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Plausible prediction of renoprotective effects of sodium-glucose cotransporter-2 inhibitors in patients with chronic kidney diseases

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Abstract

This narrative review was conducted due to uncertainty in predicting the beneficial impact of sodium-glucose cotransporter-2 (SGLT2) inhibitors on a dip of estimated glomerular filtration rate (eGFR), regardless of albuminuria presence, with the aim of elucidating plausible predictors of kidney function outcome among patients treated with SGLT2 inhibitors. The PubMed and Web of Science databases were searched in May 2023 for relevant articles published in English between 2013 and 2023. A total of 25 full-length scientific publications (comprising 11 large randomized trials and two cohort studies) were included for analysis. The majority of studies demonstrated a limited value of conventional biomarkers, such as initial decline in eGFR, a trajectory of eGFR during SGLT2 inhibitor administration, and urine albumin-to-creatinine ratio (UACR), in prediction of renoprotection. Included studies showed that the tendency to decreased eGFR, UACR, hemoglobin, glycosylated hemoglobin, lipid profile, serum uric acid, inflammatory biomarkers and natriuretic peptides did not predict clinical outcomes in groups without heart failure (HF) treated with SGLT2 inhibitors. In HF groups, biomarkers of inflammation, kidney injury, oxidative stress, mitochondrial dysfunction, ketogenesis, energy metabolism, and adipose tissue dysfunction (adropin and irisin), were detected with the aim of finding potential biomarkers. Biomarkers of adipose tissue dysfunction and inflammation may be promising for predicting SGLT2 inhibitor benefit compared with N-terminal pro-B-type natriuretic peptide and energy metabolism indicators.

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Introduction

Heart failure (HF) is a leading cause of mortality among patients with cardiovascular disease (CVD) that often coexists with numerous comorbidities, such as type 2 diabetes mellitus (T2DM) and overweight/obesity, which directly and indirectly lead to worsening kidney function.[1,2] About 40% of patients with HF have concomitant T2DM, and up to 50% of individuals with any established HF phenotype demonstrate different stages of chronic kidney disease (CKD).[3] In addition, both T2DM and CKD have been associated with elevated risk of incident *de novo* HF or progression of known cardiac dysfunction.[4] A reduction in the number of nephrons may not only be a result of acute kidney injury or CKD, but may also be associated with HF progression and may overlap with numerous cardiovascular risk factors, which mutually accelerate the progression of T2DM, kidney dysfunction and HF. Indeed, approximately 6% of patients with HF have both T2DM and CKD, and these three coexisting conditions substantially increase the risk for urgent hospital admission and all-cause mortality.[5]

Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce cardiovascular morbidity and mortality and improve kidney function in patients with T2DM, CKD and established HF, regardless of the presence of T2DM.[6–8] An analysis of data from the Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (DAPA-CKD trial) showed a significantly lower risk of adverse kidney events or all-cause mortality in a mixed population of patients with T2DM and non-T2DM-induced CKD receiving dapagliflozin compared with placebo.[9] In other studies that included patients with HF, such as the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-Reduced) and the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (DAPA-HF) trial (investigating the effects of dapagliflozin on major adverse events in patients with HF with reduced ejection fraction with or without T2DM), the risk of the secondary renal endpoints (chronic dialysis or renal transplant or sustained reduction of estimated glomerular filtration rate [eGFR] and composite worsening renal function or renal death) was significantly lower in those who were treated with SGLT2 inhibitor than placebo.[10,11] Meanwhile, the composite renal event (including sustained decline in eGFR $\geq 50\%$, end-stage renal disease, sustained dialysis, and renal transplantation), or renal death, was not reduced by dapagliflozin in the DAPA-HF trial.[11] A meta-analysis by Li et al.,[12] conducted in 2022, conceded that the benefits of SGLT2 inhibitors were found among patients with different kidney dysfunctions, even in stage 4 CKD. In addition, a reduction in eGFR decline and improvement in urine albumin-creatinine ratio among patients with HF have been established in previous clinical studies (the Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure [DELIVER] trial, and the

Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients [EMPA-REG OUTCOME] trial).[13,14] However, a previous study reported that the proportions of participants in dapagliflozin and placebo groups who had worsening kidney function remained relatively high, comprising approximately 50–60%.[15] This is an extremely important clinical issue, because in a real-life experience, the favorable impact of SGLT2 inhibition on eGFR and/or albuminuria/proteinuria was noted in about 30% of the entire patient population, and was markedly variable.[15] Numerous large clinical trials depicting an efficacy of SGLT2 inhibitors in CKD have yielded a wide range of plausible predictors for kidney outcomes, such as body weight, levels of hemoglobin and glycosylated hemoglobin (HbA1c), systolic blood pressure, urine albumin-to-creatinine ratio (UACR), high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, uric acid, and potassium.[7–12,14–16] However, there is no strong evidence regarding which particular factors may reliably predict the beneficial impact of SGLT2 inhibitors on kidney function. The purpose of the present review was to determine plausible predictors of kidney function outcome among patients treated with SGLT2 inhibitors.

