Empagliflozin in the treatment of heart failure and type 2 diabetes mellitus: Evidence from several large clinical trials

Bo Liang[1,2], Ning Gu[3]

1. Nanjing University of Chinese Medicine, Nanjing, China

2. Department of Cardiology, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China

3. Nanjing Hospital of Chinese Medicine Affiliated to Nanjing University of Chinese Medicine, Nanjing, China

Correspondence: Ning Gu, guning@njucm.edu.cn

Abstract

Heart failure coexists with type 2 diabetes mellitus, which seriously affects the clinical treatment and prognosis. At present, the treatment for patients with established heart failure and type 2 diabetes mellitus is usually combined with two treatment strategies for heart failure and type 2 diabetes mellitus. Recently, increasing studies showed that empagliflozin, a sodium-glucose co-transporter-2 inhibitor, has a positive effect on the treatment of patients with established heart failure and type 2 diabetes mellitus. Here, we summarize the latest and current understanding of the management for patients with established heart failure and type 2 diabetes mellitus and further present contemporary treatment options, sodium-glucose co-transporter-2 inhibitor, for these particular populations.

Keywords: empagliflozin; SGLT2i; heart failure; type 2 diabetes mellitus

Background

Heart failure (HF) and type 2 diabetes mellitus (T2DM) are common medical diseases[1, 2], especially among the elderly. Two diseases are usually diagnosed in the same patient at the same time, which undoubtedly increases the difficulty of clinical management and worsens the prognosis of patients[3, 4]. The clinical condition of patients with T2DM complicated with HF, both HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), is worse than that of patients with HF without T2DM, and all-cause mortality and cardiovascular mortality are higher[5-7]. In another word, T2DM exacerbates the prognosis of HF. Moreover, studies show that HF is an independent predictor of clinical prognosis, whether fatal or nonfatal, in diabetic patients[8-11]. The interaction between HF and T2DM makes the prognosis of patients more unsatisfactory.

When a patient is diagnosed with HF and T2DM at the same time, our current understanding is that, in general, all HF treatments are similarly effective irrespective of T2DM. In recent years, many hypoglycemic drugs, such as sodium-glucose co-transporter-2 inhibitors (SGLT-2is), have emerged in the treatment of HF. Although the potential benefits and risks of SGLT-2is are unclear[12], SGLT-2is significantly reduce cardiovascular events, including hospitalization for HF (HHF) and all-cause hospitalization or death[13-17]. Scandinavian register-based cohort study indicated that SGLT-2i lowers HF risk compared with dipeptidyl peptidase-4 inhibitor[18], another glucose-lowering drug. This benefit from SGLT-2i may contribute to the upregulation of the renin-angiotensin-aldosterone system[19]. Empagliflozin, an SGLT2i, significantly reduces HHF in patients with established cardiovascular disease or at risk of cardiovascular disease and improves cardiac function in HFrEF independent of loading conditions[20]. The latest guideline recommended that empagliflozin should be considered in patients with T2DM and either established cardiovascular disease or at high cardiovascular risk to delay or prevent the onset of HF or prolong life[21]. A meta-analysis also indicated that compared with placebo, empagliflozin reduced all-cause and cardiovascular mortality independent of baseline risk[22]. Of note, few trials

supported the recommendation where the presence of HF at baseline well-characterized or phenotyped, indicating that evidence supporting empagliflozin for patients with HF and T2DM is still insufficient. Here, we critically review and distill contemporary evidence of empagliflozin for treating established HF and T2DM, with a view to provide a more systematic, comprehensive and rational understanding of this treatment option.

EMPA-REG OUTCOME

The EMPA-REG OUTCOME trial was conducted to assess the effect of empagliflozin on cardiovascular events in adults with T2DM at high cardiovascular risk[23]. The investigators also set different doses of empagliflozin and placebo. The primary outcome was cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke, and the key secondary composite outcome was the primary outcome plus hospitalization for unstable angina. After a median observation time of 3.1 years, patients in the empagliflozin group had 13.56% and 10.44% reduction in the primary outcome and the key secondary composite outcome, respectively, compared with those in the placebo group. Moreover, empagliflozin significantly lowers HHF, cardiovascular mortality, and all-cause mortality than placebo, whereas reduces nonfatal myocardial infarction and nonfatal stroke with no significance to placebo. Furthermore, the effects of different empagliflozin doses were insignificant. In short, the EMPA-REG OUTCOME trial demonstrated that empagliflozin reduces HHF risk by 35% on top of the standard of care in patients with T2DM and established cardiovascular disease[24]. The post hoc evaluation showed that the changes in haematocrit and haemoglobin were the most important mediators of the reduction in HHF and death from HF[25].

EMPRISE

The EMPRISE study program used real-world data from three databases in the USA to evaluate the effectiveness, safety, and impact on healthcare utilization of empagliflozin[26]. The interim analysis of EMPRISE evaluated the impact of

empagliflozin on HHF and compared it with sitagliptin, a dipeptidyl peptidase-4 inhibitor, which has proven to have a neutral impact on HHF[27]. After propensity-score matching, there were 16443 patients left in both groups from EMPRISE. Only approximately 5% had records of existing HF. Over a mean follow-up of 5.3 months, the initiation of empagliflozin decreased HHF-specific risk, defined as discharge diagnosis of HF in the primary position, by 50%, and HHF-broad risk, defined as discharge diagnosis of HF in any position, by 49%, compared with the initiation of sitagliptin. Results of HHF-broad risk were consistent in patients with and without HF history[26]. It should be noted that in the outcome analysis, due to a small change in the definition of HF history, the number of patients with HF history in empagliflozin and sitagliptin increased by 132% and 119%, respectively, which indicates that some patients who did not suffer from HF at baseline developed HF during the follow-up.

