Published in final edited form as:

Curr Opin Pharmacol. 2020 October ; 54: 11–17. doi:10.1016/j.coph.2020.06.001.

Evolving understanding of cardiovascular protection by SGLT2 inhibitors: focus on renal protection, myocardial effects, uric acid, and magnesium balance

Evan C Ray

University of Pittsburgh School of Medicine, Renal-Electrolyte Division, A915 Scaife Hall, 3550 Terrace St, Pittsburgh, PA 15261, United States

Abstract

Robust clinical data indicate that inhibitors of the sodium/glucose cotransporter 2 (SGLT2) dramatically improve clinical outcomes in diabetes, especially heart failure and progression of kidney disease. Factors that may contribute to these findings include: 1) improved glycemic control, 2) diuresis and reduced extracellular fluid volume, 3) reduced serum uric acid levels, 3) direct myocardial effects, 4) reduction in proteinuria and preservation of kidney function, and 5) correction of diabetic magnesium deficiency. Understanding the mechanisms by which SGLT2 inhibitors improve cardiovascular outcomes has the potential to improve clinical management not only of diabetes, but also of other cardiovascular disorders such as heart failure and chronic kidney disease.

Introduction

The last decade witnessed a tremendous advance in the management of diabetes mellitus, with the release of sodium/glucose cotransporter 2 (SGLT2) inhibitors (gliflozins). Government agencies around the world have now approved more than half a dozen SGLT2 inhibitors [1]. These agents selectively block reabsorption of filtered sodium and glucose through SGLT2 in the kidney's proximal convoluted tubule, inducing urinary glucose wasting and moderating hyperglycemia. This represents a truly novel approach to management of hyperglycemia.

Scandals surrounding post-marketing findings of increased cardiovascular risk associated with thiazolidinediones and Cox-2 selective inhibitors remain none-too-distant memories. Consequently, drug safety agencies now require greater scrutiny of cardiovascular safety [2]. In high quality clinical trials examining three different *gliflozins* (empagliflozin, canagliflozin, and dapagliflozin), study participants receiving these medications experienced unexpectedly positive cardiovascular outcomes (Table 1 and [3]). Empagliflozin and canagliflozin reduced risk of major adverse cardiovascular events. Dapagliflozin reduced

Corresponding author: Ray, Evan C (rayec@upmc.edu).

CRedit authorship contribution statement

Evan C Ray: Conceptualization, Writing - original draft, Writing - review & editing.

Conflict of interest statement

Nothing declared.

this risk non-significantly. Empagliflozin reduced mortality in a trial including diabetic participants, and dapagliflozin reduced mortality in a trial of participants with ejection fraction-reduced heart failure. Outcomes related to heart failure stood out as being among the most consistently improved, with statistically significant improvement in each of three agents in five different trials. This review discusses mechanisms that may contribute to these phenomenal cardiovascular outcomes.

Mechanisms of cardiovascular benefit

Numerous concurrent mechanisms likely contribute to improved cardiovascular outcomes with SGLT2 inhibitors. Several well-described pharmacologic effects, such as improvement in hyperglycemia, diuresis, and blood pressure improvement may contribute. Other unforeseen actions may also participate, including preservation of kidney function, enhanced uric acid secretion, direct myocardial effects, and improved magnesium balance.

Improved glycemic control

The rationale for the development of SGLT2 inhibitors for diabetes was to reduce hyperglycemia by inducing urinary glucose wasting. A meta-analysis of SGLT2 inhibitor trials found an absolute hemoglobin A1c reduction of 0.6–0.9% [10]. Another meta-analysis of solely phase 3 clinical trials of type 1 diabetes found a more modest reduction of 0.28%–0.54% [11].

Other drug classes which reduce A1c 0.7–2% do not improve macrovascular outcomes [12]. Pooling of data from three large trials of non-SGLT2 modulating antidiabetic agents was required to find significant improvement in a composite of cardiovascular outcomes (hazard ratio [HR] 0.91, 95% confidence interval [CI] 0.84–0.99), including reduction in non-fatal myocardial infarction (HR 0.85, 95% CI 0.76–0.94) [13]. The meta-analysis identified no improvement in all-cause or cardiovascular mortality (HR 1.04, 95% CI 0.90–1.20; and HR 1.10, 95% CI 0.84–1.42) or in heart failure outcomes (HR 1.00, 95% CI 0.86–1.16). These findings cast doubt on the role of improved glucose control as a major mechanism for reduced cardiovascular risk by SGLT2 inhibitors.

