found to be matching the inclusion criteria and not to be falling under the exclusion ones (n=4317). Then, 36 subgroups (n=2736) were created within this sample, each matching the key characteristics (sex, age, T2D duration, body mass index (BMI), HbA1c level, prior cardiovascular diseases, and the use of insulin therapy) of a subgroup within the target (dapagliflozin) group. Finally, using a random number generator, 449 patients were selected out of this sample and included in the control group.

Study design

A retrospective two-sample comparative study with a 48-month-long observation period.

Statistical analysis

The values of quantitative variables are expressed as medians and standard deviations; the values of categorical variables are expressed as rates and percentage shares (%). Survival rate analysis was carried out using the Cox proportional hazard regression model. The results of this regression analysis are expressed as risk ratios with a 95% confidence interval. The total mortality rate was used as the primary metric of efficacy; additional metrics included the rates of mortality caused by chronic heart failure, cardiovascular diseases, COVID-19, or COVID-19 combined with cardiovascular disease, and further subgroup analyses depending on baseline characteristics.

Ethical review

The study protocol was approved by Moscow Endocrinological Dispensary's internal Ethics Committee on 28 June 2022 (official session record unnumbered).

RESULTS

The baseline characteristics of patients in the two groups were commensurable on key parameters (Table 1). After the observation period, significant differences in several characteristics (HbA1c level, systolic blood pressure, metformin use rate) were found between the two groups. Blood pressure and HbA1c level values in the dapagliflozin group were worse than in the control group. The dapagliflozin group patients used metformin less frequently (Table 1).

Mortality rates

The results show a significant (by 39%) reduction of relative risk of death from all causes in the dapagliflozin group of patients (Figure 1): relative risk 0.614; 95% CI 0.417–0.903; p=0.013. The rate of this ultimate outcome over the 4 years of observation was 8.4% in the dapagliflozin group vs. 13.4% in the control group; the number needed to treat (NNT) was 20 (Figure 1).

Even more significant was the difference in the rates of CHF mortality: over the observation period, the relative risk of death attributable to CHF in the dapagliflozin group was 77% lower (Figure 2): relative risk 0.230; 95% CI 0.077–0.683; p=0.008. Thus, the CHF mortality rate in the dapagliflozin group was 0.7% vs. 3.4% in the control group over a comparable observation period (Figure 2).

Moreover, the dapagliflozin group showed a trend towards lower risk of death caused by cardiovascular diseases or COVID-19: relative risk of death caused by cardiovascular diseases was 0.431; 95% CI 0.177–1.048; p=0.063, the same for COVID-19: 0.667; 95% CI 0.329–1.351; p=0.261. A significant (by 44%) reduction of the rate of combined ultimate outcome (cardiovascular diseases deaths + COVID-19 deaths) was observed in the dapagliflozin group: relative risk 0.56; 95% CI 0.323–0.969; p=0.038; cardiovascular diseases + COVID-19 mortality was 2.6% in the dapagliflozin group vs. 3.8% in the control group.

Subgroup analyses depending on baseline characteristics showed that patients who were receiving insulin therapy prior to this study had a tendency towards lower mortality from all causes within the dapagliflozin group: relative risk 0.62; 95% CI 0.37–1.10; p=0.064. Besides, a reduction (by 46% vs. female patients in the control group) of the risk of mortality from all causes was observed in female patients in the dapagliflozin group: relative risk 0.54; 95% CI 0.30–0.98; p=0.042.

A vital factor affecting the patients' survival was whether they had any cardiovascular diseases prior to inclusion in the study. Patients having no confirmed cardiovascular diseases prior to inclusion in the study had a risk of death 39% lower than T2D patients with prior cardiovascular diseases (relative risk 0.616; 95% CI 0.419–0.905; p=0.014) (Figure 3).

Dapagliflozin therapy in the subgroup of patients with confirmed cardiovascular diseases led to a reduction of the relative risk of death from all causes by 47%, whereas the reduction of relative risk of death from all causes in the cohort without confirmed cardiovascular diseases amounted to 23% only (Figure 4).