EMPA-TROPISM

The EMPA-TROPISM trial, a randomized, double-blind, parallel-group, placebo-controlled, trial, compared the efficacy of and safety of empagliflozin in non-diabetic HFrEF (below 50%) patients[28]. Empagliflozin significantly improved left ventricular end-diastolic and end-systolic volumes decreased left ventricular mass, increased left ventricular ejection fraction, enhanced functional capacity as per peak O_2 consumption oxygen uptake efficiency slope, and 6-min walk test, and improved quality of life as per the Kansas City Cardiomyopathy Questionnaire-12 when compared with placebo[29]. EMPA-TROPISM also demonstrated that empagliflozin regresses left ventricular interstitial fibrosis, improves aortic stiffness, regresses epicardial adipose tissue, and exerts an anti-inflammatory effect[30], which provides a new clue for the mechanism of empagliflozin. Of the utmost importance, the favorable reversal of left ventricular remodeling by empagliflozin has also been verified in SUGAR-DM-HF in patients with HFrEF (≤ 40%) and T2DM or prediabetes [31] and Empire HF in both diabetic and non-diabetic HFrEF (below 40%) patients[32].

EMPEROR-Reduced

The EMPEROR-Reduced trial can well determine whether empagliflozin can significantly increase the clinical benefit of HFrEF patients[33]. EMPEROR-Reduced included 3730 HFrEF patients with or without T2DM, 1863 in the empagliflozin group and 1867 in the placebo group, and empagliflozin significantly lowered HHF by 28% and cardiovascular mortality by 7% than placebo, regardless of combining T2DM or not[34].

EMPEROR-Preserved

The EMPEROR-Preserved trial enrolled 5988 patients with HFpEF, with and without T2DM. The primary outcome was HHF or cardiovascular mortality. The results indicated that empagliflozin reduced HHF by 27.12% and cardiovascular mortality by 10.98%[35]. What's more, EMPEROR-Preserved will drive the evolution of HFpEF through a series of biomarkers that reflect important pathophysiological mechanisms of HFpEF, and thus highlight more therapeutic options in HFpEF.

Discussion

EMPA-REG OUTCOME, EMPRISE, and EMPEROR-Reduced all showed that empagliflozin reduces the risk of HHF among specific individuals (Table 1). Nevertheless, these patients included in the trials did not have an established HF combined with T2DM or the degree of HF combined with T2DM was low at baseline, indicating the evidence of the clinical benefits of empagliflozin on HF patients combined with T2DM are still not sufficient, therefore, long-term clinical exploration including both HF with T2DM patients is needed.

At present, the evidence for empagliflozin in the treatment of HFpEF is still sparse[36]. The prevalence of HFpEF increases with age[37]. The increased risk of HHF might be explained by the occurrence of multiple comorbidities in older adults with HFpEF[38]. However, EMPEROR-Preserved did not include the total comorbidity burden as a covariate in their analysis[39]. A prospective study was designed to assess the cognitive and physical function in consecutive frail older adults with diabetes and HFpEF,

indicating empagliflozin improved Montreal cognitive assessment scores and physical impairment assessed by the 5-m gait speed test[40]. EMPEROR-Preserved also confirmed that health status, as measured by the Kansas City Cardiomyopathy Questionnaire, improved at all time points when assessed (3, 8, and 12 months) for all domains (total symptom score, clinical summary score, and overall summary score[41]. Despite this, the benefits of empagliflozin were observed early and consistently. The nominal statistical significance was achieved for separation between the empagliflozin and the placebo arms by day 18 for time to cardiovascular death or HHF, and this significance was sustained from there to the trial period[42]. A similar pattern of early and sustained benefit was seen for health-related quality of life scores, the Kansas City Cardiomyopathy Questionnaire (total symptom score, clinical summary score, and overall summary score), and New York Heart Association functional class as well[43]. Similarly, in EMPA-REG OUTCOME, the benefit of empagliflozin in reducing the risk of HHF and cardiovascular death emerged within weeks after treatment initiation[44]. The simplest explanation for such fast and short-term effects of empagliflozin in HFpEF is its diuretic effect[45]. However, the diuretic effect of empagliflozin is different from loop diuretics in that empagliflozin caused a significant increase in 24-hour urine volume without an increase in urinary sodium and electrolyte-free water clearance[46] and a significant decrease in estimated plasma volume calculated by the Straus formula and estimated the extracellular volume determined by the body surface area[47]. A pooled analysis of both the EMPEROR-Reduced and EMPEROR-Preserved trials indicated that the magnitude of the effect of empagliflozin on heart failure outcomes and health status was similar in patients with ejection fractions < 25% to < 65%, but it was attenuated in patients with an ejection fraction ≥ 65%[48], which may herald the recognition of a new phenotype characterized by supra-normal left ventricular ejection fraction[49].

In addition to reducing HHF to a certain extent, empagliflozin also has a certain impact on a series of biomarkers that may consider vital roles in the gradual development of HF[50]. Serum adipocyte fatty acid-binding protein levels were significantly higher in

participants with T2DM without a known history of cardiovascular diseases or HHF who developed HHF than those who did not, and empagliflozin reduced the serum adipocyte fatty acid-binding protein levels[51]. The exploratory analysis of EMPA-REG OUTCOME laid the foundation for long-term and short-term benefits of empagliflozin on urinary albumin excretion, regardless of the albuminuria status at baseline[52]. EMBLEM was completed in Japan to explore the effect of empagliflozin on endothelial function in patients with T2DM and established cardiovascular disease[53]. After 24 weeks of intervention, empagliflozin significantly improved glycemic control and reduced body mass index. As for reactive hyperemia peripheral arterial tonometry index, which was used to assess the effects of treatment on endothelial function, there was no significant difference in the changes between empagliflozin and placebo[54]. This Empire HF Biomarker substudy from Empire HF showed that empagliflozin increased plasma growth differentiation factor-15, where the increase was inversely associated with a decrease in left ventricular end-systolic and end-diastolic volume, with no concomitant increase in plasma high-sensitive C-reactive protein nor high-sensitive troponin T compared to placebo[55]. Moreover, Empire HF investigated that empagliflozin did not change N-terminal pro-B-type natriuretic peptide in low-risk patients with HFrEF with mild symptoms after 12 weeks[56]. Paradoxically, we notice that empagliflozin could significantly reduce N-terminal pro-B-type natriuretic peptide in EMPEROR-Reduced[34]. Considering the longer follow-up time of EMPEROR-Reduced (16 months), this may be one of the reasons for the inconsistent results. Another ongoing EMMYtrial may provide us with more information[57].