Diuresis and reduced blood pressure

In healthy adults, the nephron reabsorbs more than 99% of filtered sodium. Roughly 6% of filtered sodium occurs as co-transport with glucose through SGLT2 in the proximal convoluted tubule. This may increase to 12% in the context of diabetes, where hyperglycemia and hyperfiltration demand greater glucose reabsorption [14]. Thus, inhibition of this transporter increases not only glycosuria but also urinary sodium excretion. Bioimpedance measurements in humans confirm that these agents rapidly reduce extracellular fluid volume [15]. Although compensatory mechanisms appear to return fluid balance to baseline within months, blood pressures remain reduced beyond five months, with systolic blood pressure being reduced by 2.8–4.9 mmHg, and diastolic blood pressure being reduced by 1.5–2.0 mmHg [10].

Even if SGLT2 inhibitors reduce total body sodium over the long-term, this may not explain improvement in heart failure outcomes, since scant evidence suggests classic diuretics

reduce cardiovascular events. An oft-cited, but subsequently withdrawn, Cochrane review suggested that diuretics improve heart failure outcomes. The collected studies included only 202 participants in examination of mortality and 169 participants in examination of heart failure [16]. A more recent meta-analysis on loop diuretics found no significant improvement in heart failure-related mortality [17]. Another meta-analysis of outcomes with thiazide diuretics pooled 12 trials and 41 993 participants and found no significant improvement in cardiac events (odds ratio [OR] 0.92, 95% CI 0.79–1.07) or heart failure (OR 0.71, 95% CI 0.44–1.15) [18]. In seven trials with over 70 120 participants, thiazide-like diuretics (chlorthalidone, indapamide, and metolazone) reduced both cardiac events (OR 0.78, 95% CI 0.68–0.90) and heart failure (OR 0.57, 95% CI 0.41–0.76). Because thiazides themselves did not show a significant effect, authors speculated that thiazide-like diuretics exert positive effects independent of blood pressure reduction, distinguishing them from thiazides. These findings suggest that diuresis also may not be a primary driver of gliflozin-associated improvement in cardiovascular outcomes.

Reduction in circulating uric acid

Whereas virtually all other diuretics reduce uric acid excretion and promote hyperuricemia, SGLT2 inhibitors reduce uric acid levels [19•]. In a meta-analysis of 62 studies, SGLT2 inhibitors reduced circulating uric acid by 0.63 mg/dL (95% CI 0.59–0.61; 38 μ mol/L, 95% CI 41–35) [20].

Blood uric acid concentrations have long been known to predict cardiovascular disease. A meta-analysis of 28 studies calculated that each 1 mg/dL (0.06 mmol/L) increase in serum uric acid was associated with a 19 % increase in risk of heart failure (HR 1.19, 95% CI 1.17–1.21) and 4% increase in mortality (HR 1.04, 95% CI 1.02–1.06) [21]. Laboratory studies find that uric acid impairs endothelial function, decreases nitric oxide production, instigates oxidative stress, and stimulates vascular smooth muscle proliferation [19•]. Furthermore, clinical use of uric acid lowering agents is associated with improved cardiovascular outcomes. A United Kingdom Clinical Research Practice Datalink study examined cardiovascular events in 2368 patients who received allopurinol, as compared to 41 663 who did not. Use of allopurinol was associated with significantly fewer cardiac vascular events (HR 0.61, 95% CI 0.43–0.87). The risk was dose-dependent, with those receiving high dose having lower risk than those receiving low-dose allopurinol (HR 0.65, 95% CI 0.46–0.93). Off-target effects of allopurinol (such as anti-oxidant effects) may have contributed to this finding, but these observational clinical data appear consistent with laboratory studies showing cardiovascular harm from elevated plasma uric acid. As such, the uric acid-lowering effects of gliflozins may contribute to improved cardio-vascular outcomes.

Myocardial effects

SGLT2 inhibitors may also exert both direct and indirect effects on myocardial function. The myocardium expresses little or no SGLT2, but does express SGLT1, especially in the context of cardiomyopathy [22]. The gliflozins vary in terms of SGLT2/SGLT1 selectivity. Canagliflozin, dapagliflozin, and empagliflozin exhibit SGLT2/SGLT1 selectivity of 155-fold, 1242-fold, and 2680-fold, respectively [23]. Laboratory findings are discrepant in terms

of whether SGLT1 activity is harmful or beneficial for cardiac function, and it remains unclear whether SGLT1 blockade by gliflozins influences cardio-vascular outcomes [24].