Changes in the clinical and laboratory-measured parameters

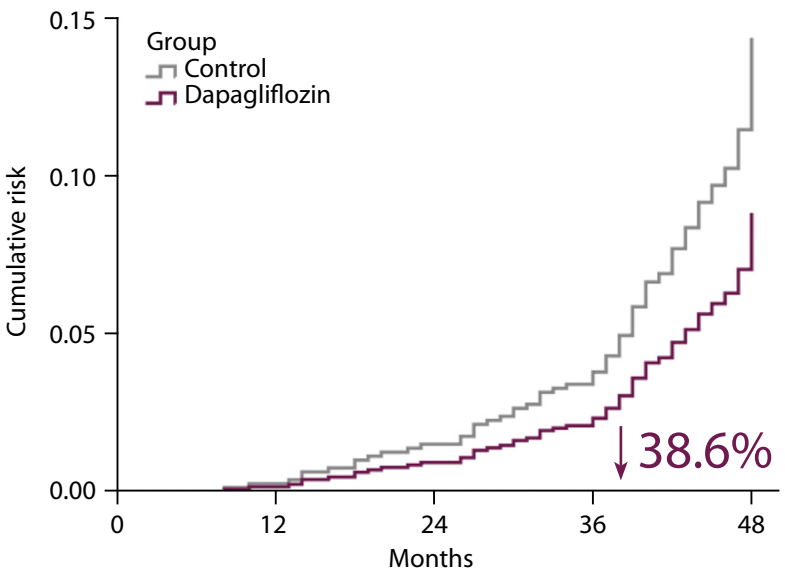
in addition to mortality metrics, we evaluated changes in several clinical and laboratory-measured parameters. Starting from the 3rd month of observation, the dapagliflozin group showed a significant reduction of HbA1c level, despite higher baseline values (Figure 5).

Similar positive tendencies were observed in body weight and BMI values. Thus, 48 months following the start of the observation, body weight in the dapagliflozin group was 92.8 kg vs. 95.3 kg in the control group (p=0.022). It ought to be noted that the baseline value of this parameter was higher in the dapagliflozin group vs. the control group (baseline body weight

Table 1. Patients' baseline characteristics

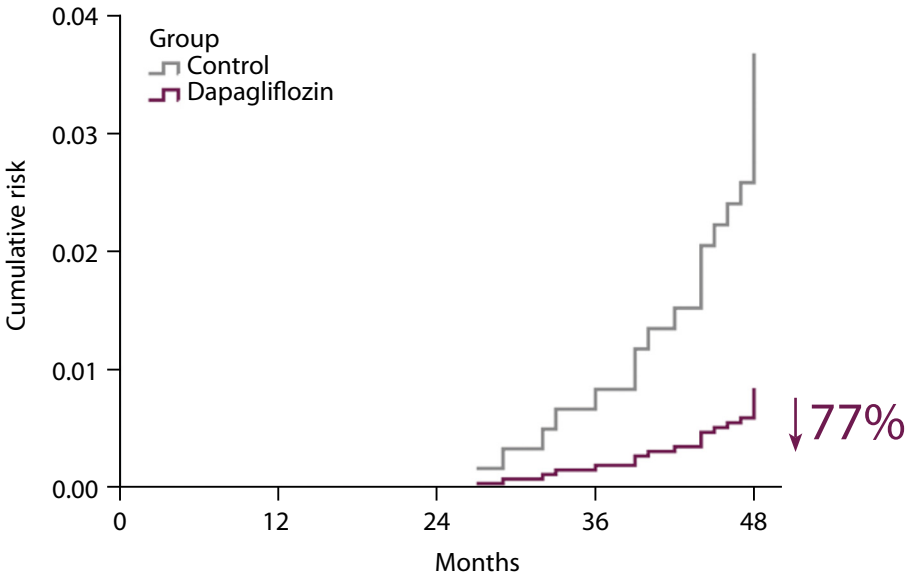
	Control Group	Dapagliflozin Group	p*
Number, n	499	499	
Age (years) (SD)	62.7 (6.0)	62.5 (5.8)	p>0.05
Sex (male), n (%)	205 (41.1)	205 (41.1)	1.000
Diabetes duration (years) (SD)	8.7 (4.5)	8.8 (5.6)	p>0.05
Body mass index (kg/m^2) (SD)	34.04	33.91	p>0.05
Systolic blood pressure (mm Hg)	133.27	134.87	**p=0.013**
HbA1c, %	8.27	8.53	**p<0.001**
Total cholesterol, mmol/L, average	5.84	5.99	p>0.05
Low density lipoproteins, mmol/L, average	2.75	2.72	p>0.05
Confirmed cardiovascular diseases	217 (43.5)	211 (42.3)	p>0.05
Therapy:			
metformin, n (%)	468 (93.8)	429 (86.0)	**p<0.001**
sulphonyl urea, n (%)	289 (57.9)	284 (56.9)	p>0.05
DPP-4 inhibitors, n (%)	63 (12.6)	56 (11.2)	p>0.05
insulin, n (%)	193 (38.7)	193 (38.7)	p>0.05

*p — for Control Group vs. Dapagliflozin Group comparisons.



	Control	Dapagliflozin	p	Relative risk	95.0% CI
Mortality	67 (13.4%)	42 (8.4%)	0.013	0.614	0.417–0.903

Figure 1. Overall mortality by group.



	Control	Dapagliflozin	p	Relative risk	95.0% CI
Chronic heart failure mortality	17 (3.4%)	4 (0.7%)	0.008	0.23	0.077–0.683

Figure 2. Chronic heart failure mortality by group.