Numerous pathophysiological pathways contribute to the cardiovascular effects of empagliflozin[58] (Figure 1). The SIMPLE trial investigated the effects of empagliflozin on myocardial flow reserve reflecting microvascular perfusion among patients with T2DM at high cardiovascular disease risk and found that empagliflozin did not improve myocardial flow reserve[59]. Empagliflozin demonstrates direct cardiac effects by lowering myocardial cytoplasmic Na^+ and Ca^{2+} and enhancing

mitochondrial Ca^{2+}, through impairment of myocardial Na^{+}/H^{+} exchanger flux[60]. Cardiac metabolism is a complex network composed of many pathways, which is responsible for providing sufficient ATP to continuously contracting organs[61]. Empagliflozin induces a cardiac metabolic shift away from the glucose-inefficient myocardial utilization toward the consumption of fatty acids and ketone bodies[62], which improves energetics. This enhanced ATP production explains the improvement in left ventricular systolic and diastolic function[63, 64]. In a longitudinal cohort study, empagliflozin significantly improved the phosphocreatine-to-ATP ratio accompanied by a 7% absolute increase in the mean left ventricular ejection fraction, 3% absolute increase in the mean global longitudinal strain, 8 mL/m^2 absolute reduction in the mean myocardial cell volume, and 61% relative reduction in the mean plasma N-terminal prohormone B-type natriuretic peptide[65]. Empagliflozin mitigates sympathetic overdrive because it reduces plasma metanephrine level (the catabolite of epinephrine)[63] and also stabilizes heart rate variability and improves heart rate turbulence (a surrogate marker of sudden cardiac death)[66]. Empagliflozin induces a diuretic and natriuretic effect that is more intense in the acute phase[67], which might explain the improved pulmonary congestion and the lower filling pressures[68]. However, this diuretic effect only partially explains the benefits of empagliflozin because it is attenuated in the chronic phase[46], and the efficacy of empagliflozin is present both in patients with and without diuretics[69]. Furthermore, empagliflozin induces an anti-inflammatory effect with inhibition of the inflammasome[70] and polarization of the macrophages away from the pro-inflammatory M1 phenotype towards the anti-inflammatory M2 phenotype[71], and anti-fibrosis effect via inhibiting the TGF-β1/Smad3 pathway[72]. Empagliflozin also improves the function of vascular endothelial cells, suppresses oxidative stress, inhibits inflammation, and regulates autophagy[73]. In a multicenter study, SGLT-2is significantly reduced the inflammatory burden and ameliorated clinical outcomes in T2DM patients at 5 years of follow-up post-coronary artery bypass grafting via minimally invasive extracorporeal circulation[74]. In addition, empagliflozin had reno-protective effects, even in patients

with acute myocardial infarction[75].

Moreover, the nephroprotective effect of empagliflozin is also important in patients with HF and T2DM. In patients with T2DM at high cardiovascular risk, EMPA-REG OUTCOME indicated that empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than placebo when added to standard care[76]. Additionally, patients in the empagliflozin group had a better estimated glomerular filtration rate mean slope change per year than those in the placebo group[35], the reduction in intraglomerular pressure of empagliflozin may contribute to the long-term preservation of kidney function[77]. EMPA-KIDNEY, another large, prospective, placebo-controlled trial, will provide more information about whether empagliflozin can reduce the risk of cardiorenal prognosis in patients with chronic kidney disease[78]. As we mentioned before, in patients with HF combined with T2DM, there are other complications, such as hypertension, atrial fibrillation, coronary artery disease, and chronic kidney disease, and the use of drugs is more cumbersome. At present, our understanding of the interaction between different drugs is still very shallow, which is an unavoidable issue in the clinical management of this special group. In future clinical trials, we may need to focus on this issue.

Conclusion

We critically review several large clinical trials about empagliflozin, however, empagliflozin was not originally developed for HF and T2DM, the inclusion population is not particularly targeted in these trials, any recommendation for the treatment of established HF and T2DM will be necessarily cautious. Additionally, well-designed clinical trials with long follow-ups may provide us with more valuable information.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was partly funded by National Natural Science Foundation of China [81774229], Jiangsu Leading Talent Project of Traditional Chinese Medicine [Jiangsu TCM 2018 No.4], and Jiangsu Universities Nursing Advantage Discipline Project [2019YSHL095].

Authors' contributions

BL and NG conceived, designed, or planned the idea. All authors collected and read the literature. BL drafted the manuscript. NG revised the manuscript. All authors read and approved the final manuscript.

Acknowledgments

We thank all scientists and participants involved in empagliflozin and HF.

References

1. Lehrke M, Marx N: **Diabetes Mellitus and Heart Failure**. *The American Journal of Medicine* 2017, **130**(6, Supplement):S40-S50.
2. Jankauskas SS, Kansakar U, Varzideh F, Wilson S, Mone P, Lombardi A, Gambardella J, Santulli G: **Heart failure in diabetes**. *Metabolism* 2021, **125**:154910.
3. Seferović PM, Petrie MC, Filippatos GS, Anker SD, Rosano G, Bauersachs J, Paulus WJ, Komajda M, Cosentino F, de Boer RA *et al*: **Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology**. *Eur J Heart Fail* 2018, **20**(5):853-872.
4. Liang B, Zhao Y-X, Zhang X-X, Liao H-L, Gu N: **Reappraisal on pharmacological and mechanical treatments of heart failure**. *Cardiovasc Diabetol* 2020, **19**(1):55.
5. MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, Solomon SD, Granger CB, Swedberg K, Yusuf S *et al*: **Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme**. *Eur Heart J* 2008, **29**(11):1377-1385.

