Sudarshan Publications

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Pharma Research

An International Peer Reviewed, Indexed Journal

10.62655/s-epub.2021.v13.i01.pp83-92

SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS BEYOND GLYCAEMIC CONTROL: CARDIORENAL MECHANISMS

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Article info

Received date:17-09-2020
Accepted date:02-02-2021
Published date:14-05-2021
ISSN;0975-8216

Keywords:

SGLT2 inhibitors, Heart failure, Diabetic kidney disease, Cardiorenal mechanisms, Glycosuria

Abstract

Sodium-glucose cotransporter-2 (SGLT2) inhibitors were developed to lower blood glucose, yet large outcome trials have shown reductions in heart failure hospitalisation and kidney disease progression that exceed what glycaemic change can explain, including in people without diabetes. This narrative review summarises the published literature on the proposed mechanisms, covering renal haemodynamics, natriuresis and volume handling, cardiac energetics and ion transport, and metabolic and vascular effects. It also considers the clinical trial evidence, safety, and practice implications. It reports no new data. Several mechanisms are plausible and probably act together, but few have been confirmed in humans, and their relative importance remains uncertain.

1. INTRODUCTION

Few drug classes have changed their own purpose as quickly as the SGLT2 inhibitors. They arrived in the early 2010s as glucose-lowering tablets with an unusual, insulin-independent mechanism, and were expected to be judged by HbA1c, weight and tolerability [1, 2]. Regulators had by then started to ask for cardiovascular safety trials for every new diabetes drug, and those trials produced a surprise. In the first of them, empagliflozin lowered cardiovascular death and hospitalisation for heart failure in people with type 2 diabetes and established

cardiovascular disease, and the separation of the curves appeared within months [3]. Further trials of canagliflozin, dapagliflozin and others confirmed a consistent reduction in heart failure events and in kidney outcomes, even though the effect on glycaemia was modest [4, 5, 6].

The result raised an obvious question: why? A drug that lowers HbA1c by less than one percentage point should not change heart failure admissions within weeks, and later trials enrolled patients with heart failure or chronic kidney disease who did not have diabetes at all [7, 8, 9]. This review summarises the published explanations, drawing on physiological studies, animal work, small human mechanistic trials and the large outcome trials. It reports no new data. The sections that follow describe the pharmacology, the renal and cardiac mechanisms that have been proposed, the clinical evidence (table 1 and fig. 1), and the safety and practical issues that follow from them [10, 11, 12].

2. PHARMACOLOGY OF SGLT2 INHIBITION

The route to these drugs began with a plant glycoside. Phlorizin, isolated from the bark of apple trees in the nineteenth century, produces glycosuria by blocking glucose transporters in the kidney, and it served for decades as a pharmacological tool [1, 2]. It was a poor drug, being poorly absorbed, rapidly hydrolysed and not selective for SGLT2 over SGLT1, which also sits in the intestine. Medicinal chemistry produced the C-glucoside inhibitors that resist glycosidases and show a high degree of selectivity for SGLT2, and the first of them reached the clinic after the observation that people with familial renal glucosuria, who carry loss-of-function mutations in the gene for SGLT2, are generally healthy [1, 2, 10]. That natural experiment gave reassurance about the safety of the target, which later outcome data have broadly justified.

SGLT2 sits on the brush border of the early proximal tubule, where it reabsorbs most of the glucose filtered by the glomerulus, with sodium moving down its gradient alongside [1, 2]. SGLT1, further along the tubule, handles much of the rest. In diabetes the capacity of SGLT2 rises, which contributes to hyperglycaemia and, importantly for this review, to excess sodium uptake in the proximal tubule [10, 13]. Inhibitors such as empagliflozin, dapagliflozin and canagliflozin block the transporter selectively, so that glucose appears in the urine in amounts of tens of grams a day, and sodium and water follow. The glucose-lowering effect is mild and falls as renal function declines, because less glucose is filtered, yet the drug effects on the kidney continue [14, 15].

The immediate physiological consequences are easy to list. Glycosuria produces a calorie loss that translates into modest weight reduction. Osmotic diuresis and natriuresis lower plasma volume and blood pressure by a few millimetres of mercury. Haematocrit rises, uric acid falls, and circulating ketones increase slightly as the body shifts towards fat metabolism [16, 17, 18]. All of these effects begin within days. They are shared, to differing extents, by all the drugs in the class, and none of them depends on the patient having diabetes, which is why the first mechanistic proposals attempted to link them to the outcomes seen in trials [11, 19, 20].

