Republic of Iraq

Ministry of Higher Education and Scientific Research

University of Diyala

College of Medicine

Department of Pharmacology 2020-2021 sixth stage

Effect of sodium-glucose co-transporter 2 inhibitor drugs on cardiovascular disease in diabete

Submitted by: Sarah Qais Khalefa

Supervised by: Dr.Qutaiba Ghanim

On this research we going to discuss the following:

- Cardiac effect and cardiovascular outcome
- Summary of large clinical trials
- Mechanism of cardiovascular benefit
- Researcher critical opinion
- Reference

Abstract

Diabetes mellitus management is becoming increasingly complicated due to the increased risk of cardiovascular diseases such as heart failure, myocardial infarction and high incidence of left ventricular diastolic dysfunction, especially with type 2 diabetes mellitus. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a new drug class for the management of diabetes mellitus with a suitable hypoglycemic effect. There are numerous clinical evidence that's shown SGLT2 inhibitors can significantly minimize the risks of atherosclerosis (so it is considered a second line after metformin), hospitalization for heart failure, cardiovascular death and slow the progression of chronic kidney disease. Therefore, it's regarded important for cardiologists, diabetes mellitus patients, and nephrologists to entirely understand this class of drugs. This review will summarize the following aspects of SGLT2 inhibitors: the recent clinical evidence of their cardiovascular benefits and cardiac effect, mechanisms of action, and its safety.

Introduction

Worldwide, morbidity of diabetes mellitus has increased in recent years. The latest reviews from the International Diabetes Federation (IDF) point that by 2045 the number of patients with diabetes mellitus will be 700.2 million **(1).** This progression in numbers attributed to several factors such as the ageing of the population, decreases physical activity, and rapid urbanization, which result in obesity. Type 2 diabetes is considered as a major risk factor for cardiovascular diseases such as myocardial infarction and heart failure, and it is the leading cause of death in patients with type 2 diabetes mellitus. There are several drug classes have demonstrated a significant reduction in adverse cardiovascular events (MACE) such as

Sodium glucose cotransporter 2 (SGLT2) inhibitors (dapagliflozin, canagliflozin, empagliflozin). SGLT2 inhibitors are glucose-lowering agents that work on proximal convoluted tubule in the kidney by block sodium-dependent glucose transporter-2 (SGLT2) and lead to increase urinary glucose excretion(glycosuria) and decrease the concentration of blood glucose**(2).** This effect leads to decrease body weight, osmotic diuresis (increase urination) and hypotensive effects **(2).**

In large clinical trials (EMPA-REG OUTCOME, CANVAS Program and DECLARE-TIMI 58) SGLT2 inhibitors, which include improving long-term clinical outcomes, including all cause of mortality, and heart failure hospitalization in T2DM by play a key role in the improvement of cardiac function in diabetic cardiomyopathy.

Meta-analysis also showed the clinical benefits of SGLT2 inhibitors in reducing the risk of stroke, myocardial infarction (MI), and cardiovascular death in patients with atherosclerotic cardiovascular disease (it is considered the second line after metformin in those patients). Recently, DAPA-HF reported that dapagliflozin improved cardiovascular outcomes among patients with heart failure with reduced ejection fraction regardless of diabetic status **(20).** We will discuss the effect of SGLT2 inhibitors on cardiac function in clinical studies and the underlying mechanisms contributing to cardio protection **(3).**

Cardiac effects and cardiovascular outcomes of SGLT2 inhibitors

There are many influential research describe the cardiovascular outcomes of Sodium-glucose cotransporter 2 inhibitors, namely Canagliflozin Cardiovascular Assessment Study software (CANVAS), Empagliflozin Cardiovascular

Outcome Trial in Diabetes Mellitus type 2 Patients-Removing Excess Glucose (EMPA-REG OUTCOME) trial and Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction (DECLARE-TIMI) trial **(4) (5) (6).** These studies investigated the effect of SGLT2 inhibitors in patients with type two diabetes (T2D) with cardiovascular sickness or excessive cardiovascular risk. SGLT2 inhibitors decreased predominant poor cardiovascular activities in T2D with an immoderate threat of cardiovascular sickness. In addition, SGLT2 inhibitors reduced all-cause mortality in T2D and had effect on cardiovascular dying hazard (RR: 0.81; 95% CI (0.63, 1.05); P = 0.116).