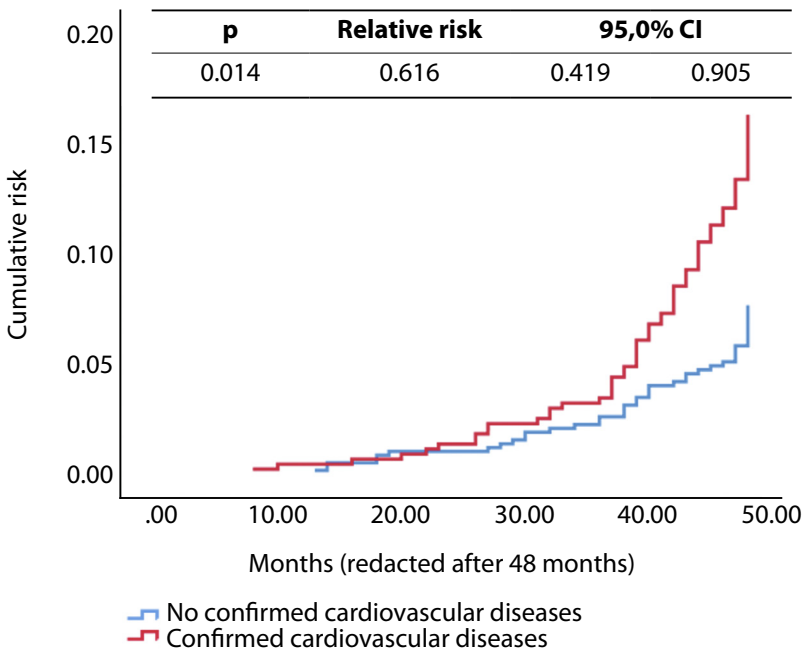


Figure 3. Mortality from all causes depending on confirmed cardiovascular diseases at the time of inclusion in data analysis.

in the dapagliflozin group: 95.9 kg vs. 94.2 kg in the control group). BMI in the dapagliflozin group at 48 months following the start of observation was 29.4 kg/m^2 (4.5 kg/m^2 lower than at the start of observation) vs. 34.3 kg/m^2 in the control group (0.4 kg/m^2 higher than at the start of observation), p<0.001. However, no significant difference in BMI between the two groups existed at the start of observation.

Over the 48 months of observation, both groups showed a trend towards a significant reduction of both systolic and diastolic blood pressure (Figure 6). Over the period of observation, a trend towards a lower rate of major cardiovascular accidents was observed in the dapagliflozin group only. No significant differences between the groups were found in several parameters (myocardial infarctions rate, revascularisation rate, acute cerebral blood flow failures rate).

Over the period of observation, a positive trend in glomerular filtration rate was found in the dapagliflozin group: at 48 months following the start of therapy, the glomerular filtration rate was 2.1% better than the baseline value (Figure 7). At 48 months following the start of the observation, the share of patients with normal glomerular filtration rate values was 12.6% in the control group vs. 22.1% in the dapagliflozin group.

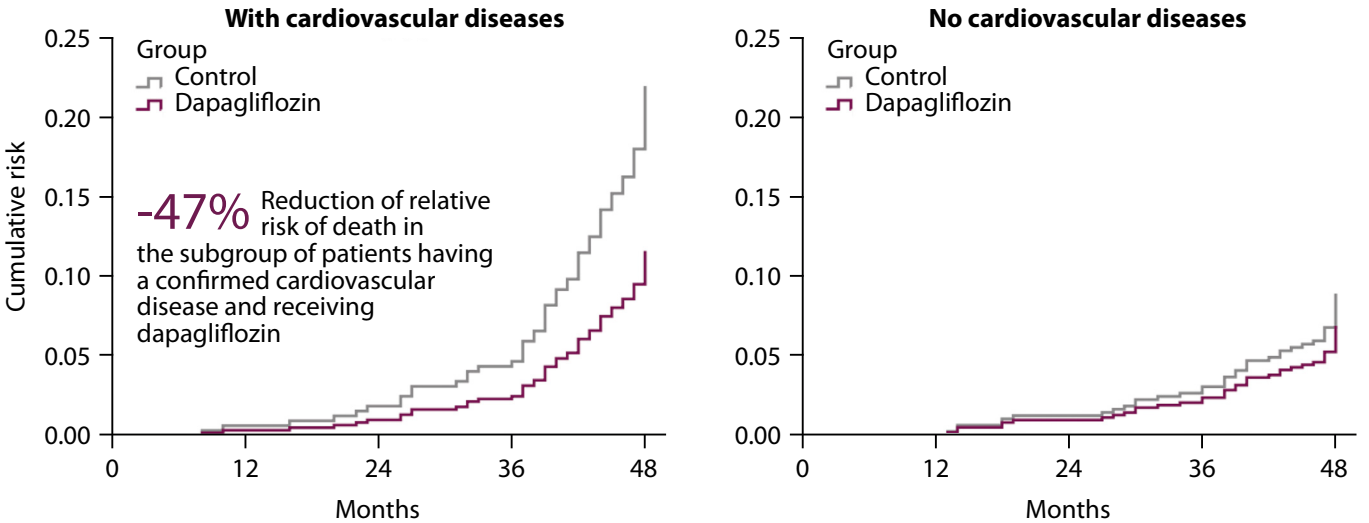
The safety profile in the dapagliflozin group was commensurable with that in the control group and consistent with the results of prior clinical studies (Table 2). In contrast to the control group, no kidney dialysis cases were registered in the dapagliflozin group.

