

Glyphozines and treatment of cardiac disease

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Abstract

Glyphozines also called SGLT2 inhibitors, are a new class of agents that inhibit reabsorption of glucose in the kidney, in proximal tubules, and therefore lower blood sugar. They act by inhibiting sodium-glucose transport protein 2 (SGLT2). Glyphozines are used in the treatment of type II diabetes mellitus. In studies with canagliflozin, a member of this class, the medication was found to enhance blood sugar control as well as reduce body weight and systolic and diastolic blood pressure. In addition to regulate blood glucose, recent studies have shown that glyphozines have important positive cardiovascular benefits, such as weight loss, decreased volaemia and PA, reduced triglycerides, natriuresis and improved endothelial wall dysfunction. Clinical studies have shown reduction in deaths from cardiovascular events among diabetic patients treated with glyphozines. At the moment these drugs are being studied for an extension of the therapeutic indication also for cardiovascular diseases such as heart failure. In this review, we discuss the class of SGLT2 inhibitors in the treatment of diabetes, and studies focused on their possible role in the treatment of cardiac disease.

Introduction

The prevalence of type II diabetes mellitus (T2DM) is on the increase worldwide, tightly linked to the expanding number of individuals who are overweight and obese. T2DM is a metabolic disease commonly characterized by an increase in blood glucose levels and characterized by tissue insulin resistance and insulin reduction production.¹⁻⁴ It is important that all forms of diabetes are diagnosed and managed in advance to prevent or slow down its potential complications other organs such as nephropathy, retinopathy, neuropathy, cardiovascular damages, diabetic foot disease and ulcer. T2DM is also a socio-economic problem consider-

ing the high incidence of the disease, therefore, this has contributed to the creation and development of numerous drug treatments. Today, a number of new classes of drugs used to treat T2D have been developed.

T2DM is strongly associated with cardiovascular disease (CVD). Several studies have shown that a significant proportion of diabetic patients are at risk of experiencing acute coronary syndrome and/or heart failure (HF). This is due to abnormal cardiac management of glucose and free fatty acids (FFAs) and the effect of metabolic changes in diabetes on the cardiovascular system (CV). Furthermore, studies have reported that the incidence of HF in diabetic patients is significantly correlated with HbA1c levels.⁵⁻⁷ Hyperglycemia is an independent risk factor for ischemic heart disease (IHD) as several mechanisms lead to vascular damage due to long-term hyperglycemia.^{8,9} To clarify the mechanisms responsible for decreased myocardial contractility in the diabetic population, several explanations have been proposed.^{10,11} In patients with diabetes, altered metabolism has been associated with increased myocardial oxygen consumption and increased serum free fatty acid (FFA) concentrations.¹⁰ Abnormalities in contractile and regulatory protein expression and cardiomyocyte sensitivity Ca²⁺ are also found in DM. In diabetes, reduced activity of the sarcoplasmic reticular calcium pump (SRCP) and the rate of removal of Ca²⁺ from the cytoplasm in the diastole may be responsible for diastolic dysfunction.^{10,11} The main pathogenetic mechanism in HF and DM leading to structural alteration is hyperglycemia. Hyperglycemia leads to the glycation of several macromolecules that result in a decrease in the elasticity of the vessel walls and in myocardial dysfunction.^{10,11} Hyperglycemia also induces diabetes-specific changes in the microvascular architecture, such as reduced nitric oxide production resulting in endothelial dysfunction. The rennin-angiotensin-aldosterone (RAAS) system is activated at the beginning of T2DM. As HF progresses, the activation of the sympathetic nervous system (SNS) and RAAS increases, leading to a worsening of CV and renal function.^{10,12}

Current therapy

For the treatment of T2DM there are several pharmacological treatment options available. Among the medications used routinely there is insulin replacement therapy. Insulin replacement therapy when used correctly at the appropriate doses and times has shown a significant reduction in mortality in patients with T2DM due to cardiovascular

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Key words: Cardiology; diabetes; glyphozine; SGLT2; T2DM.

Conflict of interests: the authors declare no potential conflict of interests.

Ethical approval and consent: the authors declare that: there are no sensitive data and no patients were recruited for this study; the document does not conflict with ethical legislation.

Received for publication: 4 May 2020.
Revision received: 23 June 2020.
Accepted for publication: 7 July 2020.