Advantages of the Sodium-glucose cotransporter-2 inhibitors on cardiovascular death are not the identical. For example, Englitazone can diminish the risk of cardiovascular death and allcause mortality. Recent studies have shown that the risk of CVD events was decreased by 11% in type 2 diabetes when patients use dapagliflozin, canagliflozin and empagliflozin. These category of drugs also limits the risk of hospitalization for heart failure **(21)** and decreased Myocardial infarction risk **(23).**

Other studies have shown that SGLT2 inhibitors are superior to other glucose lowering agents (such as insulin, metformin, sulfonylurea, DPP-4i, alpha glucosidase inhibitor and thiazolidinedione) in decreasing the incidence of heart failure hospitalization and all-cause death **(8).** It has also been demonstrated that SGLT2 inhibitors reduce the incidence of cardiovascular death, cerebral infarction, myocardial infarction and heart failure

Table1

Study title	Study type	Number of patient	Follow up	Study population	Primary outcom	
GAR_APME **CMOCPA**	RCT 1:1:1 Empagliflozine 10 mg vs Empaglioflozine 25 mg vs blacebo	7028	3.1	• Type 2 Dm • CV Diseas • BMI more than 45	Decrease MI CV death in empagliflozin vs placebo (HR 0.86, 95% CI 0.74 to 0.99)	
CANVAS trial	CT 1:1:1 Canagliflozin 300 mg vs canagliflozin 100 mg vs placebo	10142	2.4	Patients with: Type 2 diabetes mellitus High CV risk	Reduction CV death, non-fatal myocardial infarction or stroke (HR 0.86, 95% CI 0.75 to 0.87)	
DECLARE-TIMI 58	RCT Dapagliflozin 10 mg vs placebo	17160	4.2	Patients with: Type 2 diabetes mellitus Established CV disease or multiple risk factors	Reduction CV death, non-fatal myocardial infarction or stroke (HR 0.93, 95% CI 0.84 to 1.03)	

VERTIS CV trial	RCT 1:1:1 Ertugliflozin 5 mg vs ertugliflozin 15 mg vs placebo	8246	3.5	Patients with: Type 2 diabetes mellitus Established CV disease	CV death, non-fatal MI or stroke (HR 0.97, 95% CI 0.85 to 1.11	

Summary of large clinical trials of the SGLT2-inhibitor class

Mechanisms of cardiovascular benefits

1. Reduce vessels stiffness and blood pressure

Increase vessels stiffness lead to increase cardiovascular mortality and heart failure. Forty percent of patients with Type 2 diabetes mellitus are diagnosed with hypertension. Type 2 DM patients with arterial stiffness have a high incidence of hypertension due to activation of renin-angiotensin-aldosterone system and decrease the level in nitric oxide. However, empagliflozin has been shown to improve vascular resistance and decrease arterial stiffness. This has a positive effect on the metabolism of myocardial muscle and calcium Overload **(23).** According to recent studies, empagliflozin also reduces the stiffness of the artery by decrease systolic blood pressure after 8 week of treatment **(23).** In the sympathetic nervous system, the flow of renal blood and the angiotensin system all play a role in the reabsorption of sodium in the proximal convoluted tubule. SGLT2 inhibitors and in response to volume contractions, increase the level of aldosterone and angiotensin II and reducing blood pressure by direct vascular effect **(12).**In summary, SGLT2 inhibitors can reduce arterial stiffness by

vascular smooth muscle relaxation mainly because of the negative sodium balance and diuretic effect.