DISCUSSION

The purpose of T2D treatment is to prevent the onset of complications. This is done by achieving and maintaining target glycaemic control values. At present, several classes of antihyperglycemic drugs are used in T2D treatment; they differ from one another in their mechanism of action.

In most cases, first-line therapy includes a change in lifestyle, *i.e.*, a reduction of body weight (in overweight or obesity patients) and an increase in physical activity, as well as metformin intake (subject to contraindications and tolerability) [4, 5]. Other types of therapy are to be selected individually based on medical history, body weight, hypoglycaemia risks, existing cardiovascular diseases and/or CKD, the cost of drugs and the patient's preferences. One ought to consider that cardiovascular diseases are the most frequent cause of death in T2D patients. Most of the mortality in such patients is attributable to CHF, myocardial infarction or stroke. Thus, it is highly important to use drugs that reduce the rate of cardiovascular diseases and mortality [18].

SGLT2i are a relatively new class of diabetes drugs. They reduce blood sugar by increasing sugar excretion in urine. Since these drugs' effect is unrelated to insulin, SGLT2i may be combined with other antihyperglycemic drugs, including insulin, without involving a significant risk of hypoglycaemia [19]. Dapagliflozin is a highly selective SGLT2i drug with proven efficacy and safety in the treatment of T2D patients [19]. In clinical studies, dapagliflozin, whether used



	Control	Dapagliflozin	p	Relative risk	95,0% CI
With cardiovascular diseases	43 (19.8%)	23 (10.9%)	0.013	0.53	0.32–0.88
No cardiovascular diseases	24 (8.5%)	19 (6.6%)	0.4	0.77	0.042–1.4

Figure 4. Mortality from all causes by cohort and by the presence of a confirmed cardiovascular disease.

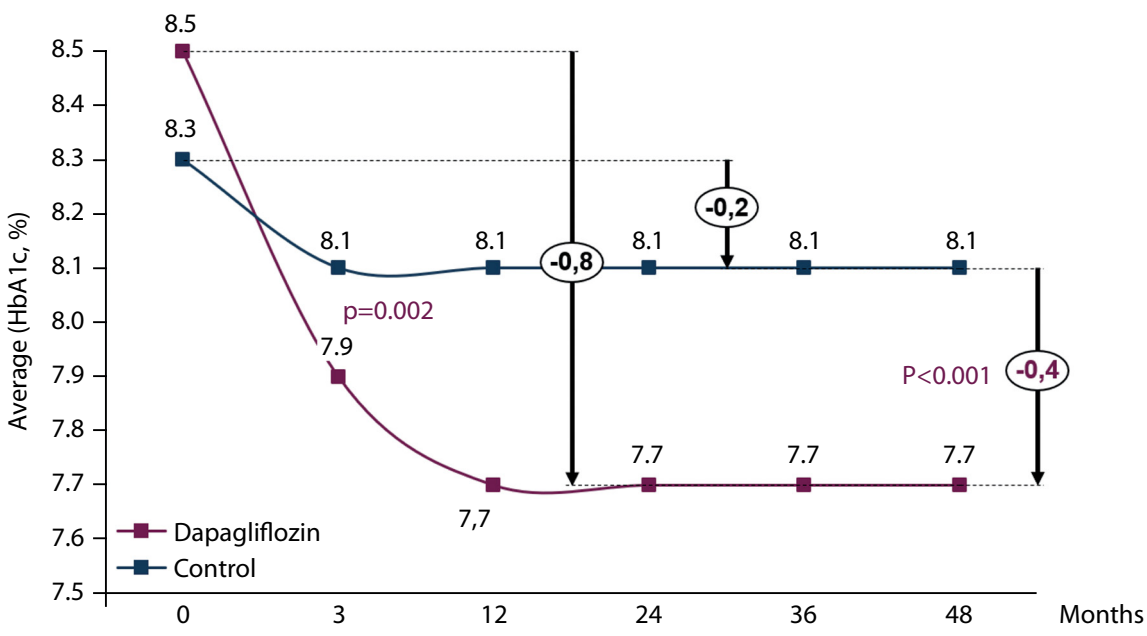


Figure 5. Glycated haemoglobin levels by group over the 48 months of observation.

