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Challenges and opportunities in real-world evidence on the renal effects of sodium-glucose cotransporter-2 inhibitors

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Abstract

With increasing population aging and prevalence of type 2 diabetes (T2D) worldwide, prevention of diabetic complications remains a major unmet need. While cardiovascular outcomes of diabetes are improving over time, diabetic kidney disease (DKD) still leads to an exceedingly high rate of end-stage kidney disease (ESKD). A game-changing opportunity is offered by treatment with sodium-glucose cotransporter-2 (SGLT2) inhibitors. Randomized controlled trials (RCTs) have indisputably shown that SGLT2 inhibitors reduce the rate of DKD progression, the decline in estimated glomerular filtration rate (eGFR), and the development of ESKD. In parallel, SGLT2 inhibitors improve cardiovascular outcomes, especially the risk of hospitalization for heart failure. Real-world studies (RWSs) have largely confirmed the findings of RCTs in broader populations of subjects with T2D followed under routine care. In the present paper, we review RWSs exploring the renal effects of SGLT2 inhibitors and highlight the most critical challenges that can be encountered in designing and conducting such studies. Channelling bias (confounding by indication), time-lag bias, conditioning on the future, database heterogeneity, linearity of eGFR change over time, and duration of observation are critical issues that may undermine the robustness of RWS findings. We then elaborate on the new opportunities to overcome such limitations by describing the design and objectives of the DARWIN (DApagliflozin Real-World evIdeNce)-Renal study, a new RWS promoted by the Italian Diabetes Society. Fine-tuning of methods for comparative observational research will improve evidence derived from RWSs on the renal effects of SGLT2 inhibitors, aiding the evolving discussion regarding the place of SGLT2 inhibitors in T2D treatment algorithms in different stages of DKD.

KEYWORDS
effectiveness, kidney disease, observational, pharmacoepidemiology, slope

1 | FOCUS ON DIABETIC KIDNEY DISEASE

Landmark studies have illustrated the importance of glucose-lowering therapy, statin use, blood pressure control, and multifactorial intervention in reducing the risk of cardiovascular outcomes among people with type 2 diabetes (T2D).[1,2] The clinical implementation of these findings along with lifestyle interventions are probably responsible for the reductions in cardiovascular events and mortality in T2D

subjects over the past two decades. However, recent data from the Swedish nationwide registry from 1998 to 2014, although showing marked reductions in mortality and in the incidence of cardiovascular complications among adults with T2D, clearly demonstrated that individuals with T2D continue exhibiting a higher rate of fatal outcomes than nondiabetic controls.[3] There remains a substantial excess overall rate of all adverse outcomes analysed among people with T2D as compared with the general population. Worryingly, in face of improved cardiovascular prognosis in people with T2D, the number of people developing end-stage kidney disease (ESKD) and entering dialysis is not reducing.[4-6] Mortality and morbidity rates due to chronic kidney disease (CKD) remain high, the quality of life of CKD patients is poor, and the clinical limitations associated with dialysis have not changed in decades. The progressively growing incidence of ESKD is paralleled by a steady increase in renal replacement therapy (RRT) worldwide, and a doubling of cases is expected by 2030. Diabetes is the leading cause of ESKD, and the need for RRT and the onset of diabetic kidney disease (DKD) shortens lifespan by approximately 16 years.[7]