6. Seferović PM, Coats AJS, Ponikowski P, Filippatos G, Huelsmann M, Jhund PS, Polovina MM, Komajda M, Seferović J, Sari I *et al*: **European Society of Cardiology/Heart Failure Association position paper on the role and safety of new glucose-lowering drugs in patients with heart failure**. *Eur J Heart Fail* 2020, **22**(2):196-213.
7. McHugh K, DeVore AD, Wu J, Matsouaka RA, Fonarow GC, Heidenreich PA, Yancy CW, Green JB, Altman N, Hernandez AF: **Heart Failure With Preserved Ejection Fraction and Diabetes: JACC State-of-the-Art Review**. *J Am Coll Cardiol* 2019, **73**(5):602-611.
8. MacDonald MR, Petrie MC, Hawkins NM, Petrie JR, Fisher M, McKelvie R, Aguilar D, Krum H, McMurray JJV: **Diabetes, left ventricular systolic dysfunction, and chronic heart failure**. *Eur Heart J* 2008, **29**(10):1224-1240.
9. Seong J-M, Kim JJ, Kim HJ, Sohn HS: **Comparison of heart failure risk and medical costs between patients with type 2 diabetes mellitus treated with dapagliflozin and dipeptidyl peptidase-4 inhibitors: a nationwide population-based cohort study**. *Cardiovasc Diabetol* 2020, **19**(1):95.
10. Vaur L, Gueret P, Lievre M, Chabaud S, Passa P: **Development of congestive heart failure in type 2 diabetic patients with microalbuminuria or proteinuria: observations from the DIABHYCAR (type 2 DIABetes, Hypertension, CArdiovascular Events and Ramipril) study**. *Diabetes Care* 2003, **26**(3):855-860.
11. Tanaka H, Tatsumi K, Matsuzoe H, Matsumoto K, Hirata K-I: **Impact of diabetes mellitus on left ventricular longitudinal function of patients with non-ischemic dilated cardiomyopathy**. *Cardiovasc Diabetol* 2020, **19**(1):84.
12. Udell JA, Yuan Z, Rush T, Sicignano NM, Galitz M, Rosenthal N: **Cardiovascular Outcomes and Risks After Initiation of a Sodium Glucose Cotransporter 2 Inhibitor: Results From the EASEL Population-Based Cohort Study (Evidence for Cardiovascular Outcomes With Sodium Glucose Cotransporter 2 Inhibitors in the Real World)**. *Circulation* 2018, **137**(14):1450-1459.
13. Kosiborod M, Lam CSP, Kohsaka S, Kim DJ, Karasik A, Shaw J, Tangri N, Goh S-Y, Thuresson M, Chen H *et al*: **Cardiovascular Events Associated With SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL 2 Study**. *J Am Coll Cardiol* 2018, **71**(23):2628-2639.
14. Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, Norhammar A, Birkeland KI, Jørgensen ME, Thuresson M *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**(3):249-259.
15. Giugliano D, Longo M, Scappaticcio L, Bellastella G, Maiorino MI, Esposito K: **SGLT-2 inhibitors and cardiorenal outcomes in patients with or without type 2 diabetes: a meta-analysis of 11 CVOTs**. *Cardiovasc Diabetol* 2021,

20(1):236.
16. Real J, Vlacho B, Ortega E, Vallés JA, Mata-Cases M, Castelblanco E, Wittbrodt ET, Fenici P, Kosiborod M, Mauricio D *et al*: **Cardiovascular and mortality benefits of sodium-glucose co-transporter-2 inhibitors in patients with type 2 diabetes mellitus: CVD-Real Catalonia**. *Cardiovasc Diabetol* 2021, **20**(1):139.
17. Thomsen RW, Knudsen JS, Kahlert J, Baggesen LM, Lajer M, Holmgaard PH, Vedin O, Ustyugova A, Sørensen HT: **Cardiovascular Events, Acute Hospitalizations, and Mortality in Patients With Type 2 Diabetes Mellitus Who Initiate Empagliflozin Versus Liraglutide: A Comparative Effectiveness Study**. *Journal of the American Heart Association* 2021, **10**(11):e019356.
18. Pasternak B, Ueda P, Eliasson B, Svensson A-M, Franzén S, Gudbjörnsdottir S, Hveem K, Jonasson C, Wintzell V, Melbye M *et al*: **Use of sodium glucose cotransporter 2 inhibitors and risk of major cardiovascular events and heart failure: Scandinavian register based cohort study**. *BMJ* 2019, **366**:l4772.
19. Schork A, Saynisch J, Vosseler A, Jaghutriz BA, Heyne N, Peter A, Häring H-U, Stefan N, Fritsche A, Artunc F: **Effect of SGLT2 inhibitors on body composition, fluid status and renin-angiotensin-aldosterone system in type 2 diabetes: a prospective study using bioimpedance spectroscopy**. *Cardiovasc Diabetol* 2019, **18**(1):46.
20. Liang B, Zhao Y-X, Gu N: **Empagliflozin improves cardiac function in heart failure with reduced ejection fraction independent of loading conditions**. *Cardiovasc Diabetol* 2020, **19**(1):29.
21. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR *et al*: **2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines**. *J Am Coll Cardiol* 2022.
22. Odutayo A, da Costa BR, Pereira TV, Garg V, Iskander S, Roble F, Lalji R, Hincapié CA, Akingbade A, Rodrigues M *et al*: **Sodium-Glucose Cotransporter 2 Inhibitors, All-Cause Mortality, and Cardiovascular Outcomes in Adults with Type 2 Diabetes: A Bayesian Meta-Analysis and Meta-Regression**. *Journal of the American Heart Association* 2021, **10**(18):e019918.
23. Zinman B, Inzucchi SE, Lachin JM, Wanner C, Ferrari R, Fitchett D, Bluhmki E, Hantel S, Kempthorne-Rawson J, Newman J *et al*: **Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME™)**. *Cardiovasc Diabetol* 2014, **13**:102.
24. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ *et al*: **Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes**. *The New England journal of*