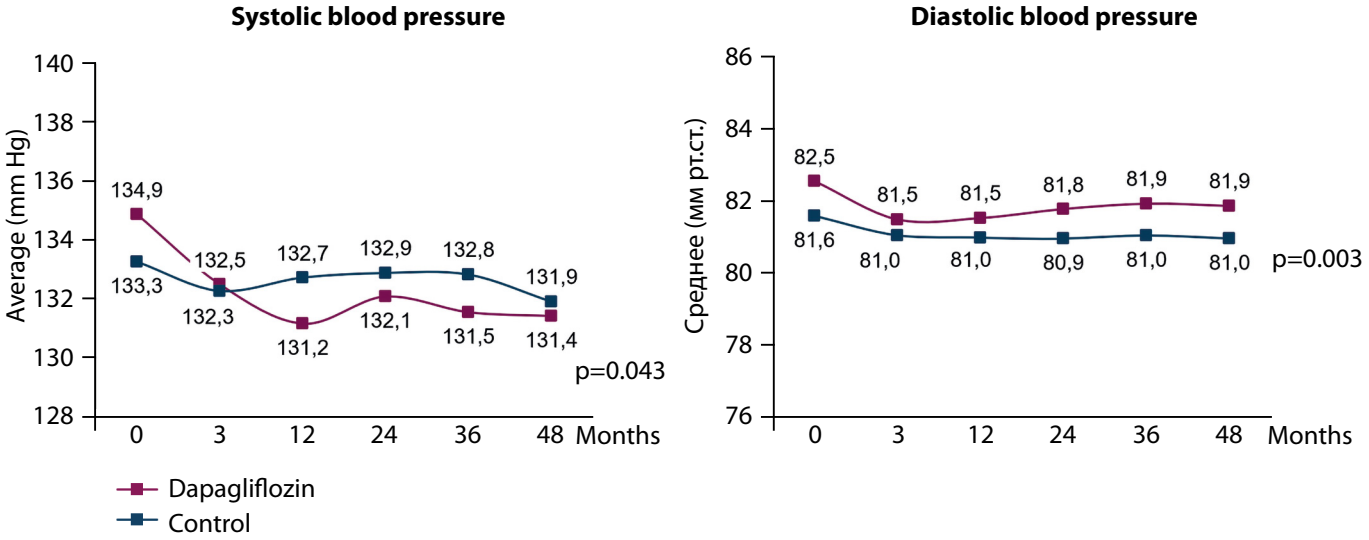


Figure 6. Blood pressure by group over the 48 months of observation.

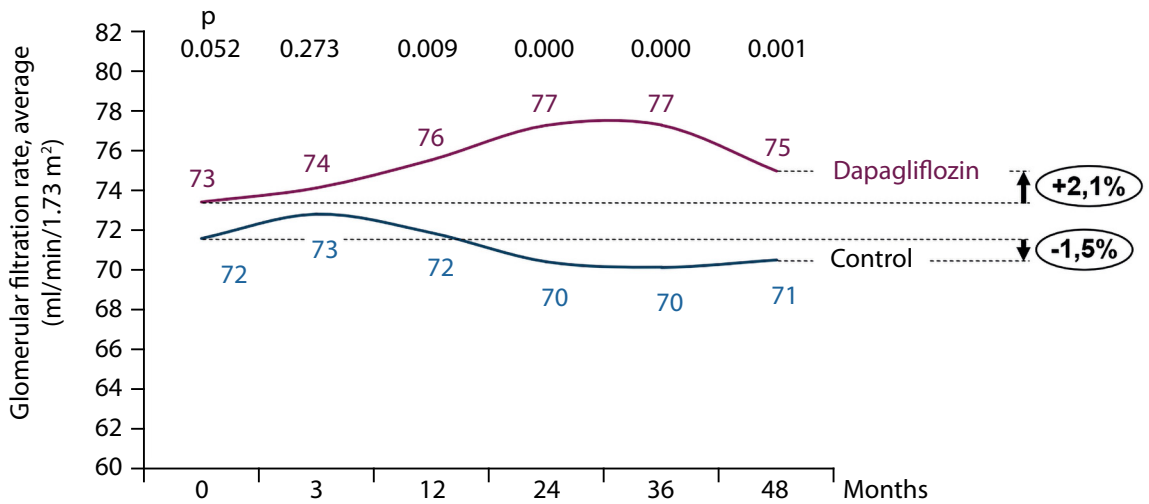


Figure 7. Glomerular filtration rate by group over the 48 months of observation.

solo or in combination with other drugs, ensured efficient glycaemic control, body weight reduction and blood pressure reduction in T2D patients, including those with arterial hypertension and/or other cardiovascular diseases [14–17]. Data from real clinical practice confirm dapagliflozin efficacy in T2D patients [20–23].

