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The impact of dapagliflozin on cardiovascular system in the course of type 2 diabetes mellitus

ABSTRACT

The following paper is an attempt to revise current data and the results of clinical trials concerning the impact of dapagliflozin on long-term cardiovascular complications of type 2 diabetes mellitus. Short-term clinical trials, including relatively small groups of patients, suggest positive influence of dapagliflozin on the cardiovascular system. Currently ongoing long-term trials are likely to confirm these data, but so far we can assume that dapagliflozin not only acts as an efficient antihyperglycaemic drug, but also protects the circulatory system in patients with type 2 diabetes mellitus. (Clin Diabetol 2017; 6, 4: 142–146)

Key words: dapagliflozin, risk factors, cardiovascular events, atherosclerosis

Introduction

Cardiovascular complications of diabetes are one of the basic, still unresolved issues in the treatment of type 2 diabetes. Cardiovascular (CV) risk in these patients is even 2–4 times higher than in those without carbohydrate metabolism disorders [1]; therefore, CV risk reduction is one of the most important therapeutic goals. The choice of a drug used to normalize blood glucose in type 2 diabetic patient should be made considering the effect of this drug on cardiovascular risk factors and the morbidity and mortality associated with cardiovascular diseases [2].

Dapagliflozin — general characteristics of the drug

Dapagliflozin is an oral hypoglycaemic agent indicated for the treatment of type 2 diabetes in adult patients. According to the Summary of Product Characteristics (SPC), dapagliflozin may be used alone or in combination, usually at a dose of 10 mg once daily [3].

The mechanism of action of dapagliflozin is selective inhibition of sodium-glucose co-transporter 2 (SGLT2) located in the proximal tubule of the nephron. The role of SGLT2 is to reabsorb about 90% of glucose and sodium cations from the urine in a 1:1 molar ratio — therefore blocking SGLT2 leads to urinary excretion of these substances. The amount of glucose excreted in the urine in patients receiving dapagliflozin depends on the severity of hyperglycaemia and on glomerular filtration rate (GFR) [4]. Clinical studies have demonstrated the efficacy of dapagliflozin in the reduction of HbA_{1c} and fasting plasma glucose, both when used alone and in combination with other antidiabetic agents. It has also been observed that the efficacy of dapagliflozin in glycaemic control is comparable to that of metformin, sulphonylureas or sitagliptin [4].

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Dapagliflozin and cardiovascular risk factors

Available results of basic research and experimental clinical trials of the effect of dapagliflozin on cardiovascular system in type 2 diabetes did not give a clear answer to whether dapagliflozin reduces macrovascular complications (Table 1).

At the same time, further intensive clinical trials are underway to evaluate the effect of dapagliflozin on cardiovascular diseases, and the results of one of these studies — CVD-REAL Nordic — are very promising. The study confirmed that the use of SGLT2 inhibitors significantly reduced cardiovascular mortality. Although the study included patients treated with one of three different SGLT2 inhibitors, most of the observations were from patients treated with dapagliflozin [5].

Dapagliflozin has been used since several years, also in Poland, although its use is significantly limited by the lack of reimbursement. Therefore, knowledge of the currently available data relating to the relationship between dapagliflozin use and vascular complications, especially in the circulatory system, has become indispensable.

Hypertension

Dapagliflozin decreases blood pressure due to osmotic diuresis. The loss of sodium ions and water resulting from the inhibition of SGLT2 leads to a decrease in both systolic and diastolic blood pressure. This has been demonstrated in clinical studies and results have been confirmed in a meta-analysis of the effect of dapagliflozin on blood pressure. The effect of dapagliflozin on this aspect of cardiovascular risk is observed only 12 weeks after initiation of therapy and the diuretic potency of dapagliflozin is comparable to that of hydrochlorothiazide [6].

Body mass

Dapagliflozin reduces obesity by decreasing the amount of body fat. In patients treated with dapagliflozin for 24 weeks, body mass was reduced by an average of 2 kg compared to placebo. Weight loss in the dapagliflozin group was significantly higher and 2/3 of this reduction was due to loss of adipose tissue, whereas in placebo-treated patients only 50% of weight loss resulted from body fat reduction and 50% — from decrease in total body water (TBW) [7]. The mechanism by which dapagliflozin causes weight loss is most likely to be associated with urinary glucose excretion, which means elimination of calories from the food [4].

Lipid profile

Dapagliflozin, like other SGLT2 inhibitors, influences the lipid profile, resulting in decreased serum triglyceride levels and elevated HDL levels. Some studies have shown that SGLT2 inhibitors also increase LDL levels, but the ratio of cardioprotective HDL to atherogenic LDL remains unchanged [8, 9]. Other reports have shown a reduction in total cholesterol after 90 days of dapagliflozin therapy in patients with type 2 diabetes [10].