Materials and methods

This narrative review focused on predictors of worsening kidney function among patients with any phenotype of chronic HF with concomitant T2DM. In May 2023, the PubMed and Web of Science databases were searched for relevant studies published in English language between 2013 and 2023, using the keywords "sodium-glucose cotransporter 2 inhibitors", "SGLT2i", "acute kidney injury", "chronic kidney disease", "heart failure", "diabetes mellitus", "SGLT2i and heart failure", "SGLT2i and diabetes mellitus", "SGLT2i and worsening kidney function," and "SGLT2i and renoprotection", "biomarkers and SGLT2i and renoprotection".

Two researchers (AEB and TAB) independently selected and extracted articles using predefined data fields. Papers were identified according to topic specificity, data quality, credibility, availability of data for extraction, and non-bias criteria. Articles were enrolled in the analysis according to eligibility criteria for inclusion in the narrative review. Inclusion criteria for the narrative review were: full-length English written manuscript; study aim focused on predictors of worsening kidney function; target patient population with any phenotype of chronic HF with concomitant T2DM; treatment included SGLT2 inhibitors; primary or secondary end points affected adverse kidney outcomes; and biomarker determination in connection with outcomes at baseline or during follow-up. Exclusion criteria were: topic irrelevance; misleading title; missing keywords; review studies; experimental/animal studies or case report studies; a lack of control group; small sample size; unclear results; or a lack of connection with SGLT2-inhibitor therapy or biomarker determination.

Ethics approval and informed patient consent were not required for this comprehensive narrative review, as the study was purely based on existing findings, which had been published in scientific articles, along with the personal clinical experience of the authors.

Definition of worsening kidney function and renoprotection

In a previous large clinical study (the Empagliflozin in Patients with Chronic Kidney Disease [EMPA-KIDNEY] trial), the primary endpoint for kidney outcome was defined as a composite event, including 40% decrease in eGFR from baseline, newly diagnosed end stage kidney disease,

or kidney mortality or cardiovascular (CV) death.[7] In the EMPA-REG OUTCOME trial, delaying the decline in eGFR and improving UACR (< 300 mg/g) compared with baseline levels were used to determine renoprotection during SGLT2 inhibitor administration.[8] In addition, in these trials, sub-analysis in subgroups by change in eGFR categories at the end of the study compared with baseline eGFR range (<45, 45–<60, 60–<90, ≥90 ml/min/1.73 m^2) was performed. Thus, in the present study, delaying the decline in eGFR and improving UACR (<300 mg/g) were defined as a nephroprotective impact of SGLT2 inhibitors on kidney function.

Results

Overall, 58 articles were identified according to topic specificity, data quality, credibility, potential for data extraction, and non-bias criteria. The search and screening of articles yielded 25 English-written full-length scientific publications, comprising 13 studies (11 large randomized clinical trials and two nonrandomized clinical studies), according to eligibility criteria for inclusion in the narrative review. Thus, 25 articles comprising 13 studies were enrolled in the analysis (Figure 1).

Predictors of worsening kidney function in T2DM patients without concomitant heart failure treated with SGLT2 inhibitors

Among patients with CKD with or without T2DM with a wide range of eGFRs (mostly between 20 and 90 ml/min/1.73 m^2) and any levels of albuminuria, SGLT2 inhibitors safely reduced the risk of kidney disease progression (Table 1).[7–9,11,17–26] In the EMPA-KIDNEY trial, 6609 patients with CKD with UACR ≥200 mg/g and eGFR ≥20 to <90 ml/min/1.73 m^2 were enrolled.[7] The primary outcome measure was a composite of end-stage kidney disease, a sustained eGFR <10 ml/min/1.73 m^2, a sustained decline in eGFR of ≥40%, or renal death along with cardiovascular death. During 2 years of follow-up, the primary outcome was noted in 13.1% patients from the empagliflozin group and 16.9% patients from the placebo group. Despite a significant reduction of absolute risk (−3.8%), there was no statistically significant impact of the therapy on HF hospitalization, cardiovascular death, or death from any cause. In addition, the slope of eGFR decline, UACR and N-terminal pro-B-type natriuretic peptide (NT-proBNP) did not predict clinical outcomes in the SGLT2 inhibitor group. Sub-group analysis showed that sufficient initial acute drop in eGFR might be associated with long-term renoprotective effect of SGLT2 inhibitors.[7] However, the study revealed that renoprotective ability of SGLT2 inhibitors was not associated with etiology of CKD and did not relate to an improvement of any specific cause of mortality.[7] In the EMPA-REG OUTCOME trial, 7020 patients with T2DM, established CVD, and eGFR ≥30 ml/min/1.73 m^2 were included.[8] The study revealed that empagliflozin improved the risk of cardiovascular death, HF admission, and all-cause hospitalization regardless of eGFR and UACR at baseline.