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Geriatric Care 2020; 6:9079
doi:10.4081/gc.2020.9079

causes, however, some studies show that insulin has not provided benefits for cardiovascular diseases in patients with diabetes that are more severe compared to the standard of care with oral therapies. In this regard, several studies have shown that metformin and glucagon-like peptide 1 agonists (GLP-1) provide greater benefits for cardiovascular disease in diabetic patients. In addition, dipeptidil peptidase-4 inhibitors (DPP4) are associated with increased HF hospitalizations and in 2016 the Food and Drug Administration (FDA) issued an alert for increased HF risk associated with both saxagliptin but not sitagliptin.¹³ Therefore, a positive strategy is needed to address the risk of heart failure in diabetes. The first-line drug to manage hyperglycemia in type 2 DM is metformin. The diabetic patient with HF represents a particular challenge in the pharmacological treatment of diabetes. Current management strategies focus on known modifiable risk factors such as glucose, lipids and blood pressure (BP) which produce modest effects. Although these are important risk markers, none of these interventions substantially prevent HF or improve its outcome.^{14,15}

SGLT-2 inhibitors: an overview

Glyphozines are oral antidiabetic agents that inhibit the SGLT-2 protein in the proximal renal tubules and expel glucose in the

urine, thereby lowering blood glucose. Glyphozines are antidiabetic agents because they lower blood glucose independently of insulin. In addition to glycemic control, glyphozines also have several pleiotropic effects, in fact they are the only class of antidiabetic agents that have been shown to decrease the risk of CV events mainly by reducing the development or progression of HF. Infact glyphozines reduces blood pressure, reduces the activity of the sympathetic nervous system, reduces uric acid, reduces glucagon, reduces oxidative stress, and, of course, reduces blood sugar levels. All these factors could theoretically contribute to the blood pressure lowering effect of this class. In addition, glyphozines could improve myocardial energy efficiency through the oxidation of β -hydroxybutyrate and increase hematocrit by improving oxygen transport. Finally, there is a decrease in vascular rigidity and an improvement in endothelial function with the use of glyphozines in diabetes.¹⁶⁻¹⁸ Glyphozines can be used in both monotherapy and polytherapy.¹⁹⁻²⁶ The first large-scale study on the safety of CV with SGLT2 inhibitors in patients with T2DM (EMPA-REG OUTCOME) reported beneficial effects on CV events and hospitalization for HF in patients without baseline HF, suggesting that SGLT2i is a only glucose reducing agent and has multiple effects on hemodynamic and metabolic parameters. SGLT2i can be used in selected patients with substantial CV risk, but should be prescribed with great caution in patients taking diuretics.

The EMPA-REG OUTCOME study reported that patients with T2DM and high CV risk who received empagliflozin as an adjunct therapy to standard drugs compared to placebo showed a lower incidence rate of primary CV outcomes and overall mortality. The study reported a 0.38%-0.85% reduction in HbA1c levels with empagliflozin compared to placebo.^{27,28} Another study reported that empagliflozin reduced weight, waist circumference and adiposity indices compared to placebo concluding that empagliflozin significantly reduced weight and adiposity indices with the potential to improve cardiometabolic risk among T2DM patients.

The Canagliflozin Cardiovascular Assessment (CANVAS) study evaluated the efficacy, safety and duration of canagliflozin in more than 10,000 patients with diabetes who had a previous history of CV disease or at least two CV risk factors. The results showed that canagliflozin reduced CV and non-fatal myocardial infarction. The drug also demonstrated potential renal protective effects. Another study with T2DM patients showed that treatment with canagliflozin was associated with clinically significant and

dose-dependent reductions in HbA1c, as monotherapy and as part of combination therapy. In addition to reducing HbA1c levels, phase 3 studies on canagliflozin have reported dose-dependent reductions in body weight that are increased by reduction in visceral adiposity, which can reduce CV complications and mortality.²⁹ A further study reported the effects of canagliflozin on CV biomarkers in elderly DM patients. The study showed that the natriuretic serum N-terminal pro-B serum peptide, high-sensitivity troponin I and soluble ST2 remained unchanged in canagliflozin. These cardiac biomarker data support the beneficial CV effect of SGLT2Is in T2DM patients. When pitted against the two other new HF medication approved in the last 5 years (ivabradine and angiotensin receptor blocker and neprilysin inhibitor, ARNI), SGLT-2i have shown comparable benefits although they were not primarily developed for HF patients.³⁰⁻⁴⁷

Conclusions

Glyphozines are agents with an indication for the treatment of diabetes. In addition to antihyperglycemic agents, these drugs also possess various pleiotropic effects, thus providing benefits that go beyond glycemic control. Several studies have shown beneficial effects on CV risk factors by reducing BP, improving endothelial function and arterial stiffness, promoting weight loss, improving the lipid profile. Moreover, this is reinforced by a good safety profile, in fact the incidences of adverse events in clinical trials of glyphozine were similar to those observed with other antidiabetic drugs. The most frequently observed adverse events in subjects with glyphozine are urogenital tract infections. The risk of hypoglycaemia is minimal. These extraordinary characteristics of this class of drugs suggest that glyphozines could add a new dimension to the management of T2DM, on the contrary, a significant reduction in CV deaths and heart failure hospitalizations with these agents has opened a new path for the management of HF with T2DM.