2 | THERAPEUTIC OPPORTUNITIES WITH SGLT2 INHIBITORS

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are widely used for the treatment of T2D.[8] They lower glycaemia by increasing urinary glucose excretion. In turn, glycosuria results in a significant reduction in body weight, osmotic diuresis, and reduction in blood pressure.[9] In Italy, first-in-class dapagliflozin received reimbursement approval in March 2015. Since then, large cardiovascular outcome trials (CVOTs) have been performed to test the noninferiority of SGLT2 inhibitors versus placebo (eg, standard care with alternative glucose-lowering medications [GLMs]) in terms of cardiovascular safety. In the EMPA-REG Outcome trial,[10] the CANVAS trial programme,[11] and the DECLARE-TIMI 58 trial,[12] however, a significant reduction in the risk of major adverse cardiovascular events (MACE) and/or hospitalization for heart failure (hHF) was reported among patients randomized to empagliflozin, canagliflozin or dapagliflozin, respectively. Empagliflozin also reduced all-cause and cardiovascular mortality. In addition, by exploring secondary renal outcomes (either prespecified or not), these three CVOTs showed significant renal protective effects, both in terms of reducing albuminuria progression and slowing the decline of estimated glomerular filtration rate (eGFR) over time.[11,13-15] Similar results have been obtained in the VERTIS-CV trial where, despite not meeting superiority versus placebo for the primary cardiovascular endpoint, ertugliflozin reduced the risk of hHF and the rate of a prespecified exploratory composite renal endpoint.[16] However, most of these trials were not specifically designed to address renal outcomes and, most importantly, the percentage of patients with CKD was low, ranging from 27% in EMPA-REG and 20% in CANVAS to only 7% in DECLARE-TIMI 58.[17] This was to preserve the glycaemic efficacy of SGLT2 inhibitors, whose glucose-lowering effect is reduced at lower eGFR values because of less glucose being filtered.[18] As indication for the use of SGLT2 inhibitors for prevention and delaying of the progression of DKD should not be drawn from secondary analyses, an advancement was achieved thanks to the CREDENCE trial.[19] CREDENCE enrolled 4401 patients with T2D, stage II to III CKD, and macroalbuminuria, who were receiving standard of care including a maximum tolerated daily dose of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and were randomized to receive canagliflozin 100 mg or placebo. The study demonstrated a 30% reduction in the risk of the primary composite endpoint (progression to ESKD, doubling of serum creatinine or renal/cardiovascular death) in the canagliflozin group. The study also showed a reduced risk of secondary cardiovascular endpoints, including the risk of cardiovascular death and hHF by 31%, MACE (composite of nonfatal myocardial infarction, nonfatal stroke and cardiovascular death) by 20%, and the risk of hHF alone by 39% in the canagliflozin arm. CREDENCE provides solid evidence in favour of nephroprotection exerted by SGLT2 inhibitors in T2D and is changing the treatment paradigm of T2D patients with DKD. However, the study population in which such striking results have been obtained is representative of a minority of the whole population of T2D with impaired renal function. Data from the RIACE study,[20] a prospective ongoing study under the auspices of the Italian Diabetes Society, showed that approximately 37.5% of T2D patients have a certain degree of impaired renal function, but only 4% combine macroalbuminuria with an eGFR of less than 60 mL/min/1.73 m^2 (ie, the CREDENCE-like population). Furthermore, the prevailing phenotype of renal impairment in T2D seems to be the normoalbuminuric one, that is, patients who progressively lose eGFR but remain normoalbuminuric over time. This normoalbuminuric DKD phenotype, whose prevalence ranges from 35% to over 65% in different studies, has been confirmed in clinical trials and real-world cohorts.[21-23] These patients rapidly progress toward ESKD and are characterized by a high prevalence of cardiovascular disease and elevated risk of all-cause mortality,[24,25] thereby representing a wide high-risk subset of individuals with T2D for whom most effort should be exerted to improve renal and cardiovascular outcomes. For these reasons, the major limitation of the CREDENCE trial lies in the marginal proportion of patients who satisfy its enrolment criteria, making it hard to extrapolate trial results to other, more common, clinical phenotypes of DKD. This gap is being partially filled by the ongoing EMPA-KIDNEY trial, which will include patients with an eGFR of 20 to 45 mL/min/1.73 m^2 or an eGFR of 45 to 90 mL/min/1.73 m^2 with albuminuria greater than or equal to 200 mg/g.[26,27] On the other hand, the dual SGLT1/2 inhibitor sotagliflozin improved cardiovascular outcomes but not the composite renal outcome in patients with T2D and CKD (eGFR 25-60 mL/min/1.73 m^2 with or without micro-/macroalbuminuria),[28] possibly because of short duration (14.2 months) or due to molecular specificity.