The DAPA-CKD trial enrolled 4304 patients with CKD who were randomly assigned to 10 mg dapagliflozin, once daily, or placebo.[9] The results of the trial revealed that the beneficial effect of dapagliflozin on kidney outcome (decline in eGFR of at least 50% from baseline, newly diagnosed end-stage kidney disease, or kidney-related death) was not associated with the etiology of nephropathy, or baseline eGFR and UACR values. Meanwhile, larger reductions in UACR were significantly related to improved eGFR during subsequent follow-up.[11]

The Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular

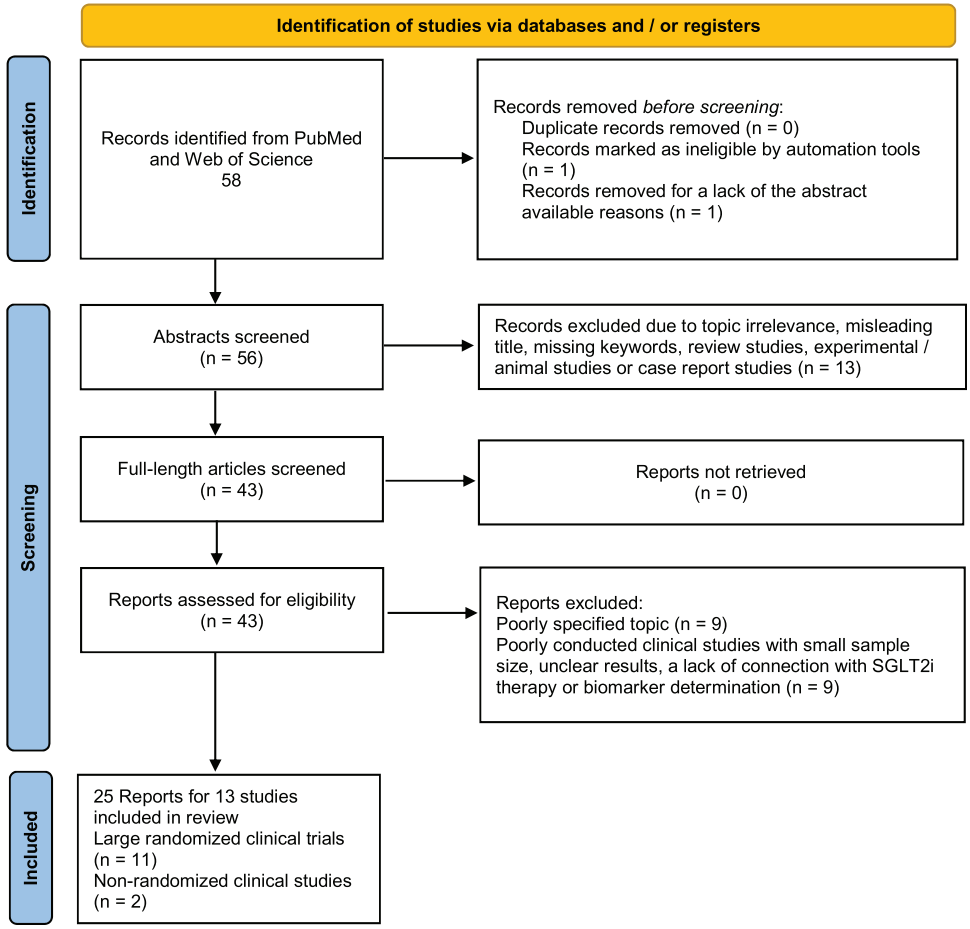

Figure 1. PRISMA flow diagram for the present narrative review.

Outcomes in Participants With Diabetic Nephropathy (CREDENCE) trial was stopped earlier than planned (a median follow-up of 2.62 years) according to the recommendation of the data and safety monitoring committee, because the composite of end-stage kidney disease (dialysis/kidney transplantation, or eGFR <15 ml/min/1.73 m^2), serum creatinine level doubling or renal death, or cardiovascular mortality, was found to be lower (up to 32%) in the canagliflozin versus placebo group.[17] Levels of hemoglobin, HbA1c, HDL cholesterol and LDL cholesterol were not found to be predictors for the kidney event. Subgroup analysis revealed that the greatest benefit for renal outcomes was observed in patients in the lowest eGFR subgroup.[18] Post hoc analysis of CREDENCE trial data showed that canagliflozin was able to slow the progression of CKD and to prevent acute kidney injury, even without the presence of early decreasing eGFR, and this effect was found in patients with eGFR <30 ml/min/1.73 m^2.[19,20]

Finally, post-hoc analysis of the Canagliflozin Cardiovascular Assessment Study (CANVAS) program, which included 10 142 patients with T2DM at high risk of CVD and eGFR ≥ 30 ml/min/1.73 m^2,

Table 1. Plausible predictors of the benefits of SGLT2 inhibitors in patients with CKD without heart failure.