Hyperglycaemia and diurnal variations of blood glucose

Dapagliflozin has been shown to reduce glycaemia and, after 6 months, also HbA_{1c} level by 0.5%. Glucose reduction has been observed both in fasting and postprandial glucose level measurements as well as in glucose tolerance test results. The mechanism of action of dapagliflozin was not associated with insulin secretion and did not increase the incidence of hypoglycaemia [11–14].

Due to the high efficacy in reducing postprandial hyperglycaemia and the lack of effect on the incidence of hypoglycaemia, dapagliflozin may be a drug specifically indicated for use in patients with significant diurnal blood glucose fluctuations, particularly in those with high postprandial glucose excursions. It is known that both postprandial hyperglycaemia and increased blood glucose variability have a negative effect on the development of chronic cardiovascular complications of diabetes [15, 16].

Clinical studies showed a beneficial effect of dapagliflozin monotherapy on the reduction of diurnal glycaemic variability, assessed as the mean amplitude of glucose fluctuations, and the reduction of oxidative stress, assessed by plasma 8-prostaglandin F2α levels [17]. It was also found in 4 week-observation that dapagliflozin in combination with metformin or with insulin reduces the mean amplitude of glucose fluctuations by 10 mg/dL, whereas in patients receiving placebo in combination with metformin or with insulin, the mean fluctuation amplitude increased by 5.3 mg/dL [18].

Insulin resistance

Peripheral insulin resistance is a challenge in the treatment of type 2 diabetes. In clinical trials, dapagliflozin has been shown to increase tissue insulin sensitivity as assessed by glucose disappearance rate [19]. In another study, dapagliflozin reduced peripheral insulin resistance in patients with metabolic syndrome, causing remission of metabolic syndrome features in more than half of the patients [10]. On this basis, it can be concluded that the use of dapagliflozin is beneficial in terms of correcting peripheral insulin resistance irrespective of the severity of carbohydrate and lipid disorders.

Table 1. Review of selected clinical trials of the effect of dapagliflozin on cardiovascular risk (according to https://clinicaltrials.gov, accessed 17.09.2017). Search terms: death, HF — heart failure, MI — myocardial infarction, hospitalization, stroke

No. of the study	End of the study	Duration	Dapagliflozin dose (number of patients)	Comparator (number of patients)	Findings	
					Deaths[a]	Adverse events[b]
NCT00263276 MB102-008	2007.02	12 weeks	2.5/5/10/20/50 mg (overall 279)	Placebo (54) Metformin (56)	0:0	0:0
NCT00357370 MB102-009	2008.03	12 weeks	10/20 mg (overall 48)	Placebo (23)	0:0	0:0
NCT00528879 MB102-014	2008.11	24 + 78 weeks	2.5/5/10 mg + metformin (overall 409)	Placebo + metformin (137)	2:0	35:20
NCT00528372 MB102-013	2009.02	24 + 78 weeks	2.5/5/10 mg (overall 483)	Placebo (75)	0:0	29:4
NCT00673231 D1690C00006	2009.05	24 + 80 weeks	2.5/5/10 mg (overall 544)	Placebo (197)	2:0	38:17
NCT00643851 MB102-021	2009.08	24 weeks	5 mg ± metformin XR (overall 397)	Placebo + metformin XR (201)	1:0	4:1
NCT00680745 D1690C00005	2009.11	24 + 24 weeks	2.5/5/10 mg + glimepiride (overall 450)	Placebo + glimepiride (146)	2:0	21:10
NCT00660907 D1690C00004	2009.12	52 + 156 weeks	2.5/5/10 mg + metformin (overall 406)	Glipizide + metformin (408)	0:2	38:45
NCT00663260 MB102-029	2009.12	24 weeks	5/10 mg (overall 168)	Placebo (84)	4:3	9:7
NCT00736879 MB102-032	2009.12	24 weeks	1/2.5/5 mg (overall 214)	Placebo (68)	0:0	0:0
NCT00683878 MB102-030	2010.01	48 weeks	5/10 mg + pioglitazone (overall 281)	Placebo + pioglitazone (139)	0:0	2:0
NCT00859898 MB102-034	2010.05	24 weeks	10 mg ± metformin XR (overall 430)	Placebo + metformin XR (208)	0:NA	2:1
NCT00972244 D1692C00005	2010.05	12 weeks	1/2.5/5/10 mg (overall 225)	Placebo (54)	NA:0	1:0
NCT00855166 D1690C00012	2010.07	24 + 78 weeks	10 mg + metformin (91)	Placebo + metformin (91)	0:0	1:0
NCT00831779 MB102-045	2010.08	12 weeks	5 mg (23)	Placebo (21)	0:0	0:0
NCT00976495 MB102-035	2010.11	12 weeks	10 mg (24)	Placebo (25) Hydrochlorothiazide (26)	0:0	0:0
NCT00984867 D1690C00010	2011.03	24 + 24 weeks	10 mg+ sitagliptin ± metformin (225)	Placebo + sitagliptin ± metformin (226)	0:0	3:1
NCT01031680 D1690C00018	2011.05	24 + 80 weeks	10 mg (460)	Placebo (462)	3:3	7:10
NCT01042977 D1690C00019	2011.05	24 + 80 weeks	10 mg (482)	Placebo (483)	NA:NA	17:19
NCT01095653 MB102-054	2012.03	24 weeks	5/10 mg (overall 261)	Placebo (132)	0:0	0:1
NCT01294423 D1692C00006	2012.03	24 weeks	5/10 mg (overall 174)	Placebo (87)	0:0	3:5
NCT02397421 2014-002742-42	2017.08	1 year	10 mg (overall, dapagliflozin and placebo, 56)	Placebo		
NCT01730534 D1693C00001	2019.04	6 years	10 mg (overall, dapagliflozin and placebo, 17276)	Placebo		
NCT03036124 D1699C00001 2016-003897-41	2019.12	3 years	5/10 mg (overall about 2250)	Placebo (about 2250)		
NCT03036150 D169AC00001 2016-003896-24	2020.11	4 years	5/10 mg (overall about 2000)	Placebo (about 2000)		
TOTAL (studies which results were published until 17.09.2017)			**6868**	**3403**	**16:8 0.23%:0.24%**	**245:161 3.57%:4.73%**