A substantial advancement in the field has been achieved by the DAPA-CKD study. The trial enrolled 4304 patients with (67.6%) or without diabetes, with an eGFR between 25 and 75 mL/min/1.73 m^2 and a urinary albumin/creatinine ratio between 200 and 5000 mg/g, who were randomized to receive dapagliflozin 10 mg or placebo. As occurred in CREDENCE, the trial was terminated earlier because of

manifest efficacy after a median follow-up of 2.4 years. The primary composite endpoint of sustained decline in eGFR, ESKD or death from renal or cardiovascular causes occurred in 9.4% of patients in the dapagliflozin group versus 14.5% in the placebo group, yielding a hazard ratio (HR) of 0.61 (95% confidence interval [CI] 0.51-0.72). The effects of dapagliflozin were similar in patients with or without T2D, showing nominal superiority over placebo in both groups.[29] The DAPA-CKD trial provides compelling evidence for the efficacy of the SGLT2 inhibitors dapagliflozin against the progression of albuminuric CKD. Despite extending the renal benefits of SGLT2 inhibitors to the nondiabetic population, DAPA-CKD still has limited generalizability to patients at lower renal risk. Indeed, an outstanding question remains as to whether SGLT2 inhibitors also protect from DKD in patients with T2D and normal albuminuria and/or normal baseline kidney function. Although such primary prevention of DKD is unlikely to be tested in dedicated trials, new results from DECLARE-TIMI 58 show that the renal-specific endpoint (a composite ≥40% decline in eGFR to <60 mL/min/1.73 m^2, ESKD, or death from renal causes) was improved even in patients with an albumin excretion rate of less than 15 mg/g or between 15 and < 30 mg/g.[15] Moreover, meta-analyses suggest that SGLT2 inhibitors have the potential to reduce the rates of adverse renal outcomes even in patients with eGFR greater than 90 mL/min/1.73 m^2, thus supporting a beneficial role for these drugs across the entire continuum of DKD.[30] In the absence of further evidence from clinical trials and objective limitations in designing trials dealing with all the different CKD/DKD phenotypes, well-designed observational real-world studies (RWSs) have the potential to confirm trial findings and extend their results to different populations of patients, including those in primary renal prevention.

3 | REAL-WORLD STUDIES ON THE RENAL EFFECTS OF SGLT2 INHIBITORS

In the diabetes field, RCTs have limitations inherent to the fact that design, setting and patient characteristics are often far different from those of routine clinical practice.[31] Although RWSs cannot substitute for RCTs in establishing efficacy,[32] evidence from studies using real-world data is increasingly valued. RCTs enroll limited numbers of highly selected, relatively young participants, who are highly motivated and compliant, educated on disease management and instructed in drug use, mostly free from comorbid conditions, and regularly followed up. By contrast, real-world clinical practice addresses all patients who may receive a given drug, irrespective of age, education, compliance, concomitant medications and comorbidities, and who are followed according to local care, often with resource limitations. Furthermore, RCTs have compared SGLT2 inhibitors with placebo, while RWSs use active comparator(s) and allow testing of massive population sizes.

Several early RWSs on dapagliflozin and other SGLT2 inhibitors have been performed in many countries.[33-37] They have widely confirmed the glycaemic and extra-glycaemic effects observed in RCTs and have provided evidence in support of protection against cardiovascular disease and mortality. RWSs on the renal effects of SGLT2 inhibitors have been published more recently and are still limited. The DARWIN-T2D trial was a nationwide multicentre retrospective RWS, designed to examine the effectiveness of dapagliflozin in patients with T2D followed under routine care at Italian specialist outpatient clinics in 2015 to 2016.[38] The study produced a large body of evidence on the effectiveness of dapagliflozin in the real world. A subanalysis of the DARWIN-T2D trial, conducted in a limited number of patients during a follow-up of approximately 6 months, provided interesting data on the renal safety of dapagliflozin. This was the first RWS to confirm the antiproteinuric effect of dapagliflozin over a short-term observation.[39]

Subsequent RWSs have confirmed the beneficial effects of SGLT2 inhibitors against adverse kidney outcomes.

