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Cardiovascular safety of SGLT2 inhibitors

ABSTRACT

Sodium-glucose co-transporter-2 (SGLT2) inhibitors, also called flozins, are a new group of oral antidiabetic drugs. Due to progressive nature of type 2 diabetes and gradual deterioration of pancreatic beta cell function, achieving good diabetes control still remains a challenge. This stimulates researchers and clinicians to search for new directions in diabetes treatment and to develop optimal antidiabetic therapy. Particularly interesting in this context are (besides incretin-based therapies) SGLT2, because they reduce renal glucose reabsorption and, thereby, increase urinary glucose excretion. Their action is independent from an insulin, both in terms of an insulin secretion and action. Type 2 diabetes remains one of the major cardiovascular risk factors. The most important issue related to this group of drugs is therefore establishing the principles of safe, well-tolerated and effective long-term treatment of patients with vascular complications of various severity, including cardiovascular complications mainly. New antidiabetic drugs should not only improve glycaemic control, but also contribute to the reduction of cardiovascular morbidity and mortality. (Clin Diabet 2016; 5, 2: 62–65)

Key words: SGLT2 inhibitors, cardiovascular safety, type 2 diabetes

Despite large-scale preventive interventions, diabetes remains a significant public health problem that becomes increasingly important both from clinical and epidemiological point of view and efforts to achieve a therapeutic goal established individually for each patient, besides the normalization of increased blood pressure, coexisting lipid disorders and excessive body weight, are key elements of the treatment. From the patient's point of view, optimal diabetes therapy should be based on a simple regimen of drugs that are effective and safe and have no adverse effects. Due to progressive nature of type 2 diabetes and gradual deterioration of pancreatic beta cell function, achieving good diabetes control still remains a challenge. This stimulates researchers and clinicians to search for new solusions in diabetes treatment and to develop optimal antidiabetic therapy. Particularly interesting in this context are (besides incretin-based therapies) sodium-glucose co-transporter-2 (SGLT2) inhibitors, because they reduce renal glucose reabsorption and, thereby, increase urinary glucose excretion. Their action is independent from an insulin, both in terms of an insulin secretion and action. Thereby, the level of coexisting insulin resistance and/or pancreatic beta cell dysfunction related to the progressive nature of the disease do not influence the effectiveness of the therapy, which allows for additional beneficial and long-term effect of SGLT2 inhibitors on glycaemic control, and this effect is independent from the stage of the natural history of diabetes.

SGLT2 proteins, a group of type 2 sodium-dependent glucose transporters, are localised in the kidneys, within the brush border of the proximal tubular segment S1 of the nephron, and have a low affinity but high capacity for glucose, and under physiological condition they are responsible for 90% of glucose reabsorption [1].

Contemporary SGLT2 inhibitors are derivatives of phlorizin, an agent that was first isolated in 1835 from the root bark of the apple tree and was initially used as an antipyretic and for the treatment of infections. Stimulating effect of phlorizin on renal excretion of glucose has been discovered later, in the second half

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of the 19th century. Its activity in human kidneys has been shown in 1933, but its antidiabetic effect has been discovered quite recently — in 1987; and only from that time on researchers' interests have been focused on this new potential mechanism of anti-hyperglycaemic activity in type 2 diabetes [2].

Despite considerable progress in medicine, introducing new classes of glucose-lowering drugs and improving the methods of blood glucose monitoring, the development of late vascular complications (mainly cardiovascular ones) remains the most important problem of contemporary diabetology, leading to substantial reduction of patients' life expectancy and quality of life.

Available data indicate a close relationship between the level and duration of hyperglycaemia and the risk of late vascular complications of diabetes. Therefore, efforts to achieve blood glucose normalization, alongside the treatment of blood lipids disorders, body mass and blood pressure reduction, according to the guidelines on multidirectional, comprehensive approach to the treatment of diabetes, is of key importance in the prevention and slowing the progression of vascular complication. This has been evidenced by the results of large clinical trials such as DCCT (Diabetes Control and Complications Trial) for type 1 diabetes or UKPDS (UK Prospective Diabetes Study) for type 2 diabetes. Based on detailed analysis of the results of above-mentioned trials, as well as the results of the STENO and STENO-2 trials and the large clinical trials performed in 2008 — ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease-Preterax and Diamicron Modified Release Controlled Evaluation) and VADT (Veterans Affairs Diabetes Trial) — it can be concluded that striving for optimal glucose control is not beneficial for all patients with type 2 diabetes. Such approach proved to be the safest and most effective in patients with newly detected diabetes or in those with short disease duration and good metabolic control who did not develop macroangiopathic complications [3–11].