Trial/Study	Study population	Treatment	Predictor	Significance	Ref
EMPA-KIDNEY	6609 CKD patients with eGFR $\geq$20–$<$ 90 ml/min/1.73 m^2	Empagliflozin 10 mg once daily or matching placebo	Baseline eGFR, UACR, NT-proBNP	No discriminative value on composite clinical outcomes	7
EMPA-REG OUTCOME	7020 patients with T2DM, CVD, and eGFR $\geq$ 30 ml/min/1.73 m^2	Empagliflozin 10 mg, empagliflozin 25 mg or placebo	Baseline eGFR, UACR	No discriminative value on composite clinical outcomes	8
DAPA-CKD	4304 patients with CKD with or without T2DM	Dapagliflozin 10 mg once daily or matching placebo	Baseline eGFR/UACR	eGFR/UACR did not predict kidney-specific composite outcome	9,11
CREDENCE	4401 CKD patients with T2DM and eGFR of 30 to $<$ 90 ml/min/1.73 m^2	Canagliflozin 100 mg once daily or matching placebo	Baseline eGFR/UACR, LDL cholesterol, HDL cholesterol, HbA1c, body mass, blood pressure	No discriminative value on composite clinical outcomes. The lowest eGFR predicted benefit from SGLT2 inhibitor administration	17–20
CANVAS	10 142 CKD patients with T2DM at high CV risk and with eGFR $\geq$ 30 ml/min/1.73 m^2	Canagliflozin 100 mg or matching placebo	Baseline eGFR/UACR	No discriminative value on composite renal outcomes	21
			TNFR-alpha-1, KIM-1, MMP-7, IL-6	Model based on combination of clinical characteristics and biomarkers better predicted renal outcomes than clinical characteristics alone	22,23
DECLARE-TIMI 58	17 160 participants with T2DM, HbA1c 6.5–12.0%, with either established ACVD or multiple risk factors, and eGFR $\geq$60 ml/min/1.73 m^2	Dapagliflozin 10 mg or matching placebo	HbA1c	No discriminative value on composite renal outcomes	24
Tandem-1 and Tandem-2 trials	1575 CKD patients with T1DM and UACR $\geq$30 mg/g	Sotagliflozin 200 mg, sotagliflozin 400 mg, or placebo	UACR, serum albumin, circulating hematocrit, serum uric acid	↑ serum albumin and hematocrit and ↓ in serum uric acid predicted renoprotective effect of sotagliflozin	25
Takahashi et al. (2020)	46 patients with T2DM and CKD with normoalbuminuria	Any SGLT2 inhibitor	eGFR	↓ eGFR after initiating SGLT2 inhibitor therapy may be biomarkers of a lack of renoprotection over long-term period	26

ACVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; IL, interleukin; KIM-1, kidney injury molecule-1; LDL, low-density lipoprotein; MMP-7, matrix metallopeptidase-7; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Ref, reference; SGLT2, sodium-glucose cotransporter-2; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TNFR-alpha-1, tumor necrosis factor receptor-1; UACR, urine albumin-to-creatinine ratio; ↓, decrease; ↑, increase.

yielded strong evidence that an absolute decrease in the composite primary outcome variable of cardiovascular and kidney outcomes was more pronounced in those with higher 'Kidney Disease: Improving Global Outcomes' (KDIGO) risk categories, with the same reduction of the composite of cardiovascular death or HF hospitalization and chronic eGFR slope.[21] A study by Li et al.[22] revealed several biomarkers that potentially mediated beneficial effects of canagliflozin on kidney outcomes in the CANVAS trial. They included systolic blood pressure, UACR, gamma glutamyltransferase, hematocrit, hemoglobin, serum albumin, erythrocytes, serum uric acid, and urine pH. Interestingly, erythrocyte concentration in urine, serum uric acid, and systolic blood pressure exhibited maximal cumulative mediation (115%), which depended on initial UACR levels.[22] A post-hoc analysis of the CANVAS program, which was based on clinical findings and the available biomarker data (age, previous CVD history, systolic blood pressure, UACR, hemoglobin, body weight, albumin, eGFR, tumor necrosis factor receptor-1, kidney injury molecule-1, matrix metallopeptidase-7 and interleukin-6) obtained from 3713 patients, revealed that the combination of clinical data and biomarker data better predicted renal outcomes than clinical characteristics alone.[23]

Data from the Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI 58) were analyzed to evaluate the effects of dapagliflozin on development and progression of kidney disease in patients with T2DM, with the aim of elucidating whether dapagliflozin improves renal outcomes in T2DM patients with and without established atherosclerotic CVD and preserved kidney function.[24] The DECLARE-TIMI 58 study included 17 160 patients with T2DM, HbA1c 6.5–12.0%, either established atherosclerotic CVD or multiple risk factors, with eGFR $\geq$60 ml/min/1.73 m^2, who were randomly allocated to 10 mg daily dapagliflozin or placebo.[24] The secondary renal composite outcome measure was defined as a sustained decline of at least 40% in eGFR and end-stage renal disease. In addition, death from renal or cardiovascular causes was evaluated. Dapagliflozin was revealed to prevent, and in many cases reduce, progression of CKD, regardless of a presence of either T2DM or atherosclerotic CVD. In fact, this effect was not associated with glycemic control during SGLT2 inhibitor administration.