A large Scandinavian cohort study has compared the occurrence of serious renal events (RRT, death from renal causes, and hospital admission for renal events) between approximately 30 000 new users of SGLT2 inhibitors and an equal number of matched new users of dipeptidyl peptidase-4 (DPP-4) inhibitors.[40] The rate of such serious events was significantly lower in the SGLT2 inhibitor group by more than 50% (HR 0.42). Another large study, performed in the United Kingdom in approximately 24 000 patients in each matched group of SGLT2 inhibitor and DPP-4 inhibitor initiators, reported lower rates of hospitalization for CKD among SGLT2 inhibitor users (HR 0.49, 95% CI 0.43-0.54).[41] Similar results have been obtained in a smaller study conducted in 9219 new users of SGLT2 inhibitors and 9219 matched new users of other GLMs referred to the Maccabi Healthcare Systems in Israel. A minority of patients (8.5%) had a baseline eGFR of less than 60 mL/min/1.73 m^2, and only one-third had micro-/macroalbuminuria. Renal endpoints, defined by a reduction in eGFR by several different thresholds, or development of ESKD, occurred at a 30% to 50% lower rate among SGLT2 inhibitor initiators.[42]

While regulatory agencies accept a 30% or 40% reduction in eGFR as a surrogate endpoint in trials exploring therapies for ESKD,[43] these endpoints may not be practical for patients in the early stages of CKD,[44] such as most of those prescribed with SGLT2 inhibitors in the clinical setting. In 2018, a workshop of the National Kidney Foundation, developed in collaboration with regulatory agencies, issued recommendations on the use of change in albuminuria and eGFR slope as alternative surrogate endpoints.[44] The analysis of trials and observational studies showed that a difference of 0.75 mL/min/1.73 m^2/year in the eGFR slope (soft outcome) is predictive of a 27% higher relative hazard of ESKD at 5 years (hard outcome), equal to an absolute reduction of 1.6%.[44] Using the eGFR slope as a surrogate endpoint in place of the threshold eGFR reduction increases statistical power, allows shorter observation periods, and is more appropriate for patients with relatively preserved baseline eGFR.[44] Similarly to what is done in trials, some RWSs on SGLT2 inhibitors were conducted with the estimation of eGFR trajectories over time.

In a Japanese cohort of 1433 new users of SGLT2 inhibitors and 2739 matched new users of other GLMs, the annualized eGFR decline was significantly slower for SGLT2 inhibitors than for controls (−0.86 vs. −2.06 mL/min/1.73 m^2). In addition, the relative hazard of a

composite of renal adverse events was 30% lower with SGLT2 inhibitors, despite better glycaemic levels in the control group.[45] In a large study conducted within the Veterans Affairs (VA) Health Care System between 2015 and 2019, new users of the SGLT2 inhibitors empagliflozin compared to new users of any other GLM (including insulin) were included if they had a baseline eGFR greater than 30 mL/min/1.73 m^2. Comparability between the two groups was achieved using inverse probability of treatment weighting, which yields a pseudo-cohort of control patients with estimated characteristics similar to those in the SGLT2 inhibitor group.[46] The primary outcome was defined as an eGFR decline of greater than 50% or development of ESKD or death. Patients in the empagliflozin group had a 32% lower hazard of the primary endpoint. After an initial eGFR drop of 2 mL/min/1.73 m^2 by day 90, new users of empagliflozin had a slower decline in eGFR than patients in the control group (−5.3 vs. −8.3 mL/min/1.73 m^2 at 3 years). Results were consistent across several subgroups and on sensitivity analyses. In parallel, the authors reported that initiation of an SGLT2 inhibitor or a glucagon-like peptide-1 receptor agonist (GLP-1RA) compared with a DPP-4 or a sulphonylurea was associated with a lower risk of the composite kidney outcome, but eGFR slopes were not reported.[47] A subsequent retrospective analysis of the same database explored the possible implications of the eGFR dip that occurs early after SGLT2 inhibitor initiation. In the first 6 months of therapy, a decline in eGFR (generally 20% and 30% of the baseline value) was more common in the SGLT2 inhibitor group compared to the control group. Such an eGFR dip had no negative impact on cardiovascular outcomes, with a superimposable HR for cardiovascular or renal endpoints in the SGLT2 inhibitor versus comparator group in those with and those without the eGFR dip as it was irrespective of the degree of the initial eGFR reduction.[48]