Type 2 diabetes still remains one of the most important cardiovascular risk factors. Cardiovascular complications are responsible for about 65% deaths in diabetic patients. At the same time, about 60% of patients diagnosed with stable or unstable coronary artery disease (CAD) have glucose metabolism disturbances, such as impaired fasting glucose (IFG), IGT or overt type 2 diabetes. Additionally, diabetes has been diagnosed in 20–45% of clinical trial participants, including patients hospitalized for acute coronary syndrome (ACS), who had no history of diabetes. In this group of patients, diabetes is more prevalent in women than in men (41.6 vs. 30.7%). Many years ago, in 1998, the study results were published that suggested that diabetes should be regarded as a coronary heart disease (CHD) equivalent. The increase in cardiovascular risk in diabetic patients is caused not only by diabetes *per se*, but also by the presence of other cardiovascular risk factors overlapping with carbohydrate metabolism disorders [12–14].

Therefore, establishing the principles for long-term, safe, well-tolerated and effective therapy in patients with diabetes complications of various severities (mainly cardiovascular ones) is a significant issue related to the new classes of drugs. New antidiabetic drugs should not only influence glycaemic control, but also contribute to decrease in cardiovascular morbidity and mortality in patients with type 2 diabetes. Taking the above into account, in December 2008 Science Board of the Food and Drug Administration (FDA) issued a guidance requiring the assessment of cardiovascular risk for all new molecules used for the treatment of type 2 diabetes. This guidance specifies methodology of clinical trials and registration of cardiovascular events. It is recommended that these trials should be performed among diabetic patients with increased cardiovascular risk, in patients aged > 65 years, and in patient with kidney dysfunction, assuming the follow-up period of ≥ 2 years [15].

These trials are designed to show that the use of antidiabetic drugs as one of the standard option for the treatment of diabetes is not associated with the increase in cardiovascular risk (cardiovascular safety) compared with placebo. However, it should be highlighted that they are not designed to show cardiovascular benefits resulting from the improvement of metabolic control and HbA_{1c} reduction. Cardiovascular safety and cardiovascular benefits should be assessed regardless of the HbA_{1c} reduction [15].

SGLT2 inhibitors, also called flozins, are the newest group of oral antidiabetic drugs. Their mechanism of action is based on the inhibition of glucose reabsorption leading to its urinary excretion of 50–80 grams per day, which is equivalent to 200–320 kcal per day. These drugs improve glycaemic control, both in fasting as well as in postprandial state. As mentioned above, this effect is independent from an insulin, both in terms of its secretion and action, and, importantly, can be achieved with the low risk of hypoglycaemia. Benefits from treatment with SGLT2 inhibitors are not limited to improvement in the parameters of carbohydrate metabolism control. Negative energy balance results in body weight reduction and, subsequently, has favourable effect on insulin sensitivity and, through additional decrease in glucotoxicity, potential beta cell protective effect. Additionally, SGLT2 inhibitors decrease both sys-

tolic and diastolic blood pressure which are significant and well-established cardiovascular risk factors. Available results of the clinical trials show favourable effect of this class of drugs on plasma lipoproteins reflected in decreased LDL-cholesterol and triglycerides as well as increased HDL-cholesterol, decreased serum level of uric acid, inhibition of renin-angiotensin axis and decreased oxidative stress [1, 16–26].

There are three SGLT2 inhibitors available in Poland: dapagliflozin (Forxiga, AstraZeneca), canagliflozin (Invokana, Janssen-Cilag) and empagliflozin (Jardiance, Boehringer Ingelheim). All of them offer unique benefits for type 2 diabetes patients beyond the improvement of metabolic control.

Effect on body weight

Overweight and obesity are key risk factors for the development and progression of type 2 diabetes, but also cardiovascular diseases *per se*. SGLT2 inhibitors cause reduction of both visceral and subcutaneous fatty tissue, which consequently results in body mass reduction [16–21, 23].