medicine 2015, **373**(22):2117-2128.
25. Fitchett D, Inzucchi SE, Zinman B, Wanner C, Schumacher M, Schmoor C, Ohneberg K, Ofstad AP, Salsali A, George JT *et al*: **Mediators of the improvement in heart failure outcomes with empagliflozin in the EMPA-REG OUTCOME trial**. *ESC Heart Fail* 2021, **8**(6):4517-4527.
26. Patorno E, Pawar A, Franklin JM, Najafzadeh M, Déruaz-Luyet A, Brodovicz KG, Sambevski S, Bessette LG, Santiago Ortiz AJ, Kulldorff M *et al*: **Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care**. *Circulation* 2019, **139**(25):2822-2830.
27. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S *et al*: **Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes**. *The New England journal of medicine* 2015, **373**(3):232-242.
28. Santos-Gallego CG, Garcia-Ropero A, Mancini D, Pinney SP, Contreras JP, Fergus I, Abascal V, Moreno P, Atallah-Lajam F, Tamler R *et al*: **Rationale and Design of the EMPA-TROPISM Trial (ATRU-4): Are the "Cardiac Benefits" of Empagliflozin Independent of its Hypoglycemic Activity?** *Cardiovasc Drugs Ther* 2019, **33**(1):87-95.
29. Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA, Garcia-Ropero A, Mancini D, Pinney S, Macaluso F, Sartori S, Roque M, Sabatel-Perez F *et al*: **Randomized Trial of Empagliflozin in Nondiabetic Patients With Heart Failure and Reduced Ejection Fraction**. *J Am Coll Cardiol* 2021, **77**(3):243-255.
30. Requena-Ibáñez JA, Santos-Gallego CG, Rodriguez-Cordero A, Vargas-Delgado AP, Mancini D, Sartori S, Atallah-Lajam F, Giannarelli C, Macaluso F, Lala A *et al*: **Mechanistic Insights of Empagliflozin in Nondiabetic Patients With HFrEF: From the EMPA-TROPISM Study**. *JACC Heart Fail* 2021, **9**(8):578-589.
31. Lee MMY, Brooksbank KJM, Wetherall K, Mangion K, Roditi G, Campbell RT, Berry C, Chong V, Coyle L, Docherty KF *et al*: **Effect of Empagliflozin on Left Ventricular Volumes in Patients With Type 2 Diabetes, or Prediabetes, and Heart Failure With Reduced Ejection Fraction (SUGAR-DM-HF)**. *Circulation* 2021, **143**(6):516-525.
32. Omar M, Jensen J, Ali M, Frederiksen PH, Kistorp C, Videbæk L, Poulsen MK, Tuxen CD, Möller S, Gustafsson F *et al*: **Associations of Empagliflozin With Left Ventricular Volumes, Mass, and Function in Patients With Heart Failure and Reduced Ejection Fraction: A Substudy of the Empire HF Randomized Clinical Trial**. *JAMA Cardiol* 2021, **6**(7):836-840.
33. Packer M, Butler J, Filippatos GS, Jamal W, Salsali A, Schnee J, Kimura K, Zeller C, George J, Brueckmann M *et al*: **Evaluation of the effect of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality of patients with chronic heart failure and a reduced ejection fraction: rationale for and design of the EMPEROR-Reduced trial**. *Eur J Heart Fail* 2019, **21**(10):1270-1278.

34. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M *et al*: **Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure**. *The New England journal of medicine* 2020, **383**(15):1413-1424.
35. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca H-P, Choi D-J, Chopra V, Chuquiure-Valenzuela E *et al*: **Empagliflozin in Heart Failure with a Preserved Ejection Fraction**. *The New England journal of medicine* 2021, **385**(16):1451-1461.
36. Liang B, Gu N: **Sodium-glucose co-transporter-2 inhibitors in the treatment of diabetes with heart failure**. *Cardiovasc Diabetol* 2022, **21**(1):84.
37. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, Boehme AK, Buxton AE, Carson AP, Commodore-Mensah Y *et al*: **Heart Disease and Stroke Statistics—2022 Update: A Report From the American Heart Association**. *Circulation* 2022, **145**(8):e153-e639.
38. Tisminetzky M, Gurwitz JH, Fan D, Reynolds K, Smith DH, Magid DJ, Sung SH, Murphy TE, Goldberg RJ, Go AS: **Multimorbidity Burden and Adverse Outcomes in a Community-Based Cohort of Adults with Heart Failure**. *J Am Geriatr Soc* 2018, **66**(12):2305-2313.
39. Hias J, Hellemans L, Walgraeve K, Tournoy J, Van der Linden L: **SGLT2 Inhibitors in Older Adults with Heart Failure with Preserved Ejection Fraction**. *Drugs Aging* 2022, **39**(3):185-190.
40. Mone P, Lombardi A, Gambardella J, Pansini A, Macina G, Morgante M, Frullone S, Santulli G: **Empagliflozin Improves Cognitive Impairment in Frail Older Adults With Type 2 Diabetes and Heart Failure With Preserved Ejection Fraction**. *Diabetes Care* 2022, **45**(5):1247-1251.
41. Butler J, Filippatos G, Jamal Siddiqi T, Brueckmann M, Böhm M, Chopra VK, Pedro Ferreira J, Januzzi JL, Kaul S, Piña IL *et al*: **Empagliflozin, Health Status, and Quality of Life in Patients With Heart Failure and Preserved Ejection Fraction: The EMPEROR-Preserved Trial**. *Circulation* 2022, **145**(3):184-193.
42. Packer M, Butler J, Zannad F, Filippatos G, Ferreira JP, Pocock SJ, Carson P, Anand I, Doehner W, Haass M *et al*: **Effect of Empagliflozin on Worsening Heart Failure Events in Patients With Heart Failure and Preserved Ejection Fraction: EMPEROR-Preserved Trial**. *Circulation* 2021, **144**(16):1284-1294.
43. Butler J, Siddiqi TJ, Filippatos G, Ferreira JP, Pocock SJ, Zannad F, Anker SD: **Early benefit with empagliflozin in heart failure with preserved ejection fraction: insights from the EMPEROR-Preserved trial**. *Eur J Heart Fail* 2022, **24**(2):245-248.
44. Verma S, Leiter LA, Zinman B, Sharma A, Mattheus M, Fitchett D, George J, Ofstad AP, Kosiborod MN, Wanner C *et al*: **Time to cardiovascular benefits of empagliflozin: a post hoc observation from the EMPA-REG OUTCOME trial**. *ESC Heart Fail* 2021, **8**(4):2603-2607.
45. Kokhan E, Kiyakbaev G, Medovchshikov V: **Sodium–glucose co-transporter**