These studies clearly show the feasibility of analysing eGFR slopes to explore the effect of SGLT2 inhibitors versus other drugs on progression of renal function in the real-world setting. The study that more carefully described such eGFR trajectories in the real world was the third edition of CVD-Real.[49]

4 | DESIGN AND RESULTS OF CVD-REAL 3

CVD-Real 3 was dedicated to renal outcomes defined by eGFR values.[49] Out of 281 034 patients initiating SGLT2 inhibitors or other GLMs (including insulin), 35 561 patients were matched in each group by propensity scores. Patients could initiate both treatments during observation, such that initiation episodes were considered instead of individual patients and the analysis took into account interdependency of observations. Patients were matched for the eGFR value and slope during the year before initiating SGLT2 inhibitors or comparators as well as for many other clinical characteristics. The primary endpoint was the change in eGFR in the two groups, defined as the linear slope of the eGFR change over time. Patients had an average baseline eGFR of 90 mL/min/1.73 m^2. Comparator GLMs were DPP-4 inhibitors (23.1%), insulin (18.4%), GLP-1RAs (16.8%), sulphonylureas (16.6%), pioglitazone (8.3%), metformin (8.1%), glinides (6.8%) or acarbose (2.0%). Initiation of treatment with SGLT2 inhibitors, as compared to other GLMs, was associated with an acute drop in eGFR of approximately 3 mL/min/1.73 m^2 at 30 days, followed by an increase and a subsequent stabilization of eGFR. In the control group, eGFR continued to decline and, at the end of observation, up to 24 months later, mean eGFR was lower than in the SGLT2 inhibitor group. The difference in slope for SGLT2 inhibitors versus control drugs was 1.53 mL/min/1.73 m^2 per year.

5 | CRITICAL INTERPRETATION OF REAL-WORLD EVIDENCE ON RENAL EFFECTS OF SGLT2 INHIBITORS

Qualitatively, the findings of CVD-Real 3 and other RWSs are in line with those reported by CVOTs, both in terms of eGFR trends over time and reduced risk of composite kidney outcome.[39,40,45,46,49] CVD-Real 3 was conducted with "gold standard" methods for retrospective data analysis and has remarkable strengths. The sample size is large enough and the matching procedure was successful, meaning that all considered variables had similar values and distributions in the two groups at baseline. Matching eGFR values and slope in the year preceding initiation of SGLT2 inhibitors or comparators ensured that patients in the two groups were at a similar stage of renal disease.

Nevertheless, some issues in the real-world evidence analysis of renal effects of SGLT2 inhibitors make data interpretation less straightforward. First, the mean follow-up was approximately 15 months, which is not a long period in which to model eGFR changes over time. Indeed, difference in eGFR slope between treatment groups has been shown to have a much stronger correlation with a clinical endpoint when the slope is calculated over 3 years than when calculated over 1 year.[44] Second, calculating the eGFR slope using a linear mixed model for repeated measures assumes linearity of the trend over time unless one or more spline(s) are included at a specific time point(s). Linearity of the eGFR decline is generally a greater concern in people with T2D than in people without diabetes.[50] Moreover, linearity can be assumed more with control drugs than with SGLT2 inhibitors since the acute and transient drop in eGFR after SGLT2 inhibitor initiation causes deviation from linearity. As a result, modelling eGFR from baseline to end-of-observation can generate, in the SGLT2 inhibitor-treated group, a positive value of the slope even if the final mean eGFR could be significantly lower than baseline values. It can then be expected that models fit the data to a better extent in the control than in the SGLT2 inhibitor group, making a comparison between slopes problematic. Typically, the presence of a substantial acute effect of treatment(s) on eGFR attenuates the statistical power advantages of using the total eGFR slope compared to the clinical endpoint, especially over the short term.[44] The chronic eGFR slope should therefore be calculated in place of the total eGFR slope by discarding the period encompassing the acute effect. In CVD-Real 3 this would have further reduced mean observation time to less than 12 months. The CVD-Real 3 study protocol required that patients included in the analysis of eGFR slope had at least two eGFR measures before the index date (at least one <180 days before the index date) and two eGFR measures after the index date (the first of which