References

- Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; 359:1577-89.
- National Institute of Diabetes and

Digestive and Kidney Diseases. Causes of Diabetes. Bethesda: National Institute of Diabetes and Digestive and Kidney Diseases; June 2014. Available from: <https://www.niddk.nih.gov/health-information/diabetes/overview/symptoms-causes?dkrd=hispt0015> Accessed: February 10, 2016.

- Ripsin CM, Kang H, Urban RJ. Management of blood glucose in type 2 diabetes mellitus. *Am Family Phys* 2009; 79:29-36.
- World Health Organization. Diabetes mellitus. Geneva: World Health Organization. Available from: <https://www.who.int/news-room/fact-sheets/detail/diabetes>
- Bauters C, Lamblin N, Mc Fadden EP, et al. Influence of diabetes mellitus on heart failure risk and outcome. *Cardiovasc Diabetol* 2003;2:1.
- Johansson I, Dahlström U, Edner M, et al. Risk factors, treatment and prognosis in Men and Women with heart failure with and without diabetes. *Heart* 2015;10:1139-48.
- Rosano GMC, Vitale C, Seferovic P. Heart failure in patients with diabetes mellitus. *Card Fail Rev* 2017;3:52-5.
- Dresslerová I, Vojáček J. Diabetes Mellitus And Ischemic Heart Disease. *Vnitr Lek* 2010;56:301-6.
- Kumar M, Gautham RK, Singh PS, et al. A study of diastolic dysfunction in patients of type-2 diabetes mellitus in rural population of western Uttar Pradesh. *J Evid Based Med Healthc* 2017;4:1608-11.
- Cas AD, Khan SS, Butler J, et al. Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure. *JACC* 2015;3:136-45.
- Kasznicki J, Drzewoski J. Heart failure in the diabetic population-pathophysiology, diagnosis and management. *Arch Med Sci* 2014;10:546-56.
- Lehrke M, Marx N. Diabetes mellitus and heart failure. *Am J Med* 2017;13.
- Valentina R, Weiss MC, Weintraub H, et al. Cardiovascular disease leads to a new algorithm for diabetes treatment. *J Clin Lipidol* 2017;11:1126-33.
- Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm-2017 executive summary. *Endocr Pract* 2017;23:207-38.
- Thomas MC. Type 2 diabetes and heart failure: Challenges and solutions. *Curr Cardiol Rev* 2016;12:249-55.
- Packer M, Anker SD, Butler J, et al.