2 inhibitors: drugs with multiple effects, but which one is relevant to heart failure with preserved ejection fraction? Letter regarding the article 'Early benefit with empagliflozin in heart failure with preserved ejection fraction: insights from the EMPEROR-Preserved trial'. *Eur J Heart Fail* 2022, **n/a**(n/a).

46. Mordi NA, Mordi IR, Singh JS, McCrimmon RJ, Struthers AD, Lang CC: **Renal and Cardiovascular Effects of SGLT2 Inhibition in Combination with Loop Diuretics in Patients with Type 2 Diabetes and Chronic Heart Failure: The RECEDE-CHF Trial**. *Circulation* 2020, **142**(18):1713-1724.
47. Tanaka A, Shimabukuro M, Teragawa H, Okada Y, Takamura T, Taguchi I, Toyoda S, Tomiyama H, Ueda S, Higashi Y *et al*: **Reduction of estimated fluid volumes following initiation of empagliflozin in patients with type 2 diabetes and cardiovascular disease: a secondary analysis of the placebo-controlled, randomized EMBLEM trial**. *Cardiovasc Diabetol* 2021, **20**(1):105.
48. Butler J, Packer M, Filippatos G, Ferreira JP, Zeller C, Schnee J, Brueckmann M, Pocock SJ, Zannad F, Anker SD: **Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction**. *Eur Heart J* 2022, **43**(5):416-426.
49. Wehner GJ, Jing L, Haggerty CM, Suever JD, Leader JB, Hartzel DN, Kirchner HL, Manus JNA, James N, Ayar Z *et al*: **Routinely reported ejection fraction and mortality in clinical practice: where does the nadir of risk lie?** *Eur Heart J* 2020, **41**(12):1249-1257.
50. Liang B, Gu N: **Liraglutide in the treatment of heart failure: insight from FIGHT and LIVE**. *Cardiovasc Diabetol* 2020, **19**(1):106.
51. Lee CH, Kan AKC, Lui DTW, Fong CHY, Chan DSH, Yuen MMA, Chow WS, Woo YC, Xu A, Lam KSL: **Prospective association of serum adipocyte fatty acid-binding protein with heart failure hospitalization in diabetes**. *ESC Heart Fail* 2021, **8**(5):3964-3974.
52. Cherney DZI, Zinman B, Inzucchi SE, Koitka-Weber A, Mattheus M, von Eynatten M, Wanner C: **Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial**. *The lancet Diabetes & endocrinology* 2017, **5**(8):610-621.
53. Tanaka A, Shimabukuro M, Okada Y, Taguchi I, Yamaoka-Tojo M, Tomiyama H, Teragawa H, Sugiyama S, Yoshida H, Sato Y *et al*: **Rationale and design of a multicenter placebo-controlled double-blind randomized trial to evaluate the effect of empagliflozin on endothelial function: the EMBLEM trial**. *Cardiovasc Diabetol* 2017, **16**(1):48.
54. Tanaka A, Shimabukuro M, Machii N, Teragawa H, Okada Y, Shima KR, Takamura T, Taguchi I, Hisauchi I, Toyoda S *et al*: **Effect of Empagliflozin on Endothelial Function in Patients With Type 2 Diabetes and Cardiovascular Disease: Results from the Multicenter, Randomized, Placebo-Controlled,**