<120 days from baseline and the last >180 days from baseline). Therefore, the inclusion of patients in the eGFR slope analysis was conditioned on the future, that is, was based on unpredictable events occurring after the index date, with projections extending to longer than 180 days. This requirement applied to both groups of patients, thereby not formally affecting the comparison, but probably affecting the population under investigation. The compelling need to include only patients who had eGFR measures within 120 days after initiation of a new drug forced into the analysis situations that might not be representative of all patients seen in routine clinical practice. Standards of care do not recommend testing eGFR at close intervals unless there are specific reasons to do so. This issue is present also in the VA database study[46] and is well illustrated by looking at country-specific data in CVD-Real 3. In Israel, during a mean follow-up of 18.6 months, there was a median of 3 eGFR values per patient after baseline. In Italy, during a mean follow-up of 6.5 months, there still was a median of 3 eGFR values per patient after baseline. In Taiwan, during a follow-up was 9.4 months, patients had a median of 4 eGFR values. Matching was stratified by country and country-stratified analyses were performed for a composite kidney outcome, but data from all countries were pooled for the primary analysis of eGFR slope. However, slopes for Italian patients, unlike those for other countries, most likely encompassed only the phase of eGFR dip-and-recovery, thereby being poorly indicative of the long-term effect of treatments. Also, the Italian sample was composed of a particular subset of patients, because eGFR is not normally measured three times in 6 months in routine clinical practice. A prior study, performed with data from the same source, showed that, after initiation of SGLT2 inhibitors, patients had on average less than one eGFR assessment in the subsequent 3 to 12 months.[39] It can therefore be speculated that patients had several eGFR measures because they were perceived to be at risk of acute kidney injury, or adverse events upon initiation of therapy (such as dehydration), had comorbidities or concomitant conditions, or were hospitalized. SGLT2 inhibitors were probably discontinued, at least transiently, if any of those situations occurred, accounting for the rapid recovery of eGFR in the SGLT2 inhibitor group. The concern is supported by the fact that eGFR curves in the two groups crossed at approximately 6 months in both CVD-Real 3 and the VA database study,[46] which is considerably earlier than in CVOTs. In the CREDENCE study, with the lowest baseline eGFR (56 mL/min/1.73 m^2) and most rapid eGFR decline (–4 mL/min/1.73 m^2/year), eGFR curves of the canagliflozin group crossed the eGFR curve of the placebo group at 1 year.[19] In VERTIS-CV, with an intermediate average baseline eGFR (76 mL/min/1.73 m^2), eGFR curves in the ertugliflozin and placebo groups crossed at approximately 1.5 years.[51] In the DECLARE-TIMI 58 trial, with the highest baseline eGFR (85 mL/min/1.73 m^2) and the slowest eGFR slope (–2 mL/min/1.73 m^2/year), the dapagliflozin and placebo curves crossed at 2 years.[12] Therefore, in the CVD-Real 3 study, with a baseline eGFR of 90 mL/min/1.73 m^2 and an average decline of eGFR of less than 2 mL/min/1.73 m^2/year in the control group, the two curves were not expected to cross at 6 months but, if at all, much later. Estimating the timing of the acute effect is important for setting the time-specific splines of the linear model for estimating total eGFR slopes or for estimating the chronic eGFR slope, which would require at least 2 years of observation after the acute phase.

6 | FURTHER OPPORTUNITIES

The RWSs so far available on the effects of SGLT2 inhibitors on renal outcomes have shown results consistent with those of RCTs. However, they have some limitations inherent to their data source and methodological approach and were generally too short. Therefore, there is room for improving the design of RWSs on this topic and

TABLE 1 Challenges and possible solutions in real-world evidence studies on renal endpoints