Hypotensive effect

Beneficial effect of SGLT2 inhibitors on systolic and diastolic blood pressure results, to some extent, from body mass reduction and subsequent improvement of insulin sensitivity; but first of all it is a consequence of increased sodium excretion in response to volume load and increased serum sodium level as well as osmotic diuresis accompanying urinary elimination of glucose. Meta-analysis of 25 RCT concerning this issue showed that there is a reduction in systolic blood pressure by 4.0 mm Hg and diastolic blood pressure by 1.6 mm Hg from baseline values [16–21, 23–28].

Antiatherogenic effect

SGLT2 inhibitors, likewise incretin-based drugs, have beneficial effect on independent cardiovascular risk factors. Besides glucose level fluctuations, in patients with diabetes these factors include obesity and associated insulin resistance, lipid disorders, hypertension and elevated serum level of uric acid. All these factors increase oxidative stress and induce epithelial dysfunction [29].

Impact on cardiovascular risk

Registration trials of SGLT2 inhibitors have proven favourable cardiovascular profile of these drugs, but the results of landmark EMPA-REG OUTCOME trial published on September 17, 2015 may establish a turning point in the treatment of type 2 diabetes (if the results of ongoing trials with other drugs from this group confirm previous data).

The EMPA-REG OUTCOME® trial, a long-term clinical trial aimed to assess the effect of the therapy with empagliflozin on cardiovascular outcomes in patients with type 2 diabetes with high risk of cardiovascular events, is the first trial that showed unequivocally that this drug added to glucose lowering therapy significantly reduced the risk of cardiovascular episodes. Importantly, the trial was designed specifically to evaluate such results. In this trial, 7020 patients who fulfilled inclusion criteria were randomised on a basis 1:1:1 to standard antidiabetic therapy or to empagliflozin 10 or 25 mg daily on top of standard antidiabetic therapy. The median observation time was 3.1 years. Primary composite endpoint was defined as time to first occurrence of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke. Secondary composite endpoint was defined as time to first occurrence of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke and, additionally, hospitalization for unstable angina. During observation, there was a significant reduction in primary endpoint (10.5% vs. 12.1%) in the empagliflozin group compared with placebo group, with relative risk reduction (RRR) of its occurrence by 14% (HR 0.86; 95% CI 0.74–0.99; $p = 0.04$). Moreover, there was a significant risk reduction in the rates of death from cardiovascular causes by 38% (HR 0.62; 95% CI 0.49–0.77; $p = 0.001$), hospitalization for heart failure by 35% (HR 0.65; 95% CI 0.50–0.85; $p = 0.002$) and death from any cause by 32% (HR 0.68; 95% CI 0.57–0.82; $p = 0.001$).

The study also showed a 11% reduction in secondary composite endpoint (12.8% vs. 14.3%) in the group treated with empagliflozin compared with placebo group (HR 0.89; 95% CI 0.78–1.01; $p < 0.001$ for non-inferiority and $p = 0.08$ for superiority). It is important and noteworthy that the rates of adverse events (AEs) and serious adverse events (SAE) leading to discontinuation of the participation in the study were similar in the group treated with empagliflozin and the group receiving placebo, and that the percentages of patients with ketoacidosis, volaemic disturbances, thromboembolic episodes and bone fractures were low — not more than 1% for ketoacidosis and thromboembolic events and 5% for volaemic disturbances [30].

In summary, it should be highlighted that SGLT2 inhibitors are effective in reducing HbA_{1c}, both in monotherapy and in combination with other oral glucose-lowering drugs and/or insulin, and offer benefits for patients with type 2 diabetes extending considerably beyond the impact on glycaemic control. Based on the analysis of available data from clinical trials, it may be stated that these drugs reduce body weight, systolic and diastolic blood pressure, have favourable

effect on lipid parameters, uric acid level and RA axis activity and have nephroprotective effect, however subsequent trials with SGLT2 inhibitors are needed to establish whether promising results of EMPA-REG OUTCOME® trial are only unique for empagliflozin or are the effect of the class.