[a]Cardiovascular mortality among dapagliflozin *vs.* comparator-treated patients; [b]number of adverse cardiovascular events among dapagliflozin *vs.* comparator-treated patients; NA — not available

Hyperuricaemia and albuminuria

Albuminuria and elevated serum uric acid levels are favorably modified by dapagliflozin [20, 21].

The adjusted mean change from baseline in serum uric acid after 12 weeks of treatment with 10 mg of dapagliflozin was –0.3 mg/dL *versus* +0.1 mg/dL in the placebo arm of the study [21].

The effect on urinary albumin excretion is independent from changes in HbA_{1c} levels, blood pressure, body mass, and estimated glomerular filtration rate [20]. Beneficial renoprotective effect of dapagliflozin is manifested by the reduction of albuminuria by 30% compared to placebo and by decreased inflammation in the kidneys [20].

Dapagliflozin therapy and cardiovascular complications

Preliminary reports on the safety of dapagliflozin in terms of cardiovascular risk are included in the 2012 report of the European Medicines Agency [22]. Meta-analysis included 14 Phase 2b and Phase 3 clinical trials completed before July 15, 2011. Also preliminary data from five further clinical trials which were to be completed later have been included there. Although the studies included in the meta-analysis were not designed to assess the effect of dapagliflozin on cardiovascular system, cardiovascular death, myocardial infarction, or major adverse cardiovascular events (MACE) were registered, as well as hospitalizations due to unstable ischaemic heart disease (IHD). In this meta-analysis of studies lasting from 12 weeks to 208 weeks, there were 145 cases of MACE or hospitalization due to unstable IHD; however, hazard ratio (HR) for these complications was 0.819 (95% CI 0.583–1.152) for the dapagliflozin-treated group versus the placebo-treated group. Thus, dapagliflozin has been shown to effectively reduce cardiovascular risk compared to placebo [22].

The beneficial effect of dapagliflozin on cardiovascular risk reduction has also been demonstrated in another meta-analysis by Sonesson et al. [23]. The incidence of MACE and unstable IHD in the dapagliflozin-treated group in relations to control group matched for age, BMI, duration of diabetes, smoking, eGFR, LDL cholesterol and blood pressure were analysed. After about four years of treatment, dapagliflozin has been shown to reduce the risk of MACE and/or unstable angina in all groups of patients, even in those with a history of cardiovascular events and hypertension [23].

The most promising clinical trial of the effect of dapagliflozin on cardiovascular risk is the ongoing phase 3 study, DECLARE-TIMI58 [24]. The main objective of this study is to analyse the incidence of MACE, the need for hospitalization for unstable IHD, and all-cause mortality. Approximately 26,000 patients with type 2 diabetes over 40 years of age who are at high risk of cardiovascular complications are enrolled. The study is underway [24].

Conclusions

Short-term clinical trials, including relatively small groups of patients, suggest positive influence of dapagliflozin on the cardiovascular system. Currently ongoing long-term trials are likely to confirm these data, but so far we can assume that dapagliflozin not only acts as an efficient antihyperglycaemic drug, but also protects the circulatory system in patients with type 2 diabetes mellitus.

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