It should be noted that the populations of patients in prior SGLT2i tests differed in their baseline characteristics. Thus, the EMPA-REG OUTCOME study [8] involved T2D patients with confirmed cardiovascular diseases; 25% of patients included in the study had a high 5-year CHF risk and another 5.1% had a very high 5-year CHF risk. A significant part of patients included in the DECLARE study [15] was a cohort of primary preventive care patients, whereas two-thirds of patients included in the CANVAS study [10] had prior cardiovascular diseases.

A meta-analysis of three randomised placebo-controlled SGLT2i tests [24] was run to evaluate cardiovascular outcomes in T2D patients; it showed that SGLT2i drugs reduced the risk of major cardiovascular accidents by 11% and the risk of a lethal cardiovascular event or a hospitalisation for heart failure in cardiovascular patients by 23%.

Table 2. Safety parameters by group at the 48th month of observation

	Control Group		Dapagliflozin Group		P
	cases (n)	share (%)	cases (n)	share (%)	
Amputations	**3**	**0.6%**	**5**	**1.0%**	0.48
Fractures	**13**	**2.6%**	**11**	**2.2%**	0.68
Acute renal failure	1	0.2%	1	**0.2%**	1.00
Dialysis	**3**	**0.6%**	**0**	-	0.08

	Relative risk	95% CI		p
Chronic heart failure mortality	0.230	0.077	0.683	0.008
Cardiovascular mortality	0.431	0.177	1.048	0.063
Covid-19 mortality	0.667	0.329	1.351	0.261
Covid-19 + cardiovascular mortality	0.560	0.323	0.969	0.038
Overall mortality by subgroup				
Insulin therapy	0.620	0.338	1.097	0.064
Other therapy	0.609	0.370	1.928	0.098
Males	0.670	0.400	1.120	0.130
Females	0.540	0.300	0.980	0.042
Cardiovascular diseases	0.530	0.320	0.88	0.013
No cardiovascular diseases	0.770	0.420	1.400	0.400
Chronic heart failure	0.830	0.480	1.440	0.500
No chronic heart failure	0.470	0.270	0.810	0.007

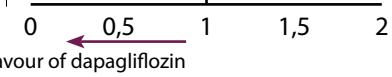


Figure 8. Risk of different outcomes in general and by patient subgroup.

Moreover, SGLT2i drugs reduced the rate of kidney function deterioration and the rate of the terminal stage of kidney failure or death from kidney dysfunction both in patients with atherosclerotic cardiovascular diseases and in those without such diagnosis.

The results of our study are generally consistent with those of major randomised clinical SGLT2i studies. Thus, the EMPA-REG OUTCOME study [24] found a 32% reduction in the risk of death from all causes in the empagliflozin group (relative risk 0.68; 95% CI 0.57–0.82; p<0.001). Our study found that the use of dapagliflozin is associated with a 39% reduction in the risk of death from all causes.

Dapagliflozin efficacy in the prevention of cardiovascular accidents was confirmed by the results of the DECLARE-TIMI 58 [15] and CVD-REAL Nordic studies [25]. Compared against DPP-4 inhibitors, dapagliflozin reduced the risk of minor cardiac abnormalities by 22% (relative risk 0.78; 95% CI 0.67–0.94), the risk of CHF hospitalisation by 38% (relative risk 0.62; 95% CI 0.50–0.77) and total mortality by 41% (relative risk 0.59; 95% CI 0.49–0.72).

A vital factor affecting the patients' survival was whether they had any cardiovascular diseases prior to inclusion in the study. In our study, patients with confirmed cardiovascular diseases likewise received a maximum benefit from dapagliflozin therapy: the risk of death from all causes was reduced by 47% (Figure 8).

Moreover, the use of dapagliflozin was associated with non-reduction in glomerular filtration rate over the 48-month-long observation period, as opposed to the control group. The impact of dapagliflozin on kidney outcomes was evaluated in DECLARE-TIMI 58 study [26]. It was shown that dapagliflozin reduced the risk of kidney failure, as demonstrated by a reduced rate of combined kidney and additional kidney endpoints in the dapagliflozin group vs. the placebo group. Moreover, at 6 months, the average reduction of estimated glomerular filtration rate vs. the baseline values was significantly greater in the dapagliflozin group vs. the placebo group (p<0.0001); however, at 24 months these values levelled up between the groups, and at 3 and 4 years after randomisation the reduction of estimated glomerular filtration rate in the placebo group was greater vs. the dapagliflozin group [27].

All the aforesaid shows that SGLT2i drugs and dapagliflozin in particular can be used in secondary preventive treatment against T2D complications in real clinical practice. The drug has obvious cardioprotective/renoprotective properties which are confirmed by both prior studies and our study. Further studies may be carried out to identify other groups of patients that may benefit from dapagliflozin therapy.