2. Changes in energy metabolism

It's the most beneficial and vital mechanisms that occur by simulating fatty acids' oxidation **(9).** Dapagliflozin increases the oxidation of glucose and fat 20% and 14%, respectively **(10).** It has also been suggested that S GLT2 inhibitors-induced cardio protection in Type 2 DM patients could be, at least in part, due to enhancing cardiac energy production via increasing ketone bodies production **(24).** Some clinical studies have shown that canagliflozin can increase plasma β-hydroxybutyrate, increase cardiac efficiency by 24%, and decrease oxidative stress and decrease the oxygen need. In patients with type 2 diabetes, oxidative stress and myocardial injury can increase with glucose toxicity **(25).** SGLT2 inhibitors are shown to prevent excessive glucose uptake by the heart. In general, fatty acids are the main source of energy for the heart. However, hyperglycemia simulate cardiocyte to uptake the glucose so the cardiac function will impairs.SGLT2 inhibitors will enlarge βhydroxybutyrate and alternate the energy furnish from fatty acids and glucose to ketones**(11)** This will elevated the metabolic affectivity of the myocardium and kidney and decrease the consumption of oxygen .Now, the ketone hypothesis is nonetheless being explored.

3. Increases in hemoglobin and hematocrit

It has been shown that empagliflozin can decrease cardiovascular mortality by increasing the level of hematocrit due to the level of plasma volume **(13).** SGLT2 inhibitors increase hematocrit level by improving tubulointerstitial oxygen shortage and erythropoiesis and reducing the workload the workload. In Chinese patients with type 2 diabetes, low hematocrit and chronic kidney disease can lead to adverse cardiovascular events. In patients with diabetes who use dapagliflozi, the levels of erythropoietin were elevated followed through a make more prominent in the hematocrit stage. SGLT2 inhibitors have been used to restore tubulointerstitial effects, decrease renal tubules and promote erythropoietin production. Acute treatment with SGLT2 inhibitors increased hematocrit ranges in diabetic

patients and reversed kidney remodeling **(26).** An extend in hematocrit levels at some stage in treatment with empagliflozin was extensively associated with a discount in cardiovascular death.

4. Myocardial remodeling improvement

The remodeling and fibrosis of cardiac muscle are complex processes related to inflammation and oxidative stress **(14).** It is a significant cause of heart failure and myocardial fibrosis. Myocardial remodeling occurs due to the activation of cardiac fibroblasts production and the release of extracellular matrix **(14).** Macrophages can speed up irritation and increase myocardial remodeling. It is composed of 2 phenotype M1 and M2. M2 macrophages is considered to be vital for post-myocardial remodeling in a mouse model of myocardial infarction **(27).** Macrophages affect the characteristics of myofibroblasts, but M1 and M2 macrophages are balanced in the tissue. It has recently been shown that dapagliflozin could modulate these phenotypes and minimize myocardial fibrosis and remodeling **(27).**

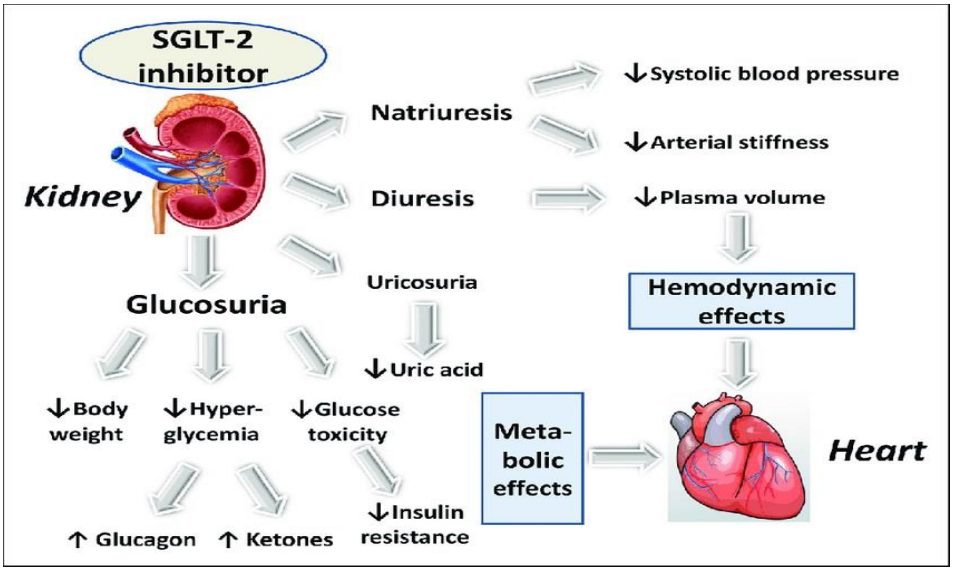

Figure 2

Primary mechanism of action of SGLT2 inhibitor and their hemodynamic and metabolic effect result in improve MI and reduce risk of heart failure