Additional direct myocardial effects of gliflozins include impairment of L-type calcium channels and the cardiac sodium-proton exchanger [25,26]. These effects attenuate increases in intracellular calcium and sodium observed in experimental heart failure and could improve mitochondrial activity. In support of improved mitochondrial function and cellular respiration, empagliflozin increases intracellular ATP of *in vitro* cardiomyocytes [27].

SGLT2 inhibitors reduce *in vivo* myocardial sensitivity to ischemia-reperfusion injury (reviewed in Ref. [28]). However, *ex vivo* administration of these agents to perfused hearts generally fails to improve infarct size, except in the context of supratherapeutic concentrations. Extracardiac, systemic mechanisms likely contribute to protection against ischemia-reperfusion injury.

Among the systemic effects of gliflozin use is reduced insulin secondary to improved plasma glucose [29]. Correction of hyperinsulinemia allows increased lipolysis and production of β -hydroxybutyrate. Diabetic hearts manifest reduced metabolic flexibility, exhibiting increased reliance on fatty acid oxygenation for energy and decreased glycolytic activity [30]. Thus, SGLT2 inhibitors could improve cardiac function by augmenting availability of this more metabolically accessible energy source. However, reductions in insulin secondary to improved glycemic control would presumably be reflected by improved hemoglobin A1c. As discussed above, improvement in cardiovascular outcomes with SGLT2 inhibitors seem to exceed what would be predicted based on reduction in hemoglobin A1c alone. Other systemic factors, discussed below may play a role.

Preservation of kidney function

Decline in kidney function in diabetes contributes to cardiovascular disease through increased blood pressure and decreased clearance of injurious metabolites. In the CREDENCE Trial, participants receiving canagliflozin experienced 30% reduction in renal outcomes (HR 0.70, 95% CI 0.59–0.82) [9•]. Other trials, where renal outcomes were secondary, generally showed improvement in risk (Table 1). Thus, SGLT2 inhibitors preserve kidney function in individuals with diabetes.

Albuminuria is a strong predictor of decline in kidney function, incident hypertension, and cardiovascular death in types 1 and 2 diabetes [31,32]. SGLT2 inhibitors reduce proteinuria within 12 weeks [33]. Tubular protein likely promotes progression of chronic kidney disease by inciting oxidative stress and inflammation in the tubule [34]. Additionally, tubular protein appears to increase extracellular fluid volume by encouraging tubular sodium reabsorption [35]. Presumably, the resulting extracellular fluid volume overload promotes hypertension and progression of cardiovascular disease.

SGLT2 inhibitors attenuate proteinuria by reducing intraglomerular filtration pressure. In rodent models, impaired proximal tubular sodium reabsorption results in increased delivery of sodium (and chloride) to the nephron's macula densa. This has been suggested to trigger tubuloglomerular feedback, stimulating afferent arteriolar vasoconstriction and decreasing

intraglomerular pressures [36•]. A recent study contests this mechanism in people with type 2 diabetes, showing evidence that SGLT2 inhibitors increase efferent arteriolar vasodilation, which would similarly reduce filtration pressure and filtration of protein [37•].

Regardless of the mechanism, SGLT2 inhibitors preserve kidney function in individuals with diabetes, reducing accumulation of extracellular fluid volume and uremic toxins that promote cardiovascular disease.

Correction of diabetic magnesium deficiency

Diabetic individuals frequently suffer from magnesium depletion. Prevalence of hypomagnesemia in diabetic individuals has been reported at 14–48%, compared to 2.5–15% of non-diabetic individuals [38]. Numerous mechanisms contribute to hypomagnesemia. Nearly half of U.S. residents over one year of age fail to consume the estimated average minimum requirement for magnesium [39]. Additionally, high fat diets common in industrialized countries decrease expression of renal magnesium transporters and promote hypomagnesemia [40•]. In diabetes, hyperglycemia increases renal magnesium excretion [41]. Finally, commonly used medications, including loop diuretics, thiazide diuretics, and proton pump inhibitors promote hypomagnesemia [42]. Therefore, numerous factors contribute to magnesium depletion in individuals with diabetes.

The frequency of hypomagnesemia underrepresents the prevalence of magnesium depletion because magnesium depletion can exist in the absence of frank hypomagnesemia. Only 0.3% of the body's magnesium stores reside in the plasma [43]. Thus, individuals with depleted magnesium stores frequently exhibit normal serum magnesium [44•]. Systemic magnesium depletion is common and easily overlooked clinically.