Table 1: Mechanisms and clinical findings reported for SGLT2 inhibitors beyond glucose lowering

Mechanism or study	Reported finding	Ref.
Tubuloglomerular feedback type 1 diabetes	Empagliflozin reduced glomerular hyperfiltration in patients with raised filtration rate.	[21]
Intravital imaging diabetic mice	Afferent arteriolar constriction and lower glomerular hypertension after treatment.	[22]
Initial eGFR dip EMPA-REG	Early fall in eGFR was usually reversible and not linked to worse kidney outcomes.	[23]
Substrate shift ketones	Greater fat oxidation and higher ketone levels, proposed as a thrifty myocardial fuel.	[16, 17]
Cardiomyocyte sodium rats and rabbits	Lower cytoplasmic sodium through sodium–hydrogen exchanger inhibition.	[24]

Mechanism or study	Reported finding	Ref.
Differential volume regulation model	Interstitial fluid removed more than intravascular volume, easing congestion.	[25]
Blood pressure and stiffness	Empagliflozin lowered blood pressure and markers of arterial stiffness.	[18]
EMPA-REG OUTCOME	Fewer cardiovascular deaths and heart failure admissions in type 2 diabetes.	[3]
CREDENCE and DAPA-CKD	Lower risk of kidney failure and death, with or without diabetes in DAPA-CKD.	[7, 26]
DAPA-HF and EMPEROR-Reduced	Fewer worsening heart failure events or deaths, irrespective of diabetes status.	[8, 9]
Ketoacidosis and infections	Rare ketoacidosis and genital infections reported in cohort and trial data.	[27, 28]

A feature that distinguishes SGLT2 inhibitors from loop diuretics is the nature of the sodium loss. Because blockade takes place in the proximal tubule, delivery of sodium and chloride to the macula densa increases, which switches on tubuloglomerular feedback and constricts the afferent arteriole [21, 29]. Natriuresis is also self-limiting. After the first days the urinary sodium excretion falls back toward baseline as other nephron segments compensate, so that the lasting change is a modest contraction of extracellular volume rather than continuing diuresis [12, 25]. These details matter for interpreting the heart failure results, because they suggest an effect on how fluid is distributed as much as on how much is lost [25, 30].

Pharmacokinetic details seldom feature in the cardiorenal discussion but are relevant to practice. The drugs are taken once daily, are largely metabolised by glucuronidation in the liver and have half-lives of roughly twelve hours or more. Efficacy at the transporter depends on delivery to the tubular lumen, which requires filtration, and this partly explains why glucose lowering diminishes in kidney disease [2, 14, 15]. Dose adjustment for hepatic impairment is seldom needed, but renal function determines which indications are appropriate.

3. RENAL MECHANISMS

The best-supported renal mechanism concerns glomerular haemodynamics. In diabetes, enhanced proximal sodium reabsorption lowers the sodium load reaching the macula densa, which reads this as low volume, relaxes the afferent arteriole and raises intraglomerular pressure, a state called hyperfiltration [10, 13]. SGLT2 blockade restores distal delivery, so tubuloglomerular feedback constricts the afferent arteriole again and pressure falls. In people with type 1 diabetes and hyperfiltration, empagliflozin reduced the elevated glomerular filtration rate, consistent with this model [21]. In diabetic mice, intravital imaging showed that the drug narrowed the afferent arteriole and lowered glomerular hypertension [22]. Similar findings were reported in the Akita mouse, in which empagliflozin lessened hyperfiltration and albuminuria in proportion to the degree of hyperglycaemia [31].

The same mechanism explains a clinical oddity. Soon after starting an SGLT2 inhibitor, estimated glomerular filtration rate (eGFR) typically dips by a few millilitres per minute, then stabilises, and over the longer term declines more slowly than with placebo [15, 32]. A detailed analysis of the empagliflozin outcome trial found that the initial dip was usually reversible and was not associated with worse long-term kidney outcomes [23]. This pattern resembles that seen when renin–angiotensin system blockers are started, and it supports the idea that lowering intraglomerular pressure is protective in the long run, even if it costs a little filtration at first [10, 15]. Clinically it means that a small early fall in eGFR should not by itself prompt withdrawal.