5. Weight reduction and good glycemic control

It has been postulated that exact glycemic control and weight reduction management underlie the Cardio protective impact seen with SGLT2 inhibitors therapy (28). However, weight loss by SGLT2 inhibitors takes place due to amplify the ratio of glucagon: insulin which causes an elevation in lipid mobilization. This effect has also been linked decrease mortality in heart failure patients **(28).** It has been shown that more than 2.7 kg weight loss was noted in type 2

diabetes patients with SGLT2inhibitors **(28).** However, these findings have later been challenged since no evidence of weight loss are observed in patients with heart failure without diabetes which would be an argument against weight reduction being the vital mechanism of gain with SGLT2 inhibitors **(28).** Moreover, regardless of the excessive prevalence of obesity in heart failure, there is little definitive evidence related to the effects of weight loss on cardiac function, quality of existence and exercise tolerance in patients

With heart failure. Therefore, weight loss by itself can't explain SGLT2inhibition–related benefits in heart failure **(15).**

6. Electrolyte change

In cardiac muscle SGLT2 Inhibitors will reduce sodium level secondary to sarcolemma and mitochondrial Ca2+ exchange and decreasing Ca2 attention. The mitochondrial Ca2+ level, as the essential agonist of antioxidant dealers and ATP, increases at some stage in heart failure to enhance cardiac function. More research is needed to make clear these effects **(16).**

7. Decrease in serum uric acid

There is a strong correlation between hyperuricemia, diabetes mellitus, hypertension, kidney sickness and cardiovascular sickness (17).—Hyperuricemia is an important hazard elements for development of cardiovascular disorder (17). It has been shown that SGLT2 inhibitors minimize the degree of uric acid and glucose-induced diuretic diminution in patients with diabetes **(17).**

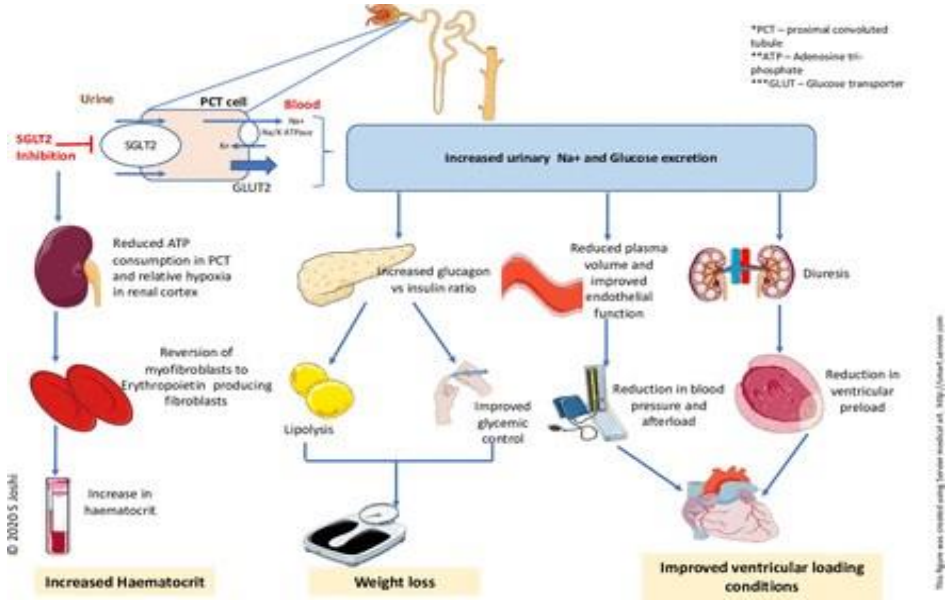

Figure 2 mechanism of action of SGLT2 Inhibitor

Conclusions

In summary, as a new category of drug for diabetes mellitus type 2 treatment, SGLT2 inhibitors are good hypoglycemic agents that can lower the risk of cardiovascular disease and, in addition to benefits on cardiovascular and renal function. SGLT2 inhibitors can exert their cardiovascular protective effects by the super fuel theory, electrolyte factors and improved hemodynamics, elevate erythropoietin, increase glucagon, and decrease oxidative stress and inflammation. However, further research is required to clarify the particular mechanisms.