Magnesium deficiency is associated with cardiovascular disease, as demonstrated by clinical studies. A meta-analysis of 40 prospective studies showed that higher magnesium in-take was associated with reduction in risk of heart failure (RR 0.78, 95% CI 0.69–0.89) and mortality (RR 0.90, 95% CI 0.81–0.99) [45]. In contrast, a 2016 meta-analysis of seven studies (5172 participants) examining primarily elderly men with low ventricular ejection fraction failed to find an association between serum magnesium and mortality [46]. However, subsequent studies provide more evidence suggesting a correlation between serum magnesium and heart failure risk. A prospective cohort study followed 2181 Finnish men for 24.8 years and found that baseline serum magnesium levels predicted incident heart failure (adjusted HR 0.87, 95% CI 0.76–0.98, for each standard deviation decrement in serum magnesium) [47]. A prospective study of 3523 British participants followed for 15 years also demonstrated an inverse correlation between serum magnesium and risk of incident heart failure. (The highest quintile serum magnesium group exhibited HR 0.56, 95% CI 0.36–0.86 compared to the lowest quintile group) [48]. A retrospective Japanese study in 452 patients with ejection fraction-preserved heart failure found that individuals with serum magnesium less than 2.0 mg/dl (0.8 mmol/L) had significantly increased risk of heart failure-related events (HR 2.37, 95% CI 1.27–4.41) [49•]. A trial that randomized 79 individuals with stage IV heart failure to receive oral magnesium orotate or placebo for twelve months showed that magnesium supplementation improved heart failure symptoms

and survival (75.7% versus 51.6%) [50]. These human studies strongly suggest that magnesium deficiency contributes to cardiovascular disease.

Mechanisms by which magnesium promotes cardiovascular health are numerous, and have been reviewed in detail elsewhere [51]. Briefly, effects on the vasculature include calcium channel blockade, reduction in sympathetic tone and blood pressure, and suppression of oxidative stress and inflammation. Additionally, in the heart, increased magnesium is associated with improved cellular respiration, improved cardiac output, and reduced myocardial fibrosis in various experimental models. Together, these findings suggest that magnesium depletion associated with diabetes contributes to adverse cardiovascular outcomes.

SGLT2 inhibitors increase plasma magnesium. A meta-analysis of SGLT2 inhibitor trials found that these agents increased serum magnesium levels in diabetic trial participants by 0.01 to 0.24 mg/dL (0.004 to 0.097 mmol/L) [52]. Although increases in serum magnesium levels were greatest in study participants receiving canagliflozin, increased serum magnesium was observed in each of four SGLT2 inhibitors examined, suggesting a class effect. Another meta-analysis found that, among participants with baseline hypomagnesemia, SGLT2 inhibition corrected serum magnesium levels in 47.8% of participants (95% CI 41.4–53.9) [53]. However, data addressing the effects of SGLT2 inhibitors on tissue or whole-body magnesium stores are lacking.

Mechanisms by which SGLT2 inhibitors improve magnesium levels remain speculative. Because SGLT2 inhibitors slow glomerular filtration, decreased filtration of magnesium may contribute. However, the recent observation that SGLT2 inhibitors reduce urinary fractional excretion of magnesium in at least some patients suggests increased renal tubular reabsorption [54•]. Several factors could enhance tubular magnesium absorption: 1) Increased electrical driving force. SGLT2-mediated absorption of glucose and sodium is electrogenic. SGLT2 inhibition would be expected to increase lumen potential in the renal tubule, augmenting the electrical driving force for magnesium reabsorption. 2) Increased angiotensin II activity. Extracellular fluid volume depletion from diuresis raises angiotensin II levels. Angiotensin II stimulates tubular magnesium reabsorption, decreasing urinary magnesium excretion [55]. 3) Increased expression of magnesium transporters. No published studies have explored the effects of SGLT2 inhibitors on expression of renal or gastrointestinal magnesium transporters. While mechanisms remain to be confirmed, correction of diabetic magnesium deficiency likely contributes to improvement in cardiovascular outcomes associated with the use of SGLT2 inhibitors.

Conclusions

The new availability of SGLT2 inhibitors represents a monumental advance in the management of cardiovascular disease. Numerous mechanisms associated with these agents likely synergize to promote improved cardiovascular health in diabetic patients. These include improved glycemic control, diuresis, reduced blood pressure, reduced uric acid levels, improved myocardial function, preservation of kidney function, and improved magnesium balance. Completely novel mechanisms may also contribute.