Other renal effects are probably contributory. Reduced proximal reabsorption lowers the oxygen consumption of tubular cells, since transport work is a major energy cost, and the resulting relief of tubular hypoxia has been proposed to limit injury and interstitial fibrosis [13, 15]. The drugs also reduce albuminuria, an effect that appears early and cannot be explained by blood pressure or glucose alone [7, 29, 32]. In experimental models, inhibition of SGLT2 was linked to less renal inflammation and oxidative stress

and to reduced glomerular growth, but data from human kidney tissue are scarce [15, 31]. Increased erythropoietin production and the rise in haematocrit are a further effect that might improve oxygen delivery, a hypothesis that is still debated [11, 19].

Interaction with the renin–angiotensin system helps explain why the benefit is additive to existing therapy. Angiotensin-converting enzyme inhibitors and receptor blockers lower intraglomerular pressure by dilating the efferent arteriole, whereas SGLT2 inhibitors act on the afferent side through tubuloglomerular feedback [10, 29]. The two effects work from opposite ends of the glomerulus, and in the major kidney trials nearly all participants were already on maximally tolerated renin–angiotensin blockade [7, 26]. Benefits were therefore shown on top of standard care, not instead of it. Hyperkalaemia, a recognised problem with renin–angiotensin inhibitors, did not appear to be worsened and may even be reduced, a point of practical interest for patients who otherwise cannot tolerate full-dose blockade [7, 15].

Kidney outcome trials have broadly matched these mechanistic predictions. In the CREDENCE trial of patients with type 2 diabetes and albuminuric chronic kidney disease, canagliflozin lowered the risk of the composite of end-stage kidney disease, doubling of serum creatinine and renal or cardiovascular death by roughly a third [26]. DAPA-CKD then showed a similar relative benefit with dapagliflozin in patients with chronic kidney disease with or without diabetes, which is the strongest evidence that the effect is not mediated by glucose [7]. A meta-analysis of trials in type 2 diabetes found a reduction in the risk of kidney failure and of its progression across the class [33]. Benefit was seen even at low eGFR values, where glucose lowering is negligible [7, 26, 33].

4. CARDIAC AND VASCULAR MECHANISMS

Volume handling is the most immediate explanation for the reduction in heart failure admissions. Hallow and colleagues used a computational model to suggest that SGLT2 inhibitors remove interstitial fluid more than intravascular fluid, whereas loop diuretics deplete both in proportion, which would reduce congestion with less drop in circulating volume and less neurohormonal activation [25]. Support for this idea comes from clinical observations of a greater rise in haematocrit than would be expected from haemoconcentration alone, and a limited effect on heart rate and sympathetic tone [18, 20]. The proposal is plausible and consistent with the fast onset of benefit in the DAPA-HF and EMPEROR-Reduced trials, but direct measurements of fluid compartments in patients are few [8, 9, 25].

Cardiac metabolism provides a second line of explanation. In a failing heart, energy production is inefficient and the myocardium struggles to use its fuels. Ferrannini and colleagues observed that SGLT2 inhibition shifts the whole body toward fat oxidation and raises ketone body levels, and proposed that ketones act as a 'thrifty' fuel yielding more ATP per unit of oxygen consumed [16, 17]. This idea has appeal because it links glycosuria, ketosis and improved myocardial efficiency. Critics point out that the increase in circulating ketones is small, and that direct evidence of improved myocardial energetics in patients is limited [11, 19]. The hypothesis is still best described as attractive but unproved, with some supportive animal and imaging data [19, 34].

Ion handling in the heart cell offers a third possibility. In rats and rabbits, empagliflozin lowered cytoplasmic sodium in cardiomyocytes by inhibiting the sodium–hydrogen exchanger, and the associated reduction in intracellular calcium would be expected to improve contractile and diastolic behaviour and reduce arrhythmia [24]. Packer and colleagues drew on such findings to propose a unifying mechanism in which inhibition of the exchanger, together with effects on nutrient sensing pathways, would activate pathways of cellular housekeeping and reduce cardiac remodelling [30]. This work remains largely preclinical, and the drug concentrations needed were not always clearly achievable in vivo, so the sodium–hydrogen exchanger model has attracted caution as well as interest [12, 19].