Researcher's critical opinion

In compare with other population patients with diabetes mellitus type 2 are at higher risk for development of cardiovascular disorder such as MI and heart failure. SGLT2-inhibitor therapies are a promising class of drugs for treating patients with type 2 diabetes and reduce cardiovascular events and heart failure hospitalizations through combination of systemic and direct effects on the myocardium such as blood pressure reduction, diuresis, weight reduction, good glycemic control,

Improved hemodynamics, increased erythropoietin, elevated glucagon, and inhibition of oxidative stress However, further research is still needed to clarify the specific mechanisms. The different SGLT2 inhibitors type are associated with clinical heterogeneity so more studies are expected in the future to clarify the role of SGLT2 inhibitors and there great effect.

References

1-International Diabetes Federation. IDF Diabetes Atlas, 8th ed. Brussels, Belgium: International Diabetes Federation; 2017

2-MJB van Baar, CC van Ruiten, MHA Muskiet, L van Bloemendaal, RG Ijzerman, DH van Raalte SGLT2 inhibitors in combination therapy: from mechanisms to clinical considerations in type 2 diabetes management Diabetes Care, 41 (2018), pp. 1543-1556 CrossRefView Record in ScopusGoogle Scholar PubMed

3-Udell JA, Cavender MA, Bhatt DL, et al. Glucose-lowering drugs or strategies and cardiovascular outcomes in patients with or at risk for type 2 diabetes: a meta-analysis of randomised controlled trials. Lancet Diabetes Endocrinol 2015;3:35666.doi:10.1016/S2213-8587(15)00044-3pmid:http://www.ncbi.nlm.nih.gov/pubmed/25791290PubMedGoogle Scholar

4-B. Zinman, C. Wanner, J.M. Lachin, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes N Engl J Med, 373 (2015), pp. 2117-2128 View Record in ScopusGoogle Scholar PubMed

5- B.Akinci Dapagliflozin and cardiovascular outcomes in type 2diabetes N Engl J Med, 380 (2019), p. 1881 View Record in ScopusGoogle Scholar.

6- B. Neal, V. Perkovic, D.R. Matthews Canagliflozin and cardiovascular and renal events in type 2 diabetes N Engl. J Med, 377 (2017), p. 2099 View Record in ScopusGoogle Scholar.

7- T.A. Zelniker, S.D. Wiviott, I. Raz, 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, 393 (2019), pp. 31-39 ArticleDownload PDFView Record in ScopusGoogle Scholar

8- T.A. Zelniker, S.D. Wiviott, I. Raz, 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, 393 (2019), pp. 31-39 ArticleDownload PDFView Record in ScopusGoogle Scholar

9-Ganbaatar, D. Fukuda, M. Shinohara, et al. Empagliflozin ameliorates endothelial dysfunction and suppresses atherogenesis in diabetic apolipoprotein E-deficient mice Eur J Pharmacol, 875 (2020), p. 173040 ArticleDownload PDFView Record in ScopusGoogle Scholar

10_M. Merovci, C. Solis-Herrera, G. Daniele, et al.Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production J Clin Invest, 124 (2014), pp. 509514 View Record in ScopusGoogle Scholar

11- N. Inagaki, K. Kondo, T. Yoshinari, N. Takahashi, Y. Susuta, H. Kuk Efficacy and safety of canagliflozin monotherapy in Japanese patientswith type 2 diabe Tes inadequately controlled with diet and exercise: a 24-week, randomized, double-blind, placebo-controlled, Phase III study Expet Opin Pharmacother, 15 (2014), pp. 1501-1515 CrossRefView Record in ScopusGoogle Scholar

12-F.H. Verbrugge, M. Dupont, P. Steels, et al.The kidney in congestive heart failure: 'are natriuresis, sodium, and diuretics really the good, the bad and the ugly?' Eur J Heart Fail, 16 (2014), pp. 133-142CrossRefView Record in ScopusGoogle Scholar 13-M.