With such provocative cardiovascular and renal outcomes in diabetes, whether these agents have a role in management of disorders beyond diabetes represents an intriguing question. Early results show that a gliflozin can improve outcomes in normoglycemic patients with ejection fraction reduced heart failure. Might SGLT2 inhibitors also improve outcomes in heart failure with preserved ejection fraction? Similarly, the ability of SGLT2 inhibitors to reduce proteinuria and preserve kidney function suggests these agents could have a role in management of non-diabetic proteinuric kidney diseases. The next decade promises to bring exciting results further exploring effects of these agents within, and beyond, the context of diabetes.

Acknowledgements

Thanks to M. F. Muldoon and K. N. Ray for critical review and proofing of the manuscript.

Funding

This work has been supported by the National Institutes of Health: NIDDKK08 DK110332.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
 - of outstanding interest
1. Scheen AJ: Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. *Drugs* 2015, 75:33–59. [PubMed: 25488697]
 2. U.S. Food and Drug Administration: In Guidance for industry. Diabetes Mellitus - evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes Edited by U.S. Department of Health and Human Services. 2008.
 3. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM 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* 2019, 393:31–39. [PubMed: 30424892]
 - 4•. 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. *N Engl J Med* 2015, 373:2117–2128 [PubMed: 26378978] This trial demonstrated improved cardiovascular outcomes in diabetic individuals who received empagliflozin.
 - 5•. 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. *N Engl J Med* 2016, 375:323–334 [PubMed: 27299675] This trial demonstrated improved renal outcomes in diabetic individuals who received empagliflozin.
 - 6•. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erond N, Shaw W, Law G, Desai M, Matthews DR: Canagliflozin and cardiovascular and renal events in Type 2 diabetes. *N Engl J Med* 2017, 377:644–657 [PubMed: 28605608] This trial demonstrated improved clinical outcomes in diabetic individuals who received canagliflozin.
 - 7•. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA et al.: Dapagliflozin and cardiovascular outcomes in Type 2 diabetes. *N Engl J Med* 2019, 380:347–357 [PubMed: 30415602] Demonstrated improved cardiovascular outcomes in diabetic individuals receiving dapagliflozin.
 - 8••. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Belohlavek J et al.: Dapagliflozin in patients with heart failure and

reduced ejection fraction. *N Engl J Med* 2019, 381:1995–2008 [PubMed: 31535829]
 Demonstrated improvement in heart failure outcomes in individuals with ejection fraction-reduced heart failure. These findings provide evidence that dapagliflozin can be safe and effective even in non-diabetic individuals.

- 9•. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S et al.: Canagliflozin and renal outcomes in Type 2 diabetes and nephropathy. *N Engl J Med* 2019, 380:2295–2306 [PubMed: 30990260] Demonstrated improved renal outcomes in diabetic individuals who received canagliflozin.
10. Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ: 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, 18:783–794. [PubMed: 27059700]
11. Patel K, Carbone A: Sodium-glucose cotransporters as potential therapeutic targets in patients with Type 1 diabetes mellitus: an update on Phase 3 clinical trial data. *Ann Pharmacother* 2019, 53:1227–1237. [PubMed: 31226886]
12. Riddle MC: Glycemic control and cardiovascular mortality. *Curr Opin Endocrinol Diabetes Obes* 2011, 18:104–109. [PubMed: 21522000]
13. Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, Evans GW, Gerstein HC, Holman RR, Moritz TE et al.: Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2009, 52:2288–2298. [PubMed: 19655124]
14. Brady JA, Hallow KM: Model-based evaluation of proximal sodium reabsorption through SGLT2 in health and diabetes and the effect of inhibition with canagliflozin. *J Clin Pharmacol* 2018, 58:377–385. [PubMed: 29144539]
15. Schork A, Saynisch J, Vosseler A, Jaghutriz BA, Heyne N, Peter A, Haring HU, 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, 18:46. [PubMed: 30953516]
16. Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJ: WITHDRAWN: diuretics for heart failure. *Cochrane Database Syst Rev* 2016, 4 Cd003838. [PubMed: 27040884]
17. Tager T, Frohlich H, Seiz M, Katus HA, Frankenstein L: READY: relative efficacy of loop diuretics in patients with chronic systolic heart failure-a systematic review and network meta-analysis of randomised trials. *Heart Fail Rev* 2019, 24:461–472. [PubMed: 30874955]
18. Chen P, Chaugai S, Zhao F, Wang DW: Cardioprotective effect of thiazide-like diuretics: a meta-analysis. *Am J Hypertens* 2015, 28:1453–1463. [PubMed: 25926533]
- 19•. Bailey CJ: Uric acid and the cardio-renal effects of SGLT2 inhibitors. *Diabetes Obes Metab* 2019, 21:1291–1298 [PubMed: 30762288] This review discusses data supporting lowering of uric acid levels by SGLT2 inhibitors, the role of uric acid in pathogenesis of cardiovascular disease, and mechanisms by which SGLT2 inhibitors reduce uric acid levels.
20. Zhao Y, Xu L, Tian D, Xia P, Zheng H, Wang L, Chen L: Effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors on serum uric acid level: A meta-analysis of randomized controlled trials. *Diabetes Obes Metab* 2018, 20:458–462. [PubMed: 28846182]
21. Huang H, Huang B, Li Y, Huang Y, Li J, Yao H, Jing X, Chen J, Wang J: Uric acid and risk of heart failure: a systematic review and meta-analysis. *Eur J Heart Fail* 2014, 16:15–24. [PubMed: 23933579]
22. Di Franco A, Cantini G, Tani A, Coppini R, Zecchi-Orlandini S, Raimondi L, Luconi M, Mannucci E: Sodium-dependent glucose transporters (SGLT) in human ischemic heart: a new potential pharmacological target. *Int J Cardiol* 2017, 243:86–90. [PubMed: 28526540]
23. Fujita Y, Inagaki N: Renal sodium glucose cotransporter 2 inhibitors as a novel therapeutic approach to treatment of type 2 diabetes: clinical data and mechanism of action. *J Diabetes Investig* 2014, 5:265–275.
24. García-Ropero Á, Vargas-Delgado AP, Santos-Gallego CG, Badimon JJ: Inhibition of sodium glucose cotransporters improves cardiac performance. *Int J Mol Sci* 2019, 20.
25. Hamouda NN, Sydorenko V, Qureshi MA, Alkaabi JM, Oz M, Howarth FC: Dapagliflozin reduces the amplitude of shortening and Ca²⁺ transient in ventricular myocytes from streptozotocin-induced diabetic rats. *Mol Cell Biochem* 2015, 400:57–68. [PubMed: 25351341]