Erythropoiesis and oxygen delivery are a further proposed route. The rise in haematocrit seen within weeks of starting treatment was initially put down to haemoconcentration from diuresis, but a rise in erythropoietin and in reticulocyte count points to a true increase in red-cell production, perhaps because relief of tubular hypoxia allows interstitial fibroblasts to resume erythropoietin synthesis [11, 19, 20]. More haemoglobin means better oxygen delivery to the myocardium and kidney, which might help in heart failure and anaemia of chronic kidney disease. Evidence of structural benefit comes from an imaging trial in which empagliflozin reduced left ventricular mass over six months in patients with diabetes and coronary disease [35], an effect compatible with reverse remodelling, although the study was small and short [19, 34].

Vascular effects add further possibilities. In patients with type 2 diabetes, empagliflozin reduced blood pressure and markers of arterial stiffness and vascular resistance in short studies, with little change in heart rate [18]. Lower blood pressure and arterial stiffness reduce afterload, a benefit for the failing ventricle. The class has also been linked to modest reductions in visceral fat, uric acid and body weight, and to less inflammation and oxidative stress in experimental settings [11, 20, 34]. None of these changes is large enough alone to account for the trial results, which is why most reviewers propose a combination of effects acting at once [12, 19].

Metabolic side effects of treatment may add to the haemodynamic ones. Weight falls by a couple of kilograms on average, mostly fat, and includes a reduction in visceral and epicardial fat depots that have been linked with inflammation and heart failure with preserved ejection fraction [2, 11, 20]. Insulin sensitivity improves modestly, circulating uric acid falls, and blood pressure and albuminuria both decrease [16, 18, 29]. Each is a recognised cardiovascular risk marker. Yet the magnitude is small, and trials of other weight-lowering or glucose-lowering drugs with similar changes did not reproduce the heart failure benefit [6, 12]. The metabolic effects look like supporting players, not the explanation, and they probably contribute most through long-term remodelling.

Several authors have asked whether SGLT2 inhibitors act on the heart directly, since the transporter is hardly expressed in cardiac muscle. The balance of evidence is that any direct actions are probably off-target, mediated for instance through the sodium–hydrogen exchanger, or indirect, through changes in the systemic environment, such as ketones, volume and blood pressure [12, 19]. AMP-activated protein kinase activation by canagliflozin in cell systems fits this picture, since it depends on mitochondrial effects not on glucose transport [36]. Heart failure trials that included patients without diabetes also argue against a glycaemic route, and they showed benefits on top of established neurohormonal therapy [8, 9, 37].

Atherosclerosis has not been ignored. Meta-analyses show little reduction in myocardial infarction or stroke with the class as a whole, with benefit concentrated in heart failure and kidney outcomes [5, 6]. Still, subgroup data suggest that benefit on major adverse cardiovascular events is clearest in patients with established atherosclerotic disease, and that heart failure and kidney benefit extend to people without it [6, 12]. This pattern, rather than a uniform anti-atherosclerotic effect, is the main reason the cardiorenal framing has displaced the older cardiovascular one. Epicardial and perivascular fat reduction, and its relation to diastolic function, is another suggested route that is still being explored.

5. CLINICAL EVIDENCE AND SYNTHESIS

The major mechanistic and clinical findings are brought together in table 1, and the entries are counted by category in fig. 1. The outcome trials form the foundation. In EMPA-REG OUTCOME, empagliflozin reduced the primary composite of cardiovascular death, non-fatal myocardial infarction and stroke, and the benefit was driven by a large fall in cardiovascular death and hospitalisation for heart failure [3]. CANVAS, with canagliflozin, showed a reduction in the primary composite as well,

together with an increase in amputations that has made that drug the focus of safety discussion [4]. DECLARE-TIMI 58 with dapagliflozin did not meet its superiority endpoint for major adverse cardiac events but reduced the composite of cardiovascular death or heart failure hospitalisation [5]. VERTIS CV with ertugliflozin showed non-inferiority [38].

Timing is one of the most informative clues available. In EMPA-REG OUTCOME the curves for cardiovascular death and heart failure hospitalisation separated within the first few months, long before any plausible effect on atherosclerotic plaque could occur [3, 12]. In DAPA-HF and EMPEROR-Reduced, benefit on worsening heart failure was also seen early, and in DAPA-CKD the divergence in kidney events appeared within the first year [7, 8, 9]. A fast onset of benefit fits haemodynamic and volume mechanisms better than slow structural changes, although reverse remodelling and effects on fibrosis may add later [19, 25]. It also fits the observation that the benefit appears during the first weeks of treatment in patients with established heart failure, a point of some practical importance.