Pooled analysis of the TANDEM-1 and TANDEM-2 trials, in which patients were administered the dual SGLT1 inhibitor and SGLT2 inhibitor sotagliflozin, in two different doses (200 mg or 400 mg daily), or placebo, showed that the favorable effects of sotagliflozin on kidney function in adults with type 1 diabetes was associated with increase in serum albumin and hematocrit, as well as reductions in serum uric acid.[25] In a small retrospective study, Takahashi et al.[26] noted that a higher initial decrease in eGFR may be a potential indicator of worsening renal function after the initiation of SGLT2 inhibitors in patients with T2DM and CKD with UACR $<$30 mg/g. Although patients were followed for 1 year, it remained uncertain whether a trend for eGFR was a predictive biomarker for renoprotection in both groups (treated with either SGLT2 inhibitors or other antidiabetic medication).

Thus, in patients with CKD at higher HF risk, SGLT2 inhibitors demonstrated their ability to improve renal outcomes across KDIGO risk categories. In all of the above trials, apart from CREDENCE, SGLT2 inhibitors minimally increased hemoglobin, magnesium and potassium levels, and reduced phosphate reabsorption and serum uric acid levels. However, these studies were not initially designed to elucidate specific biomarkers for prediction of

kidney protection and were directed to the determination of major clinical cardiovascular and kidney outcomes.

Predictors of kidney outcomes in patients with T2DM and concomitant heart failure during SGLT2 inhibitor administration

The DAPA-HF trial revealed that among 4742 patients with HF and reduced ejection fraction (41% had eGFR <60 ml/min/1.73 m^2), the composite renal outcome was not reduced by dapagliflozin administration and this effect was not predicted by baseline eGFR and a presence of T2DM (Table 2).[27] Post-hoc analysis of the DAPA-CKD trail showed that dapagliflozin was effective on kidney and cardiovascular outcomes across KDIGO risk categories.[28]

In the EMPEROR-Reduced trial, the annual rate of eGFR decline was significantly slower in the empagliflozin group compared with the placebo group.[29] Additionally, in 3730 patients with class II–IV HF and left ventricular ejection fraction (LVEF) < 40%, the higher quartile NT-proBNP levels compared with lowest quartile (≥3480 pg/ml versus <1115 pg/ml) at baseline were associated with greater risk for both HF severity and renal outcomes.[29] However, 52-week administration of empagliflozin reduced the risk of kidney outcomes, regardless of baseline eGFR and NT-proBNP concentrations. The authors concluded that post-treatment NT-proBNP concentrations had better discriminative potency for subsequent prognosis than pretreatment levels. In the Empagliflozin outcome trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) that included 5988 patients with HF and preserved ejection fraction, with and without T2DM, who were treated with the SGLT2 inhibitor empagliflozin or placebo, empagliflozin reduced the combined risk of cardiovascular death and HF hospital admission.[30] Although this trail was not specifically designed to elucidate how kidney benefit from SGLT2 inhibitor administration may be predicted, more than 1250 circulating biomarkers were evaluated to identify plausible predictors for worsening kidney function, and changes of nine of these (insulin-like growth factor-binding protein 1, transferrin receptor protein 1, carbonic anhydrase 2, erythropoietin, protein-glutamine gamma-glutamyltransferase 2, thymosin beta-10, U-type mitochondrial creatine kinase, insulin-like growth factor-binding protein 4, and adipocyte fatty acid-binding protein 4) were found to be related with this event.[31] The authors suggested that these molecules are expressed on target organs, including the heart and kidney, and they are involved in the down-regulation of oxidative stress, suppression of inflammation and tissue fibrosis, and the modulation of mitochondrial integrity, energy homeostasis, and endogenous reparative and regenerative function.[31]

The Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease (VERTIS CV) trial included 8246 patients with known HF (32% of whom had LVEF ≤45%), T2DM and atherosclerotic CVD.[32] Although ertugliflozin did not significantly reduce the risk of first HF hospitalization and death, the greatest benefit was found in those with baseline eGFR <60 ml/min/1.73 m^2 or albuminuria.[32] Segar et al.[33] established that early changes in four biomarkers (HbA1c, circulating hemoglobin levels, hematocrit and serum uric acid), as well as average changes in early biomarkers, including circulating hemoglobin levels, hematocrit and serum uric acid, bodyweight, and serum albumin levels, mediated the renoprotective effects of ertugliflozin. In addition, Berezina et al.[34] reported that low serum levels of adropin (<2.30 ng/ml) predicted CKD progression in patients with T2DM and concomitant HF treated with

Table 2. Predictors of kidney outcomes in patients with T2DM with concomitant heart failure during SGLT2 inhibitor administration.