26. 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, 60:568–573. [PubMed: 27752710]
27. Andreadou I, Efentakis P, Balafas E, Togliatto G, Davos CH, Varela A, Dimitriou CA, Nikolaou P-E, Maratou E, Lambadiari V et al.: Empagliflozin limits myocardial infarction in vivo and cell death in vitro: role of STAT3, mitochondria, and redox aspects. *Front Physiol* 2017, 8.
28. Andreadou I, Bell RM, Bøtker HE, Zuurbier CJ: SGLT2 inhibitors reduce infarct size in reperfused ischemic heart and improve cardiac function during ischemic episodes in preclinical models. *Biochim Biophys Acta Mol Basis Dis* 2020, 1866 165770. [PubMed: 32194159]
29. Ferrannini E, Muscelli E, Frascerra S, Baldi S, Mari A, Heise T, Broedl UC, Woerle HJ: Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. *J Clin Invest* 2014, 124:499–508. [PubMed: 24463454]
30. Larsen TS, Aasum E: Metabolic (in)flexibility of the diabetic heart. *Cardiovasc Drugs Ther* 2008, 22:91–95. [PubMed: 18247112]
31. Gimeno-Orna JA, Blasco-Lamarca Y, Campos-Gutierrez B, Molinero-Herguedas E, Lou-Arnal LM, Garcia-Garcia B: Risk of mortality associated to chronic kidney disease in patients with type 2 diabetes mellitus: a 13-year follow-up. *Nefrologia* 2015, 35:487–492. [PubMed: 26306974]
32. Ray EC, Miller RG, Demko JE, Costacou T, Kinlough CL, Demko CL, Unruh ML, Orchard TJ, Kleyman TR: Urinary Plasmin (ogen) as a prognostic factor for hypertension. *Kidney Int Rep* 2018, 3:1434–1442. [PubMed: 30450470]
33. 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. *Lancet Diabetes Endocrinol* 2017, 5:610–621. [PubMed: 28666775]
34. Liu D, Lv LL: New understanding on the role of proteinuria in progression of chronic kidney disease. *Adv Exp Med Biol* 2019, 1165:487–500. [PubMed: 31399981]
35. Ray EC, Rondon-Berrios H, Boyd CR, Kleyman TR: Sodium retention and volume expansion in nephrotic syndrome: implications for hypertension. *Adv Chron Kidney Dis* 2015, 22:179–184.
36. Thomson SC, Vallon V: Renal effects of sodium-glucose cotransporter inhibitors. *Am J Cardiol* 2019, 124(Suppl. 1):S28–s35 [PubMed: 31741437] Reviews glomerular hemodynamic changes associated with diabetes and the role of SGLT1 and 2. Discusses primary micropuncture data demonstrating increased delivery of sodium and chloride to the macula densa and reduction in single nephron glomerular filtration rate in the setting of SGLT2 inhibition. Discusses caveats associated with these findings, including possible acute versus long-term effects.
37. van Bommel EJM, Muskiet MHA, van Baar MJB, Tonneijck L, Smits MM, Emanuel AL, Bozovic A, Danser AHJ, Geurts F, Hoorn EJ et al.: The renal hemodynamic effects of the SGLT2 inhibitor dapagliflozin are caused by post-glomerular vasodilatation rather than pre-glomerular vasoconstriction in metformin-treated patients with type 2 diabetes in the randomized, double-blind RED trial. *Kidney Int* 2020, 97:202–212 [PubMed: 31791665] Individuals with type 2 diabetes (many on renin-angiotensin-aldosterone system, RAAS, inhibitors) given dapagliflozin for 12 weeks exhibited reduced calculated post-glomerular arteriolar resistance but did not increase pre-glomerular resistance. In contrast to previous studies on animal models or in type 1 diabetes, these findings do not support enhanced tubuloglomerular feedback and suggest more complex hemodynamic mechanisms in this population.
38. Pham PC, Pham PM, Pham SV, Miller JM, Pham PT: Hypomagnesemia in patients with type 2 diabetes. *Clin J Am Soc Nephrol* 2007, 2:366–373. [PubMed: 17699436]
39. Moshfegh A, Goldman J, Ahuja J, Rhodes D, LaComb R: What we eat in America, NHANES 2005–2006. Usual Nutrient Intakes From Food And Water Compared to 1997 Dietary Reference Intakes for Vitamin D, Calcium, Phosphorus, and Magnesium. US Department of Agriculture ARS; 2009.
40. Kurstjens S, Smeets B, Overmars-Bos C, Dijkman HB, den Braanker DJW, de Bel T, Bindels RJM, Tack CJJ, Hoenderop JGJ, de Baaij JHF: Renal phospholipidosis and impaired magnesium handling in high-fat-diet-fed mice. *FASEB J* 2019, 33:7192–7201 [PubMed: 30848940] A high fat diet was shown to prevent upregulation of renal magnesium transporters in the context of