Double-Blind EMBLEM Trial. *Diabetes Care* 2019, **42**(10):e159-e161.
55. Omar M, Jensen J, Kistorp C, Højlund K, Videbæk L, Tuxen C, Larsen JH, Andersen CF, Gustafsson F, Køber L *et al*: **The effect of empagliflozin on growth differentiation factor 15 in patients with heart failure: a randomized controlled trial (Empire HF Biomarker)**. *Cardiovasc Diabetol* 2022, **21**(1):34.
56. Jensen J, Omar M, Kistorp C, Poulsen MK, Tuxen C, Gustafsson I, Køber L, Gustafsson F, Faber J, Fosbøl EL *et al*: **Twelve weeks of treatment with empagliflozin in patients with heart failure and reduced ejection fraction: A double-blinded, randomized, and placebo-controlled trial**. *Am Heart J* 2020, **228**:47-56.
57. Tripolt NJ, Kolesnik E, Pferschy PN, Verheyen N, Ablasser K, Sailer S, Alber H, Berger R, Kaulfersch C, Leitner K *et al*: **Impact of EMpagliflozin on cardiac function and biomarkers of heart failure in patients with acute MYocardial infarction-The EMMY trial**. *Am Heart J* 2020, **221**:39-47.
58. Varzideh F, Kansakar U, Santulli G: **SGLT2 inhibitors in cardiovascular medicine**. *Eur Heart J Cardiovasc Pharmacother* 2021, **7**(4):e67-e68.
59. Jürgens M, Schou M, Hasbak P, Kjær A, Wolsk E, Zerahn B, Wiberg M, Brandt-Jacobsen NH, Gæde P, Rossing P *et al*: **Effects of Empagliflozin on Myocardial Flow Reserve in Patients With Type 2 Diabetes Mellitus: The SIMPLE Trial**. *Journal of the American Heart Association* 2021, **10**(15):e020418.
60. Baartscheer A, Schumacher CA, Wüst RCI, Fiolet JWT, Stienen GJM, Coronel R, Zuurbier CJ: **Empagliflozin decreases myocardial cytoplasmic Na through inhibition of the cardiac Na/H exchanger in rats and rabbits**. *Diabetologia* 2017, **60**(3):568-573.
61. McGarrah RW, Crown SB, Zhang G-F, Shah SH, Newgard CB: **Cardiovascular Metabolomics**. *Circ Res* 2018, **122**(9):1238-1258.
62. Garcia-Ropero A, Santos-Gallego CG, Zafar MU, Badimon JJ: **Metabolism of the failing heart and the impact of SGLT2 inhibitors**. *Expert Opin Drug Metab Toxicol* 2019, **15**(4):275-285.
63. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, Ishikawa K, Watanabe S, Picatoste B, Flores E, Garcia-Ropero A, Sanz J, Hajjar RJ *et al*: **Empagliflozin Ameliorates Adverse Left Ventricular Remodeling in Nondiabetic Heart Failure by Enhancing Myocardial Energetics**. *J Am Coll Cardiol* 2019, **73**(15):1931-1944.
64. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, Garcia-Ropero A, Ishikawa K, Watanabe S, Picatoste B, Vargas-Delgado AP, Flores-Umanzor EJ, Sanz J *et al*: **Empagliflozin Ameliorates Diastolic Dysfunction and Left Ventricular Fibrosis/Stiffness in Nondiabetic Heart Failure: A Multimodality Study**. *JACC Cardiovascular imaging* 2021, **14**(2):393-407.
65. Thirunavukarasu S, Jex N, Chowdhary A, Hassan IU, Straw S, Craven TP, Gorecka M, Broadbent D, Swoboda P, Witte KK *et al*: **Empagliflozin Treatment Is Associated With Improvements in Cardiac Energetics and**

Function and Reductions in Myocardial Cellular Volume in Patients With Type 2 Diabetes. *Diabetes* 2021, **70**(12):2810-2822.

66. Shimizu W, Kubota Y, Hoshika Y, Mozawa K, Tara S, Tokita Y, Yodogawa K, Iwasaki Y-K, Yamamoto T, Takano H *et al*: **Effects of empagliflozin versus placebo on cardiac sympathetic activity in acute myocardial infarction patients with type 2 diabetes mellitus: the EMBODY trial**. *Cardiovasc Diabetol* 2020, **19**(1):148.
67. Griffin M, Rao VS, Ivey-Miranda J, Fleming J, Mahoney D, Maulion C, Suda N, Siwakoti K, Ahmad T, Jacoby D *et al*: **Empagliflozin in Heart Failure: Diuretic and Cardiorenal Effects**. *Circulation* 2020, **142**(11):1028-1039.
68. Nassif ME, Qintar M, Windsor SL, Jermyn R, Shavelle DM, Tang F, Lamba S, Bhatt K, Brush J, Civitello A *et al*: **Empagliflozin Effects on Pulmonary Artery Pressure in Patients With Heart Failure: Results From the EMBRACE-HF Trial**. *Circulation* 2021, **143**(17):1673-1686.
69. Tromp J, Ponikowski P, Salsali A, Angermann CE, Biegus J, Blatchford J, Collins SP, Ferreira JP, Grauer C, Kosiborod M *et al*: **Sodium-glucose co-transporter 2 inhibition in patients hospitalized for acute decompensated heart failure: rationale for and design of the EMPULSE trial**. *Eur J Heart Fail* 2021, **23**(5):826-834.
70. Kim SR, Lee S-G, Kim SH, Kim JH, Choi E, Cho W, Rim JH, Hwang I, Lee CJ, Lee M *et al*: **SGLT2 inhibition modulates NLRP3 inflammasome activity via ketones and insulin in diabetes with cardiovascular disease**. *Nat Commun* 2020, **11**(1):2127.
71. Xu L, Nagata N, Nagashimada M, Zhuge F, Ni Y, Chen G, Mayoux E, Kaneko S, Ota T: **SGLT2 Inhibition by Empagliflozin Promotes Fat Utilization and Browning and Attenuates Inflammation and Insulin Resistance by Polarizing M2 Macrophages in Diet-induced Obese Mice**. *EBioMedicine* 2017, **20**:137-149.
72. Daud E, Ertracht O, Bandel N, Moady G, Shehadeh M, Reuveni T, Atar S: **The impact of empagliflozin on cardiac physiology and fibrosis early after myocardial infarction in non-diabetic rats**. *Cardiovasc Diabetol* 2021, **20**(1):132.
73. Xu J, Hirai T, Koya D, Kitada M: **Effects of SGLT2 Inhibitors on Atherosclerosis: Lessons from Cardiovascular Clinical Outcomes in Type 2 Diabetic Patients and Basic Researches**. *Journal of clinical medicine* 2021, **11**(1):137.
74. Sardu C, Massetti M, Testa N, Martino LD, Castellano G, Turriziani F, Sasso FC, Torella M, De Feo M, Santulli G *et al*: **Effects of Sodium-Glucose Transporter 2 Inhibitors (SGLT2-I) in Patients With Ischemic Heart Disease (IHD) Treated by Coronary Artery Bypass Grafting via MiECC: Inflammatory Burden, and Clinical Outcomes at 5 Years of Follow-Up**. *Front Pharmacol* 2021, **12**:777083.
75. Mozawa K, Kubota Y, Hoshika Y, Tara S, Tokita Y, Yodogawa K, Iwasaki Y-K, Yamamoto T, Takano H, Tsukada Y *et al*: **Empagliflozin confers reno-**

protection in acute myocardial infarction and type 2 diabetes mellitus. *ESC Heart Fail* 2021, **8**(5):4161-4173.

76. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, Johansen OE, Woerle HJ, Broedl UC, Zinman B: **Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes**. *The New England journal of medicine* 2016, **375**(4):323-334.