Trial / Study	Study population	Treatment	Predictor	Significance	Reference
DAPA-HF	4742 HFrEF patients with or without T2DM and eGFR $\geq$30 ml/min/1.73 m^2	Dapagliflozin 10 mg daily or placebo	Decline in eGFR	eGFR slope did not predict kidney outcome	27,28
EMPEROR-Reduced	3730 HFrEF patients with or without T2DM	Empagliflozin 10 mg daily or placebo	NT-proBNP	Predictive ability of post-treatment NT-proBNP was higher than pre-treatment biomarker	29
EMPEROR-Preserved	5988 patients with NYHA class II–IV HFpEF regardless of a presence of T2DM	Empagliflozin 10 mg daily or placebo	Insulin-like growth factor-binding protein 1, transferrin receptor protein 1, carbonic anhydrase 2, erythropoietin, protein-glutamine gamma-glutamyl transferase 2, thymosin beta-10, U-type mitochondrial creatine kinase, insulin-like growth factor-binding protein 4, and adipocyte fatty acid-binding protein 4	Changes of circulating biomarkers can be associated with benefits from SGLT2 inhibitor administration	31
VERTIS CV	8246 HF patients with T2DM with atherosclerotic CVD	Ertugliflozin 5 mg, 15 mg, or placebo	HbA1c, circulating hemoglobin levels, hematocrit and serum uric acid	Biomarkers mediated renoprotective effect of ertugliflozin	33
Berezina et al. (2023)	417 T2DM patients with any phenotype of chronic HF and CKD, 30 T2DM patients without HF and CKD and 25 healthy volunteers	Dapagiflozin 10 md daily	Albuminuria/proteinuria, serum levels of adropin	Serum levels of adropin $<$2.30 ng/ml predicted CKD in T2DM patients with concomitant HF	34

CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2, sodium-glucose cotransporter-2; T2DM, type 2 diabetes mellitus.

dapagliflozin. The results of included trials are summarized in Table 2.[27–29,31,33,34]

In recent post-hoc analysis of the randomized EMPEROR-Reduced and EMPEROR-Preserved trials, compared with placebo, the SGLT2 inhibitor empagliflozin reduced HF-related clinical outcomes, including hospital admission or CV death, regardless of albuminuria levels at baseline, as well as diminished the progression of albuminuria to proteinuria with a slower progressive decline in renal function in patients with chronic HF across a wide range of LVEF regardless of baseline NT-proBNP levels.[35] A meta-analysis of 13 SGLT2 inhibitor trials (four comprising only patients with CKD) involving 90 413 participants, showed that SGLT2 inhibitors modified the risk of worsening kidney function and acute kidney injury irrespective of baseline eGFR and etiology of CKD.[36] However, there were no data regarding trajectory of eGFR after administration of SGLT2 inhibitors in the meta-analysis.[36] In another study that was based on post-hoc analysis of eight large SGLT2 inhibitor trials (DAPA-HF, DAPA-CKD, DECLARE-TIMI 58, CREDENCE, CANVAS, EMPEROR-Reduced, EMPA-REG OUTCOME, VERTIS CV), the risk of renal events was shown to be more significantly decreased in those who had UACR >1000 mg/g than ≤ 1000 mg/g.[37] Thus, it remains unclear whether dynamic changes in eGFR and UACR after initiating SGLT2 inhibitor administration are enough to predict benefits of the treatment.

Discussion

The results of the present study demonstrate a limited value of conventional biomarkers, such as initial decline in eGFR, a trajectory of eGFR during SGLT2 inhibitor administration, and UACR, in prediction of renoprotection. Moreover, there are controversial issues regarding the discriminative strength of an initial dip in eGFR immediately after starting SGLT2 inhibitor therapy, which has been interpreted in different cases as a plausible predictor of further worsening kidney function,[26] or, conversely, as an indicator of renoprotective effect of SGLT2 inhibitors in relation to renal clinical outcomes during follow-up.[38] Among patients with CKD stages 2–3 and normoalbuminuria, an initial dip in eGFR was associated with an over 20% decrease in eGFR within 2 years or more after starting SGLT2 inhibitor, whereas in patients with CKD stages 2–3 and UACR ≥ 100, worsening kidney function may be temporary and eGFR restoration seemed to show an effective renoprotective effect of SGLT2 inhibition.[26,38] Although the underlying mechanisms of this effect are yet to be ascertained, decreasing intraglomerular pressure via a restoration of tubuloglomerular feedback might be a reasonable explanation of these findings.[39] However, the impact of albuminuria on prediction of eGFR trajectory remains unclear, while reduction of albuminuria may be a result of improving intraglomerular hemodynamics. It should be noted that the sample sizes of the studies mentioned above are relatively small and the results require marked caution in their interpretation.