- Effects of sodium-glucose cotransporter 2 inhibitors for the treatment of patients with heart failure: proposal of a novel mechanism of action. *JAMA Cardiol* 2017;2:1025-9.
17. Kimura G. Diuretic action of Sodium-glucose cotransporter 2 inhibitors and its importance in the management of heart failure. *Circ J* 2016;80:2277-81.
 18. Martens P, Mathieu C, Verbrugge FH. Promise of SGLT2 inhibitors in heart failure: Diabetes and beyond. *Curr Treat Options Cardiovasc Med* 2017; 19:23.
 19. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: A systematic review and metaanalysis. *Ann Intern Med* 2013;159:262-74.
 20. van Bommel EJ, Muskiet MH, Tonneijck L, et al. SGLT2 inhibition in the diabetic kidney-from mechanisms to clinical outcome. *Clin J Am Soc Nephrol* 2017;12:700-10.
 21. Sha S, Polidori D, Heise T, et al. Effect of the sodium glucose co-transporter 2 inhibitor canagliflozin on plasma volume in patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 2014; 16:1087-95.
 22. Ferrannini G, Hach T, Crowe S, et al. Energy balance after sodium- glucose cotransporter 2 inhibition. *Diabetes Care* 2015;38:1730-5.
 23. Baker WL, Buckley LF, Kelly MS, et al. Effects of sodium-glucose cotransporter 2 inhibitors on 24-hour ambulatory blood pressure: A systematic review and meta-analysis. *J Am Heart Assoc* 2017; 6:e005686.
 24. Muskiet MHA, van Bommel EJM, van Raalte DH. Antihypertensive effects of SGLT2 inhibitors in type 2 diabetes. *Lancet Diabetes Endocrinol* 2016;4: 188-9.
 25. Sumida Y, Yoneda M. Current and future pharmacological therapies for NAFLD/NASH. *J Gastroenterol* 2018;5 3:362-76.
 26. Heerspink HJ, Perkins BA, Fitchett DH, et al. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: Cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation* 2016;134: 752-72.
 27. Lytvyn Y, Bjornstad P, Udell JA, et al. Sodium glucose cotransporter-2 inhibition in heart failure: Potential mechanisms, clinical applications, and summary of clinical trials. *Circulation* 2017;136:1643-58.
 28. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:644-57.
 29. Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: A predictable, detectable and preventable safety concern with SGLT2 inhibitors. *Diabetes Care* 2015;38:1638-42.
 30. Scheen AJ. Pharmacokinetic and pharmacodynamic profile of empagliflozin, a sodium glucose co-transporter 2 inhibitor. *Clin Pharmacokinet* 2014;53: 213-25.
 31. Devineni D, Curtin CR, Polidori D, et al. Pharmacokinetics and pharmacodynamics of canagliflozin, a Sodium glucose co-transporter 2 inhibitor, in subjects with type 2 diabetes mellitus. *J Clin Pharmacol* 2013;53:601-10.
 32. Inagaki N, Kondo K, Yoshinari T, et al. Pharmacokinetic and pharmacodynamic profiles of canagliflozin in Japanese patients with type 2 diabetes mellitus and moderate renal impairment. *Clin Drug Investig* 2014;34:731-42.
 33. Saeed MA, Narendran P. Dapagliflozin for the treatment of type 2 diabetes: A review of the literature. *Drug Des Devel Ther* 2014;8:2493-505.
 34. Tucker ME. CANVAS: Canagliflozin reduces cv events, but at cost of amputations. *Medscape*, June 12, 2017. Available from: <https://www.medscape.com/viewarticle/881499>
 35. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;380:347-57.
 36. Kosiborod M, Cavender MA, Az F, et al. Lower risk of heart failure and death in patients initiated on Sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: The CVD-REAL study (Comparative effectiveness of cardiovascular outcomes in new users of sodium-glucose cotransporter-2 inhibitors) *Circulation* 2017;136:249-59.
 37. Swedberg K, Komjanda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo controlled study. *Lancet* 2010;376:875-85.
 38. Mc Murray JJ, Packer M, Desai AS, et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure (PARADIGM-HF). *N Engl J Med* 2014; 371:993-1004.
 39. Prasanna Kumar K, Ghosh S, Canovatchel W, et al. A review of clinical efficacy and safety of canagliflozin 300 mg in the management of patients with type 2 diabetes mellitus. *Indian J Endocrinol Metab* 2017;21:196--.
 40. Dave CV, Schneeweiss S, Paterno E. Comparative risk of genital infections associated with sodium-glucose cotransporter-2 inhibitors. *Diabetes Obes Metab* 2019;21:434-8.
 41. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium–Glucose Cotransporter 2 Inhibitors for Type 2 Diabetes: A Systematic Review and Meta-analysis. *Ann Intern Med* 2013; 159:262-74.
 42. Zaccardi F, Webb D, Htike Z, et al. Efficacy and safety of sodium glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: Systematic review and network meta-analysis. *Diabetes Obes Metab* 2016;18:783-94.
 43. Wu JH, Foote C, Blomster J, et al. Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: A systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2016; 4:411-9.
 44. Li D, Wang T, Shen S, et al. Urinary tract and genital infections in patients with type 2 diabetes treated with sodium-glucose co-transporter 2 inhibitors: A meta-analysis of randomized controlled trials. *Diabetes Obes Metab* 2017;19:348-55.
 45. Chang HY, Singh S, Mansour O, et al. Association between sodium-glucose cotransporter 2 inhibitors and lower extremity amputation among patients with type 2 diabetes. *JAMA Intern Med* 2018;178:1190-8.
 46. Das SR, Everett BM, Birtcher KK, et al. 2018 ACC Expert Consensus Decision Pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol* 2018;72:3200-23.
 47. Peters AL, Buschur EO, Buse JB, et al. Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter 2 inhibition. *Diabetes Care* 2015;38:1687-93.