The pooled picture comes from meta-analysis. Across the three large cardiovascular outcome trials, SGLT2 inhibitors modestly reduced major adverse cardiovascular events in patients with atherosclerotic disease but not in those with multiple risk factors alone, while they reduced hospitalisation for heart failure and progression of kidney disease irrespective of baseline atherosclerotic disease or heart failure history [6]. The renal effect appeared consistently, with fewer composite kidney events across the class [32, 33]. The consistency of heart failure and kidney results across drugs, populations and baseline HbA1c strengthens the argument for a mechanism that does not involve glycaemia [6, 12].

The dedicated heart failure trials went a step further. DAPA-HF randomised patients with heart failure with reduced ejection fraction, about half of whom did not have diabetes, and found that dapagliflozin reduced the composite of worsening heart failure or cardiovascular death by roughly a quarter, with similar benefit regardless of diabetes status [8]. EMPEROR-Reduced showed a comparable reduction with empagliflozin in a similar population [9]. SOLOIST-WHF, a trial of the dual SGLT1 and SGLT2 inhibitor sotagliflozin in patients with diabetes and a recent worsening heart failure event, also reduced events when treatment was started around hospital discharge [37]. These results moved the class from diabetes therapy into heart failure therapy [12, 34].

Several populations are less well covered by the trials. Elderly patients, those with advanced kidney disease and people with heart failure with preserved ejection fraction were under-represented or absent in the first generation of trials, and the benefit in the last group had not been established when this review was prepared [12, 37]. In kidney disease, the trials included patients down to an eGFR of about 25 to 30 mL/min/1.73 m^2, so evidence below that threshold is thin [7, 26]. Type 1 diabetes is a special case: ketoacidosis risk is higher, and the class has not been approved there in most jurisdictions, even though the physiological effect on hyperfiltration was first shown in that group [21, 27]. The trial evidence is strongest where the patients resemble the enrolled population [6, 12].

A caution is appropriate about reading the outcome trials as mechanistic experiments. They show that a drug lowers events, not why it does. Mediation analyses of the empagliflozin trial pointed to haematocrit and haemoglobin changes as the most prominent statistical mediators, which fits the volume hypothesis, but such analyses are exploratory and cannot prove causation [3, 11, 12]. Prospective mechanistic studies with imaging and invasive haemodynamics are needed, and several were still under way when this review was prepared [19, 34].

6. SAFETY AND PRACTICE IMPLICATIONS

The adverse effect profile follows from the pharmacology. Genital mycotic infections are the most common, and are more frequent in women, those with a previous history, and those with poor hygiene or uncontrolled glucose [2, 28]. Urinary tract infections are

mostly mild. Volume depletion and hypotension can occur, particularly in older people or those on loop diuretics, so doses of diuretics may need to be reduced when starting treatment [14, 15]. Diabetic ketoacidosis, sometimes with near-normal blood glucose, is a rare but serious event, reported with the class in people with type 1 diabetes or insulin deficiency, and more often when insulin is cut, during illness, with surgery or fasting, and on low-carbohydrate diets [27, 28].

Other signals have been more contested. The CANVAS programme reported an excess of lower limb amputations with canagliflozin, mostly of the toe or midfoot, and while this was not seen with other agents in their trials, the mechanism was uncertain and volume depletion has been suggested as a contributor [4]. Large observational data have also pointed to rare Fournier's gangrene and to an increased risk of diabetic ketoacidosis and genital infection compared with other drugs, and a nationwide cohort study examined these safety endpoints in some detail [28]. For most patients the benefit in heart failure and kidney disease greatly exceeds these risks, but treatment should be individualised [12, 28].

For prescribers and pharmacists, a few practical points follow. Treatment should be considered in patients with type 2 diabetes who have heart failure, chronic kidney disease or established cardiovascular disease, and the consensus reports of diabetes societies had already begun to recommend this irrespective of baseline HbA1c [12, 14]. The drug is also now used in heart failure and chronic kidney disease in people without diabetes [7, 8]. Counselling should cover genital hygiene, sick-day rules (temporarily stopping the drug during vomiting, diarrhoea or acute illness), pre-operative withholding and hydration [27, 28]. Renal function should be checked at baseline and a few weeks after starting, and an early small eGFR fall should be anticipated and explained [15, 23].