Possible limitations of the study

It ought to be noted that a significant portion of the observation period (part of 2019 and the entire of 2020) coincided with the time of COVID-19 widespread presence, which may have affected the figures of mortality in T2D patients and the profile of causes thereof.

Moreover, several patients had no cause of death entered into their medical records; determining a precise profile of mortality causes and evaluating the cardiovascular share therein was thus complicated somewhat further.

CONCLUSION

The use of SGLT2i drugs and dapagliflozin in particular in the treatment of T2D patients is expected not only to contribute to glycaemic parameters improvement, body weight reduction and blood pressure improvement, but also to reduce overall mortality. Dapagliflozin has demonstrated cardioprotective/renoprotective effects not only in randomised clinical tests but also in a study inquiring into real clinical practice with a population of Russian patients. Moreover, dapagliflozin has proven highly safe. Based on the results of our study, dapagliflozin may be recommended for the treatment of a broad population of T2D patients with cardiovascular diseases and factors of their onset.

ADDITIONAL INFORMATION

Funding source. This study was conducted on the premises of Moscow Endocrinological Dispensary which provided the resources therefor.

Conflict of interest. The authors hereby declare no actual or potential conflict of interest related to this publication.

Authors' contribution. All of the authors made an equal contribution to the study concept, data analysis and interpretation, article drafting and editing. Every author approved the final version of the text prior to publication and agreed to accept responsibility for all aspects of this study.

REFERENCES

1. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract*. 2019;157(4):107843. doi: https://doi.org/10.1016/j.diabres.2019.107843
2. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol*. 2018;14(2):88-98. doi: https://doi.org/10.1038/nrendo.2017.151
3. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2018;41(12):2669-2701. doi: https://doi.org/10.2337/dci18-0033
4. Buse JB, Wexler DJ, Tsapas A, et al. 2019 Update to: Management of Hyperglycemia in type 2 diabetes, 2018. a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2020;43(2):487-493. doi: https://doi.org/10.2337/dci19-0066
5. Российская ассоциация эндокринологов. *Клинические рекомендации. Сахарный диабет 2 типа у взрослых.* М.: Минздрав РФ; 2021. [Russian Association of Endocrinologists. Clinical guidelines. Type 2 Diabetes Mellitus in Adults. Moscow: Minzdrav RF; 2021. (In Russ.)].
6. Калашников В.Ю., Викулова О.К., Железнякова А.В., и др. Эпидемиология сердечно-сосудистых заболеваний у больных сахарным диабетом, по данным федерального регистра Российской Федерации (2013–2016 гг.). *// Сахарный диабет.* — 2019. — Т. 22. №2. — С. 105-114. [Kalashnikov VY, Vikulova OK, Zheleznyakova AV, et al. Epidemiology of cardiovascular diseases among patients with diabetes mellitus according to the federal diabetes register of the Russian Federation (2013–2016). *Diabetes mellitus.* 2019;22(2):105-114. (In Russ.)]. doi: https://doi.org/10.14341/DM10167
7. Pecoits-Filho R, Abensur H, Betônico CCR, et al. Interactions between kidney disease and diabetes: dangerous liaisons. *Diabetol Metab Syndr*. 2016;8(1):50. doi: https://doi.org/10.1186/s13098-016-0159-z
8. Fitchett D, Butler J, van de Borne P, et al. Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME® trial. *Eur Heart J*. 2018;39(5):363-370. doi: https://doi.org/10.1093/eurheartj/ehx511