On the other hand, large clinical trials of SGLT2 inhibitors have thoroughly evaluated the trajectory of eGFR in close connection with prespecified renal and cardiovascular clinical outcomes. The Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial revealed that patients experiencing HF hospital admission had a significant decline in eGFR directly prior to hospitalization, whereas patients without HF admission had a relatively stable trajectory of eGFR.[40] Overall, there is strong evidence of the fact that eGFR trajectory is associated with HF hospitalization, but not with benefits in renal outcomes

during HF management.[40,41] Of note, renal function trajectories were most often similar between both arms of the management (active treatment and placebo) and did not correspond to the beneficial effects of treatment agents, when therapy of HF is guide-recommended.[41] However, pre-specified pooled analysis of combined data from PARADIGM-HF (LVEF $\leq$40%) and PARAGON-HF (LVEF $\geq$45%) showed that sacubitril/valsartan markedly reduced the risk of poor kidney outcomes and slowed declining eGFR, compared with valsartan or enalapril alone, independent of baseline eGFR in patients with HF and reduced ejection fraction and HF and preserved ejection fraction.[42] Yet, the Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trial showed that baseline UACR or eGFR did not modify the benefit of the SGLT2 inhibitor dapagliflozin on eGFR slope in patients with HF and mildly reduced ejection fraction and those with HF and preserved ejection fraction.[13] In this trial, dapagliflozin was not able to significantly reduce the frequency of the composite kidney outcome, although overall number of CV deaths or worsening HF was low. In line with this, empagliflozin in the EMPEROR-Preserved trial did not reduce kidney outcome in patients with HF with or without CKD.[43] Finally, UACR seems to be a valid indicator of structural damage of the glomerular filtration barrier, but it does not represent a powerful predictive indicator for kidney outcomes among patients with HF treated with guideline-recommended therapy. Thus, there is a need for new promising biomarkers than can predict SGLT2 inhibitor-related benefit among patients with HF.

The results of the present narrative review showed that a large number of circulating biomarkers may be promising predictors of renoprotective effects of SGLT2 inhibition (Figure 2). The highlighted molecules have all been implicated in different pathological mechanisms of worsening kidney function and structure, such as glomerular damage (urinary immunoglobulin [Ig]G and IgG4) and tubular damage (urinary kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, liver-type fatty acid-binding protein, carbonic anhydrase 2), inflammation (monocyte chemoattractant protein-1, urinary and serum interleukin [IL]-6, IL-2-beta, matrix metalloproteinase-7, tumor necrosis factor [TNF]-alpha and its receptor, C-reactive protein [CRP]), immune response (insulin-like growth factor-binding protein-1), alteration of hematopoiesis (hemoglobin, erythropoietin, transferrin receptor protein 1), mitochondrial dysfunction, ketogenesis and oxidative stress (protein-glutamine gamma-glutamyl transferase 2, thymosin beta-10, U-type mitochondrial creatine kinase), altered glucose metabolism (insulin-like growth factor-binding protein 4, HbA1c) and adipocyte/skeletal muscle cell dysfunction (adropin, irisin, apelin, adipocyte fatty acid-binding protein 4). Indeed, SGLT2 inhibitors demonstrated their ability to reduce the levels of hepcidin, inflammatory cytokines, such as IL-6, TNF-alpha, CRP and markers of kidney injury, as well as increase the levels of hemoglobin, erythropoietin, serum uric acid, adropin, irisin, and apelin.[19,22,28,34,44–48] The majority of these studies did not report any correlations between changes in the biomarkers of glomerular/tubular injury, altered glucose and lipid metabolism, adipocyte/skeletal muscle cell dysfunction and changes in UACR, whereas benefits in their changes were closely associated with slower decline in eGFR, for instance in the CREDENCE and DAPA-CKD trials.[19,28] Moreover, SGLT2 inhibitors seem to show improving kidney function independently of their glycemic effects,[49] while they are able to reduce tubular cell glucotoxicity via inhibition of sodium transporters, modulating