77. Wanner C, Heerspink HJL, Zinman B, Inzucchi SE, Koitka-Weber A, Mattheus M, Hantel S, Woerle H-J, Broedl UC, von Eynatten M *et al*: **Empagliflozin and Kidney Function Decline in Patients with Type 2 Diabetes: A Slope Analysis from the EMPA-REG OUTCOME Trial**. *Journal of the American Society of Nephrology : JASN* 2018, **29**(11):2755-2769.

78. Herrington WG, Preiss D, Haynes R, von Eynatten M, Staplin N, Hauske SJ, George JT, Green JB, Landray MJ, Baigent C *et al*: **The potential for improving cardio-renal outcomes by sodium-glucose co-transporter-2 inhibition in people with chronic kidney disease: a rationale for the EMPA-KIDNEY study**. *Clin Kidney J* 2018, **11**(6):749-761.

Table 1. Summary of main trials

	EMPA-REG OUTCOME (N = 7020)[24]	EMPRISE (N = 32886)[26]	EMPA-TROPISM (N = 84)[29]	EMPEROR-Reduced (N = 3730)[34]	EMPEROR-Preserved (N = 5750)[35]
Patients	T2DM at high cardiovascular risk	T2DM	Nondiabetic HFrEF	HFrEF with or without T2DM	HFpEF with and without T2DM
Intervention	Empagliflozin (10 or 25 mg once daily)	Empagliflozin (10 or 25 mg once daily)	Empagliflozin (10 mg once daily)	Empagliflozin (10 mg once daily)	Empagliflozin (10 mg once daily)
Comparison	Placebo	Sitagliptin	Placebo	Placebo	Placebo
Outcomes	Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The key secondary outcome was a composite of the primary outcome plus hospitalization for unstable angina.	HHF.	The primary endpoint was change in left ventricular end-diastolic and systolic volume assessed by cardiac magnetic resonance. Secondary endpoints included changes in LV left ventricular mass, left ventricular ejection fraction, peak oxygen consumption in the cardiopulmonary exercise test, 6-min walk test, and quality of life.	A composite of cardiovascular death or HHF.	The primary endpoint is the time-to-first-event analysis of the combined risk for cardiovascular death or HHF. The trial also evaluates the effects of empagliflozin on renal function, cardiovascular death, all-cause mortality and recurrent hospitalization events.
Design	Randomized, double-blind, placebo-controlled trial	First interim analysis	Randomized, double-blind, parallel-group, placebo-controlled, trial	International, multicenter, randomized, double-blind, parallel-group, placebo-controlled, event-driven trial	International, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial
Follow-up	3.1 years	5.3 months	6 months	16 months	26.2 months
Conclusions	Patients with T2DM at high	Compared with sitagliptin,	Empagliflozin administration to nondiabetic	Empagliflozin group	Empagliflozin reduced the

	risk for cardiovascular events who received empagliflozin had a lower rate of the primary composite cardiovascular outcome and of death from any cause.	empagliflozin was associated with a decreased risk of HHF among patients with T2DM with and without a history of cardiovascular disease.	HFrEF patients significantly improves left ventricular volumes, left ventricular mass, left ventricular systolic function, functional capacity, and quality of life when compared with placebo.	had a lower risk of cardiovascular death or HHF regardless of the presence or absence of T2DM.	combined risk of cardiovascular death or HHF in patients with HFpEF, regardless of the presence or absence of diabetes.

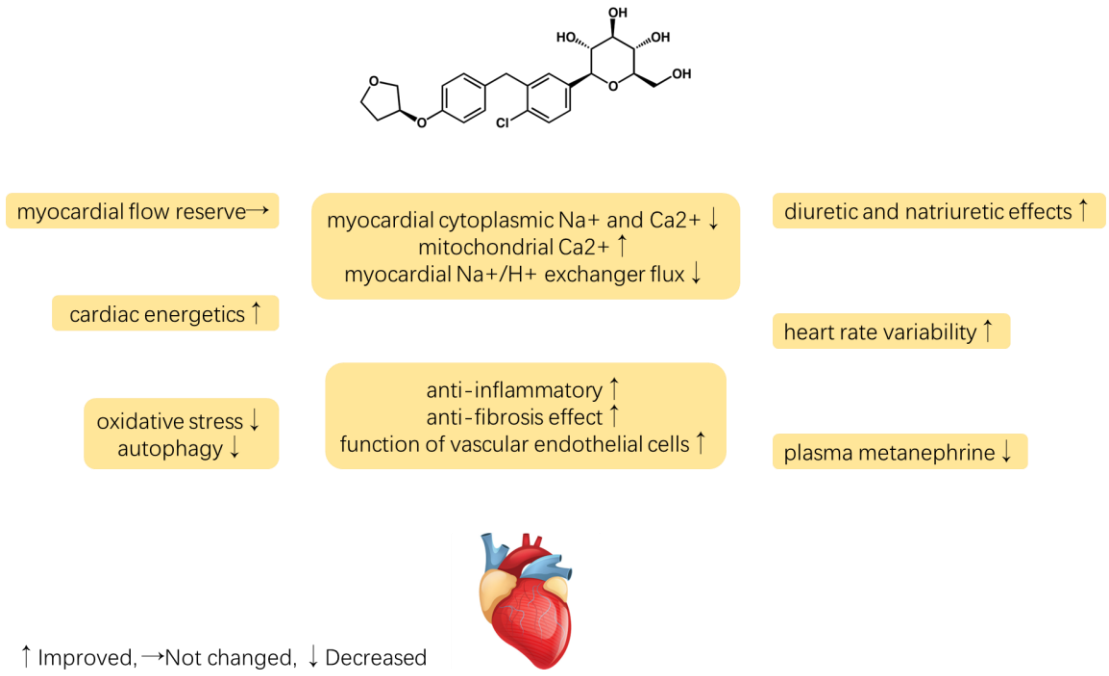

Figure 1. Cartoon depicting the mechanism of action of empagliflozin and the beneficial effects of on the cardiovascular system.