9. Home P. Cardiovascular outcome trials of glucose-lowering medications: an update. *Diabetologia*. 2019;62(3):357-369. doi: https://doi.org/10.1007/s00125-018-4801-1
10. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657. doi: https://doi.org/10.1056/NEJMoa1611925
11. Usman MS, Siddiqi TJ, Memon MM, et al. Sodium-glucose co-transporter 2 inhibitors and cardiovascular outcomes: A systematic review and meta-analysis. *Eur J Prev Cardiol*. 2018;25(5):495-502. doi: https://doi.org/10.1177/2047487318755531
12. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2019;393(10166):31-39. doi: https://doi.org/10.1016/S0140-6736(18)32590-X
13. Forxiga 10 mg film-coated tablets — Summary of Product Characteristics (SmPC) [Internet]. Available from: https://www.medicines.org.uk/emc/product/7607/smpc [cited April 18, 2022].
14. Rosenstock J, Vico M, Wei L, et al. Effects of dapagliflozin, an sglt2 inhibitor, on hba1c, body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. *Diabetes Care*. 2012;35(7):1473-1478. doi: https://doi.org/10.2337/dc11-1693
15. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357. doi: https://doi.org/10.1056/NEJMoa1812389
16. Bailey CJ, Gross JL, Hennicken D, et al. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. *BMC Med*. 2013;11(1):43. doi: https://doi.org/10.1186/1741-7015-11-43
17. Strojek K, Yoon KH, Hruba V, et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. *Diabetes, Obes Metab*. 2011;13(10):928-938. doi: https://doi.org/10.1111/j.1463-1326.2011.01434.x
18. Ferrannini E, DeFronzo RA. Impact of glucose-lowering drugs on cardiovascular disease in type 2 diabetes. *Eur Heart J*. 2015;36(34):2288-2296. doi: https://doi.org/10.1093/eurheartj/ehv239
19. Lupsa BC, Inzucchi SE. Use of SGLT2 inhibitors in type 2 diabetes: weighing the risks and benefits. *Diabetologia*. 2018;61(10):2118-2125. doi: https://doi.org/10.1007/s00125-018-4663-6
20. Wilding J, Bailey C, Rigney U, et al. Dapagliflozin therapy for type 2 diabetes in primary care: Changes in HbA1c, weight and blood pressure over 2 years follow-up. *Prim Care Diabetes*. 2017;11(5):437-444. doi: https://doi.org/10.1016/j.pcd.2017.04.004
21. Brown RE, Gupta N, Aronson R. Effect of dapagliflozin on glycemic control, weight, and blood pressure in patients with type 2 diabetes attending a specialist endocrinology practice in Canada: A retrospective cohort analysis. *Diabetes Technol Ther*. 2017;19(11):685-691. doi: https://doi.org/10.1089/dia.2017.0134
22. Han E, Kim A, Lee SJ, et al. Characteristics of dapagliflozin responders: A longitudinal, prospective, nationwide dapagliflozin surveillance study in Korea. *Diabetes Ther*. 2018;9(4):1689-1701. doi: https://doi.org/10.1007/s13300-018-0470-9
23. Fadini GP, Zatti G, Baldi I, et al. Use and effectiveness of dapagliflozin in routine clinical practice: An Italian multicentre retrospective study. *Diabetes, Obes Metab*. 2018;20(7):1781-1786. doi: https://doi.org/10.1111/dom.13280
24. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128. doi: https://doi.org/10.1056/NEJMoa1504720
25. Persson F, Nyström T, Jørgensen ME, et al. Dapagliflozin is associated with lower risk of cardiovascular events and all-cause mortality in people with type 2 diabetes (CVD-REAL Nordic) when compared with dipeptidyl peptidase-4 inhibitor therapy: A multinational observationa. *Diabetes, Obes Metab*. 2018;20(2):344-351. doi: https://doi.org/10.1111/dom.13077
26. Bajaj HS, Raz I, Mosenzon O, et al. Cardiovascular and renal benefits of dapagliflozin in patients with short and long-standing type 2 diabetes: Analysis from the DECLARE-TIMI 58 trial. *Diabetes, Obes Metab*. 2020;22(7):1122-1131. doi: https://doi.org/10.1111/dom.14011
27. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE–TIMI 58 randomised trial. *Lancet Diabetes Endocrinol*. 2019;7(8):606-617. doi: https://doi.org/10.1016/S2213-8587(19)30180-9

AUTHORS INFO

*__Nikolay A. Demidov__, MD, PhD; address: 7, Moskovskiy, microraion 3, Moscow, Russia;
ORCID: https://orcid.org/0000-0001-8289-0032; eLibrary SPIN: 7715-4508; e-mail: nicolay13@mail.ru

__Mikhail B. Antsiferov__, MD, PhD, professor; ORCID: https://orcid.org/0000-0002-9944-2997; eLibrary SPIN: 1035–4773; e-mail: antsiferov@rambler.ru
__Nikolay A. Demidov__, MD, PhD; ORCID: https://orcid.org/0000-0001-8289-0032; eLibrary SPIN: 7715-4508; e-mail: Nicolay13@mail.ru
__Maria A. Balberova__, MD; eLibrary SPIN: 7263-5503; e-mail: maria_balberova@mail.ru
__Olga V. Lobanova__, MD; ORCID: https://orcid.org/0000-0002-2196-8278; e-mail: Olia.lo2011@yandex.ru
__Irina G. Mudrikova__, MD; ORCID: https://orcid.org/0000-0002-0885-0371; eLibrary SPIN: 8965-5850; e-mail: Ramew@rambler.ru
__Dinara G. Gusenbekova__, MD, PhD; ORCID: https://orcid.org/0000-0001-8440-7809; eLibrary SPIN: 5332-2890; e-mail: drdinara@yandex.ru

TO CITE THIS ARTICLE:

Antsiferov MB, Demidov NA, Balberova MA, Lobanova OV, Mudrikova IG, Gusenbekova DG. Influence of type 2 sodium-glucose co-transporter inhibitors (dapagliflozin) on the indicators of total mortality in patients with type 2 diabetes (CARDIA-MOS study, Moscow). *Diabetes Mellitus*. 2022;25(5):439-448. doi: https://doi.org/10.14341/DM12929