REFERENCES

1. Jung CH, Jang JE, Park JY. A Novel Therapeutic Agent for Type 2 Diabetes Mellitus: SGLT2 Inhibitor. Diabetes Metab J 2014; 38: 261–273.
2. Ehrenkranz JR, Lewis NG, Kahn CR et al. Phlorizin: a review. Diabetes Metab Res Rev 2005; 21: 31–38.
3. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993; 329: 977–986.
4. UK Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837–853.
5. Adler AI, Stratton IM, Neil HA et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000; 321: 412–419.
6. Gerstein HC, Miller ME, Byington RP et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358: 2545–2559.
7. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. JAMA 2004; 291: 335–342.
8. Duckworth W, Abraira C, Moritz T et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009; 360: 129–139.
9. The Action to Control Cardiovascular Risk in Diabetes Study G. Effects of Intensive Glucose Lowering in Type 2 Diabetes. N Engl J Med 2008; 358: 2545–2559.
10. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003; 348: 383–393.
11. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008; 358: 580–591.
12. Franklin K, Goldberg RJ, Spencer F et al. Implications of diabetes in patients with acute coronary syndromes. The Global Registry of Acute Coronary Events. Arch Intern Med 2004; 164: 1457–1463.
13. Hasdai D, Behar S, Wallentin L et al. A prospective survey of characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and Mediterranean basin; the Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS). Eur Heart J 2002; 23: 1190–1201.
14. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998; 339: 229–234.
15. US FDA. Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, (December), 2008. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances//ucm071627.pdf.
16. Stenlof K, Cefalu WT, Kim KA et al. Long-term efficacy and safety of canagliflozin monotherapy in patients with type 2 diabetes inadequately controlled with diet and exercise: findings from the 52-week CANTATA-M study. Curr Med Res Opin 2014; 30: 163–175.
17. Matthaei S, Bowering K, Rohwedder K et al. Durability and tolerability of dapagliflozin over 52 weeks as add-on to metformin and sulphonylurea in type 2 diabetes. Diabetes Obes Metab 2015; 17: 1075–1084.
18. Berhan A, Barker A. Sodium glucose co-transport 2 inhibitors in the treatment of type 2 diabetes mellitus: a metaanalysis of randomized double-blind controlled trials. BMC Endocr Disord 2013; 13: 58.
19. Ridderstrale M, Andersen KR, Zeller C et al. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, activecontrolled, double-blind, phase 3 trial. Lancet Diabetes Endocrinol 2014; 2: 691–700.
20. Leiter LA, Yoon KH, Arias P et al. Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. Diabetes Care 2015; 38: 355–364.
21. Del Prato S, Nauck M, Duran-Garcia S et al. Long-term glycaemic response and tolerability of dapagliflozin versus a sulphonylurea as add-on therapy to metformin in patients with type 2 diabetes: 4-year data. Diabetes Obes Metab 2015; 17: 581–590.
22. Merovci A, Mari A, Solis C et al. Dapagliflozin lowers plasma glucose concentration and improves β-cell function. J Clin Endocrinol Metab 2015; 100: 1927–1932.
23. Cefalu WT, Stenlof K, Leiter LA et al. Effects of canagliflozinon body weight and relationship to HbA_{1c} and bloodpressure changes in patients with type 2 diabetes. Diabetologia 2015; 58: 1183–1187.
24. Sjostrom CD, Johansson P, Ptaszynska A et al. Dapagliflozin lowers blood pressure in hypertensive and non-hypertensive patients with type 2 diabetes. Diab Vasc Dis Res 2015; 12: 352–358.
25. Cherney DZI, Perkins BA, Soleymanlou N et al. Renal hemodynamic effect of sodium–glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation 2014; 129: 587–597.
26. Tikkanen I, Narko K, Zeller C et al. Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. Diabetes Care 2015; 38: 420–428.
27. Townsend RR, Machin I, Ren J et al. Reductions in mean 24-hour ambulatory blood pressure after 6-week treatment with canagliflozin in patients with type 2 diabetes mellitus and hypertension. J Clin Hypertens 2016; 18: 43–52.
28. Baker WL, Smyth LR, Riche DM et al. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: a systematic review and meta-analysis. J Am Soc Hypertens 2014; 8: e9.
29. Leiter LA, Cefalu WT, de Bruin TW et al. Dapagliflozin added to usual care in individuals with type 2 diabetes mellitus with preexisting cardiovascular disease: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. J Am Geriatr Soc 2014; 62: 1252–1262.
30. Zinman B, Wanner C, Lachin JM et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373: 2117–2128.