dietary magnesium deficiency, demonstrating how a high fat diet and dietary magnesium inadequacy synergize to promote magnesium depletion.

41. Lennon EJ, Lemann J Jr, Piering WF, Larson LS: The effect of glucose on urinary cation excretion during chronic extracellular volume expansion in normal man. *J Clin Invest* 1974, 53:1424–1433. [PubMed: 4825233]
42. Lameris AL, Monnens LA, Bindels RJ, Hoenderop JG: Drug-induced alterations in Mg²⁺ homeostasis. *Clin Sci (Lond)* 2012, 123:1–14. [PubMed: 22409531]
43. Elin RJ: Assessment of magnesium status. *Clin Chem* 1987, 33:1965–1970. [PubMed: 3315301]
- 44•. Elin RJ: Assessment of magnesium status for diagnosis and therapy. *Magnes Res* 2010, 23:S194–198 [PubMed: 20736141] This landmark review discusses the inadequacy of serum magnesium measurement for assessing bodily magnesium status and makes the case the chronic, latent magnesium deficiency is pervasive.
45. Fang X, Wang K, Han D, He X, Wei J, Zhao L, Imam MU, Ping Z, Li Y, Xu Y et al.: Dietary magnesium intake and the risk of cardiovascular disease, type 2 diabetes, and all-cause mortality: a dose-response meta-analysis of prospective cohort studies. *BMC Med* 2016, 14:210. [PubMed: 27927203]
46. Angkananard T, Anothaisintawee T, Eursiriwan S, Gorelik O, McEvoy M, Attia J, Thakkestian A: The association of serum magnesium and mortality outcomes in heart failure patients: a systematic review and meta-analysis. *Medicine (Baltimore)* 2016, 95:e5406. [PubMed: 27977579]
47. Kunutsor SK, Khan H, Laukkanen JA: Serum magnesium and risk of new onset heart failure in men: the Kuopio Ischemic Heart Disease Study. *Eur J Epidemiol* 2016, 31:1035–1043. [PubMed: 27220323]
48. Wannamethee SG, Papacosta O, Lennon L, Whincup PH: Serum magnesium and risk of incident heart failure in older men: The British Regional Heart Study. *Eur J Epidemiol* 2018, 33:873–882. [PubMed: 29663176]
- 49•. Nishihara T, Yamamoto E, Sueta D, Fujisue K, Usuku H, Oike F, Takae M, Arima Y, Araki S, Takashio S et al.: Clinical significance of serum magnesium levels in patients with heart failure with preserved ejection fraction. *Medicine (Baltimore)* 2019, 98: e17069 [PubMed: 31567942] This single center, retrospective study demonstrates the relationship between serum magnesium and outcomes in patients experiencing heart failure with preserved ejection fraction, suggesting the hypothesis that modification of magnesium balance may benefit these patients.
50. Stepura OB, Martynow AI: Magnesium orotate in severe congestive heart failure (MACH). *Int J Cardiol* 2009, 131:293–295. [PubMed: 18281113]
51. Tangvoraphonkchai K, Davenport A: Magnesium and cardiovascular disease. *Adv Chron Kidney Dis* 2018, 25:251–260.