PackerAutophagy stimulation and intracellular sodium reduction as mediators of the cardioprotective effect of sodium-glucose cotransporter 2 inhibitors Eur J Heart Fail, 22 (2020), pp. 618-628CrossRefView Record in ScopusGoogle Scholar

14- T.A. Zelniker, E. Braunwald Mechanisms of cardiorenal effects of sodium-glucose cotransporter inhibitors: JACC state-of-the-art reviewJ Am Coll Cardiol, 75 (2020), pp.

422434 ArticleDownload PDFView Record in ScopusGoogle Scholar

15- R. Sharma, L. Wilkinson, H. Vrazic, et al. Comparative efficacy of once-weekly semaglutide and SGLT-2 inhibitors in type 2 diabetic patients inadequately controlled with metformin monotherapy: a systematic literature review and network meta-analysis Curr Med Res Opin, 34 (2018), pp. 1595-1603 CrossRefView Record in ScopusGoogle Scholar

16-T. Liu, E. Takimoto, V.L. Dimaano, et al.Inhibiting mitochondrial Na+/Ca2+ exchange prevents sudden death in a Guinea pig model of heart failure Circ Res, 115 (2014), pp. 44-54 View Record in ScopusGoogle Scholar

17- Dehghan, M. van Hoek, E.J. Sijbrands, A. Hofman, J.C. Witteman High serum uric acid as a novel risk factor for type 2 diabetes Diabetes Care, 31 (2008), pp. 361-362 CrossRefView Record in ScopusGoogle Scholar

18- T. Forst, R. Guthrie, R. Goldenberg, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes on background metformin and pioglitazone Diabetes Obes Metabol, 16 (2014), pp. 467-477 CrossRefView Record in ScopusGoogle Scholar

19- L.A. Leiter, K.H. Yoon, P. Arias, 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, 38 (2015), pp. 355-364 CrossRefView Record in ScopusGoogle Scholar

20- Rosano GM, Vitale C, Seferovic P. Heart failure in patients with diabetes mellitus. Card Fail Rev. 2017;3:52–55. Doi: 10.15420/cfr.2016:20:2. [PMC free article] [PubMed]

21- Echouffo-Tcheugui JB, Xu H, DeVore AD, et al. Temporal trends and factors associated with diabetes mellitus among patients hospitalized with heart failure: findings from Get with The Guidelines-Heart Failure registry. Am Heart J. 2016;182:9–20. Doi:

10.1016/j.ahj.2016.07.025. [PubMed] [CrossRef] [Google Scholar]

22- iviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, et al.; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes.N Engl J Med. 2019; 380:347–357. Doi:

10.1056/NEJMoa1812389CrossrefMedlineGoogle Scholar

23 empagliflozin has been shown to improve vascular resistance and decrease arterial stiffness. This has a positive effect on the metabolism of myocardial muscle and calcium Overload

24 -Mabillard H., Sayer J.A. SGLT2 inhibitors—a potential treatment for Alport syndrome. Clin Sci (Lond) 2020;134:379–388. [PubMed] [Google Scholar]

25 -Ferrannini E., Mark M., Mayoux E. CV protection in the EMPA-REG outcome trial: a "Thrifty substrate" hypothesis. Diabetes Care. 2016;39:1108–1114. [PubMed] [Google Scholar]

26 -Neuen B.L., Jardine M.J., Perkovic V. Sodium-glucose cotransporter 2 inhibition: which patient with chronic kidney disease should be treated in the future? Nephrol Dial Transplant. 2020;35:i48–i55. [PMC free article] [PubMed] [Google Scholar]

27-T.M. Lee, N.C. Chang, S.Z. Lin Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts Free Radic Biol Med, 104 (2017), pp. 298-310ArticleDownload PDFView Record in ScopusGoogle Scholar

28-T.M. Lee, N.C. Chang, S.Z. Lin Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts Free Radic Biol Med, 104 (2017), pp. 298-310 Scopus Google Scholar