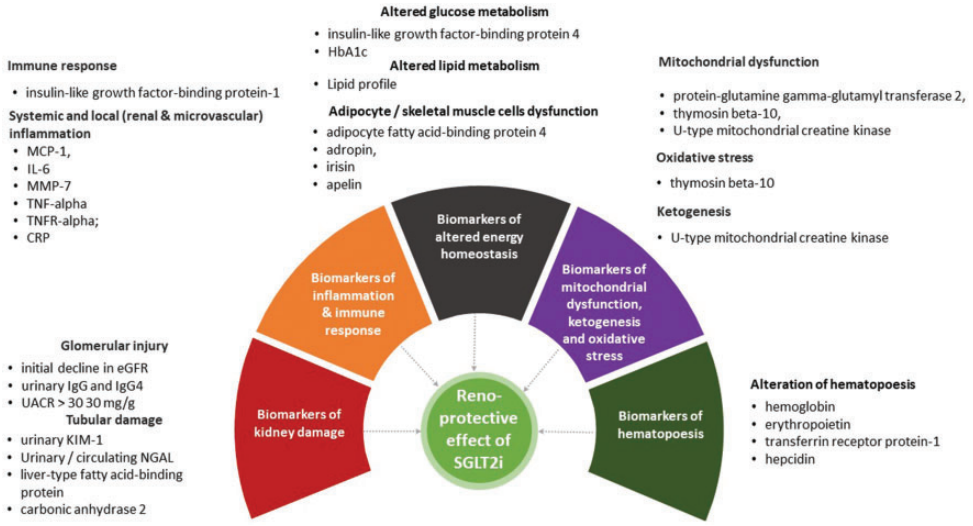

Figure 2. Plausible predictive biomarkers for renoprotective effects of sodium-glucose cotransporter-2 inhibitors. CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1C, glycosylated hemoglobin; IgG, immunoglobulin G; IL, interleukin; KIM-1, kidney injury molecule-1; MCP-1, monocyte chemoattractant protein-1; MMP, matrix metalloproteinase; NGAL, neutrophil gelatinase-associated lipocalin; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TNF-alpha, tumor necrosis factor-alpha; TNFR-alpha-1, tumor necrosis factor receptor-1; UACR, urine albumin-to-creatinine ratio.

mitochondrial dysfunction and suppressing local and systemic inflammatory reactions.[50] Thus, in turn, the molecular mechanisms, which are likely modulated by SGLT2 inhibitors, might not be totally associated with their influence on hypoxia-induced glomerular/tubular dysfunction, microvascular intrarenal inflammation and lowering the intraglomerular hypertension due to regulation of glomerular vascular tone, enhancement of vascular integrity, kidney parenchyma perfusion, and endothelium function. SGLT2 inhibitors have been suggested to prevent kidney fibrosis, podocyte injury and apoptosis of glomerular cells by increasing protective adipokine expression, such as adropin, irisin and apelin, which act directly through the activation of Akt/STAT3 and tyrosine protein kinase JAK2 (JAK2)/signal transducer pathways.[34,45,48,51,52] Finally, SGLT2 inhibitors adapt metabolic homeostasis by mediating the activity of NADPH oxidase and transcription factors (nuclear factor-κB and nuclear factor erythroid 2-related factor 2) preventing advanced glycation and autophagy.[51,52] These effects are considered to be crucial in the treatment of patients with either T2DM- or non-T2DM-related CKD who have HF.[53,54] Yet, SGLT2 inhibitors have been postulated, through their capability to change ketogenetic energy, to suppress inflammation and oxidative stress, enabling the mediation of several modalities of endogenous tissue protection, which include the enhancement of mitochondrial function and reduction of reactive oxygen species production. All of the abovementioned factors lead to reduced apoptosis-signaling kinase 1 activity and consequently attenuation of kidney fibrosis.[54]

Overall, the effect of SGLT2 inhibitors on kidney function and structure appears to be complex and, in turn, demonstrates serious overlap between pro-inflammatory response, oxidative stress, mitochondrial

dysfunction, ketogenesis and the signature of comorbidities among individuals with diabetes-induced and non-T2DM-induced CKD.[53,54] In this context, biomarkers of adipose tissue dysfunction and energy metabolism seem to be promising compared with other markers, due to their independent predictive potency of circulating cardiac biomarkers, such as NT-proBNP and glucose metabolism indicators.[54] However, there is still not enough rigorous scientific evidence to develop well-structured scientific hypotheses. More investigations are required with the aim of clearly elucidating a plausible optimal modality of the biomarkers to predict the benefits of SGLT2 inhibitors at early administration.

Conclusion

Treatment with SGLT2 inhibitors improves renal and cardiovascular clinical outcomes in patients with CKD with T2DM and HF. However, SGLT2 inhibitors exert an initial decrease in eGFR after initiation, which requires thorough monitoring. There is additional supportive evidence that the renoprotective effect of SGLT2 inhibitors may not be closely associated with improving hyperglycemia, delaying eGFR trajectory, or changes in conventional biomarker levels, such as hemoglobin, erythrocyte count, natriuretic peptides, and lipid profile. Previous large clinical trials of SGLT2 inhibitors showed a potential value of numerous biomarkers affecting inflammation, kidney injury, oxidative stress, mitochondrial dysfunction, ketogenesis and energy metabolism, as well as adipose tissue dysfunction, as predictors of renoprotection in patients with CKD, regardless of the presence of T2DM and HF. This tentative result requires further investigation to explain the discriminative significance of these findings.

Author contributions

Conceptualization, TAB and AEB; methodology, AEB; software, TAB; validation, AEB; formal analysis, TAB and AEB; investigation, TAB and AEB; resources, AEB and TAB; data curation, AEB; writing - original draft preparation, AEB and TAB; writing - review and editing, TAB and AEB; supervision, AEB; project administration, AEB. All authors have read and agreed to the published version of the manuscript.

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