52. Tang H, Zhang X, Zhang J, Li Y, Del Gobbo LC, Zhai S, Song Y: Elevated serum magnesium associated with SGLT2 inhibitor use in type 2 diabetes patients: a meta-analysis of randomised controlled trials. *Diabetologia* 2016, 59:2546–2551. [PubMed: 27628105]
53. Toto RD, Goldenberg R, Chertow GM, Cain V, Stefansson BV, Sjöström CD, Sartipy P: Correction of hypomagnesemia by dapagliflozin in patients with type 2 diabetes: a post hoc analysis of 10 randomized, placebo-controlled trials. *J Diabetes Complications* 2019:107402. [PubMed: 31375422]
- 54•. Ray EC, Boyd-Shiarski CR, Liu P, Novacic D, Cassiman D: SGLT2 inhibitors for treatment of refractory hypomagnesemia: a case report of 3 patients. *Kidney Med* 2020, 3:359–364.
55. Lima MC, Ajzen HA, Ribeiro AB, Andrade U, Ramos OL: Effect of angiotensin II on urinary magnesium, calcium, and sodium excretion in normal subjects. *Am J Med Sci* 1972, 263:173–179. [PubMed: 4337697]

Table 1

Clinical trials examining cardiovascular and renal outcomes

Trial (Year)	SGLT2 inhibitor	Subjects	N	Median follow-up (Years)	Primary outcome	Primary result(HR, 95% CI)	Hospitalization for heart failure(HR, 95% CI)	Kidney disease progression (HR, 95% CI)	Cardiovascular death(HR, 95% CI)	All-cause mortality(HR, 95% CI)
EMPA-REG (2015, 2016) [4•,5•]	Empagliflozin	Adults with diabetes with high risk of cardiovascular disease	7020	3.1	Composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke.	0.62 (0.49–.77)	0.65 (0.50–0.85)	0.61 (0.53–0.70)	0.62 (0.49–0.77)	0.68 (0.57–0.82)
CANVAS PROGRAM (2017) [6•]	Canagliflozin	Adults with diabetes with atherosclerosis or high risk of atherosclerosis.	10,142	2.4	Composite of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke.	0.86 (0.75–0.97)	0.67 (0.52–0.87)	0.60 (0.47–0.77)	0.87 (0.72–1.06)	0.87 (0.74–1.01)
DECLARE-TIMI 58 (2019) [7•]	Dapagliflozin	Over 40 years old with diabetes and atherosclerosis or high risk of atherosclerosis	17,160	4.2	Cardiovascular death, myocardial infarction, or ischemic stroke	0.93 (0.84–1.03)	0.73 (0.61–0.88)	0.53 (0.43–0.66)	0.98 (0.82–1.17)	0.93 (0.82–1.04)
DAPA-HF (2019) [8••]	Dapagliflozin	Adults with heart failure with left ventricular ejection fraction less than 40%. Only 45% had diabetes.	4744	1.5	Worsening of heart failure or death from cardiovascular causes.	0.74 (0.65–0.85)	0.70 (0.59–0.83)	0.71 (0.44–1.16)	0.82 (0.69–0.98)	0.83 (0.71–0.97)
CREDESCENCE (2019) [9•]	Canagliflozin	At least 30 years of age with diabetes and proteinuric chronic kidney disease	4401	2.6	Composite of end-stage kidney disease, doubling of creatinine, or death from renal or cardiovascular causes	0.70 (0.59–0.82)	0.61 (0.47–0.80)	0.66 (0.53–0.81)	0.78 (0.61–1.00)	0.83 (0.68–1.02)