Glucose-lowering effects fade as renal function falls, because the filtered glucose load declines. In practice this means the drug is of little use for glycaemic control at low eGFR, though cardiorenal benefits seem to persist, so the reasons for prescribing should be stated clearly [14, 15]. Hypoglycaemia is uncommon when the drug is used alone or with metformin, but the risk rises when it is added to insulin or a sulfonylurea, and dose reduction of these agents may be needed [2, 14]. Weight loss and blood pressure lowering are generally welcomed, although frail older patients may not tolerate them well. Adherence and persistence in routine care appear to be lower than in trials, which will reduce population benefit [12, 28].

Euglycaemic ketoacidosis deserves a specific mention for pharmacists because it can be missed. Blood glucose may be only modestly raised, so routine glucose checks do not flag the problem, and symptoms such as nausea, abdominal pain and malaise can be attributed to other causes. Patients and prescribers should know to check blood or urine ketones when unwell, whatever the glucose reading shows [27, 28]. Temporary withholding before major surgery or prolonged fasting is generally recommended.

7. LIMITATIONS AND FUTURE DIRECTIONS

There are real limits to what can be said about mechanism. Most mechanistic data come from rodent studies, from short human studies in small numbers of people with diabetes, and from post-hoc analyses of trials not designed to test mechanism [11, 22, 31]. The proposed explanations are not mutually exclusive, and the contribution of each is not known. Doses and tissue concentrations in animal studies may not match human exposure, and species differences in transporter expression and renal physiology complicate extrapolation [19, 24, 31]. A further difficulty is that benefits arise within weeks, which suggests haemodynamic mechanisms, while long-term effects on remodelling and fibrosis may involve others [12, 13, 15].

Several areas deserve study. Direct measurements of fluid compartments, cardiac energetics, myocardial sodium handling and kidney oxygenation in people treated with SGLT2 inhibitors would help rank the competing explanations [19, 34]. Trials in heart failure with preserved ejection fraction, in people with chronic kidney disease of non-diabetic origin and in those after

myocardial infarction would show how far the benefit extends [12, 37]. Long-term safety, including bone and amputation outcomes, needs continued surveillance outside trial populations, and cost and access will determine how many eligible patients are treated [14, 28].

Generalisability and cost also limit current knowledge. The large trials recruited patients at high cardiovascular risk, sponsored by manufacturers, with run-in periods that excluded poor adherers, and follow-up of two to four years [3, 4, 5, 38]. Real-world cohorts may include sicker, older or less adherent patients, and registry analyses can only partly adjust for this [6, 28]. Branded SGLT2 inhibitors are expensive, and access in lower-income countries is limited, which makes the translation of trial benefit into population health uncertain [12, 14]. Generic competition and cost-effectiveness analyses will shape uptake, but they lie outside the scope of this mechanistic review.

8. CONCLUSION

SGLT2 inhibitors reduce heart failure hospitalisation and the progression of chronic kidney disease in ways that cannot be explained by their modest glucose-lowering effect. The evidence reviewed here favours a set of linked mechanisms: restoration of tubuloglomerular feedback and lower intraglomerular pressure, a distinctive pattern of natriuresis and fluid removal, a shift in cardiac fuel use, and small improvements in blood pressure, arterial stiffness and tissue oxygenation [16, 18, 21, 25]. Outcome trials in people with and without diabetes make a glycaemic explanation unlikely [7, 8, 9]. The rapid onset of benefit supports a prominent role for haemodynamic mechanisms [3, 25].

The mechanisms remain hypotheses with differing support. Renal haemodynamic effects have the strongest human evidence, while the ketone and sodium–hydrogen exchanger ideas rest mainly on animal and in vitro data [19, 22, 24]. Clinicians can use the class with reasonable confidence where trials show benefit, while attending to volume status, ketoacidosis risk and genital infection [27, 28]. Better human mechanistic studies would clarify who benefits most and whether newer indications will follow [12, 34]. For the present, the safest summary is that the clinical benefit is established while the biology behind it is still being worked out [6, 12].

9. ABBREVIATIONS

ATP-Adenosine triphosphate, CKD-Chronic kidney disease, eGFR-Estimated glomerular filtration rate, HbA1c-Glycated haemoglobin, SGLT1-Sodium-glucose cotransporter-1, SGLT2-Sodium-glucose cotransporter-2, AMPK-AMP-activated protein kinase, DAPA-HF-Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure, EMPA-REG-Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients

10. FUNDING

Nil

11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

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