Challenge	Explanation	Possible solution(s)
Channelling bias (confounding by indication)	Patients assigned to different treatments under routine care have different characteristics	Use PSM to obtain similar cohorts at baseline Apply adjustment and weighting methods in sensitivity analyses
Time lag bias	Patients assigned to different treatments under routine care locate at different disease stages even if they look similar	Match for eGFR slope in the pre-index date year(s)
Conditioning on the future	eGFR slope analysis require post-index date data available	Do impose strict schedules of eGFR availability, leaving it free as in routine practice
Heterogeneity of the database	Pooling crude data from multiple databases from multiple countries or healthcare setting generates heterogeneity that can affect the pooled results	Limit to databases from the same or highly similar healthcare setting (eg, specialist care).
Nonlinearity of eGFR change	The change in eGFR may not be linear over time or during limited periods, such that slope modelling is biased	Use nonlinear models to analyse eGFR changes. Compute the chronic (not total) total eGFR slope
Short observation	eGFR slope better predicts ESKD when calculated over 3 years	Prolong duration of observation to ≥3 years (or ≥ 2 years after the acute effect)

Abbreviations: eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; PSM, propensity score matching.

TABLE 2 The DARWIN-Renal protocol synopsis

Study title	Comparative effectiveness of dapagliflozin vs non-insulin, non-SGLT2i glucose-lowering medications on renal-wide endpoints in type 2 diabetes. A real-world Italian multicenter study. DApagliflozin Real-World evIdeNce (DARWIN) - Renal
Sponsor	Italian Diabetes Society
Study rationale	See text
Study objectives	**Primary** To compare kidney function over time in patients who initiated dapagliflozin as compared to patients who initiated other non-insulin GLMs (all except SGLT2 inhibitors) in the same period. For the primary endpoint, kidney function will be evaluated as eGFR, calculated by creatinine equation developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). eGFR slope will be calculated **Secondary** To compare variations in the overall renal burden during therapy with dapagliflozin vs. other GLMs, defined as follows: • Change over time in systolic and diastolic blood pressure; • Change over time in HbA1c (for mediation analysis, see below); • Change over time in body weight (for mediation analysis, see below); • Change in the type and dosage of concomitant diuretics and blood pressure-lowering medications (prespecified categories are: calcium channel blockers, beta-blockers, drugs acting on the renin-angiotensin system, alpha-blockers); • New-onset CKD, defined as two consecutive eGFR values <60 mL/min/1.73 m^2 > 90 days apart, during the entire observation; • Deterioration of CKD stage (from categories: ≥90, 60-90, 45-60 or 30-45 ml/min/1.73 m^2) at the last observation; • ≥30% or ≥ 40% reduction in eGFR at the last observation[61]; • Doubling of serum creatinine (ie, reduction of >57% in eGFR) at any time point during observation; • ESKD (defined as confirmed eGFR <15 mL/min/1.73 m^2) or need for RRT at any time point during observation; • Change in albumin excretion rate over time; • Moving category of AER. The following categories will be considered (in mg/g creatinine): normoalbuminuric [0-10 mg/g] ←→ high-normal albuminuric [11–29 mg/g] ←→ microalbuminuric [30-299 mg/g] ←→macroalbuminuric [300+ mg/g]. We will look at any progression and any regression at the end of observation compared to baseline. We will also investigate progression from normo- to micro-/macroalbuminuria and from normo-/micro- to macroalbuminuria. • Change in uric acid concentrations.
Study design	Retrospective, observational, multicentre
Setting	Diabetes specialist outpatients clinics in Italy
Population	People with type 2 diabetes
Enrolment criteria	**Inclusion criteria** i) Age 18-80 years; ii) Diagnosis of T2D; iii) Disease duration 1 year or more, as established since the date of T2D diagnosis in the chart; iv) Initiation of dapagliflozin or comparators; between 2015 and 2020 v) Availability of pre- and post-index date information on renal outcomes (see below for the minimum set of endpoint data). **Exclusion criteria** i) Other forms of diabetes (eg, type 1 diabetes or gestational diabetes); ii) age < 18 or > 80 years; iii) previous therapy with another SGLT2 inhibitors in the 12 months before the index date; iv) CKD stage V (eGFR <15 mL/min/1.73 m^2) or ongoing dialysis at baseline
Number of patients	1130 / group post-matching (based on a eGFR slope difference > 0.8 mL/min/1.73 m^2/year)
Number of centres	50
Study duration	Enrolment between 2015 and 2020. Follow-up until last observation. Expected mean observation 2.5-3.0 years.
Expected timeline	EC approval (actual): Oct 2020 Centre enrolment (ongoing): Nov 2020 to Nov 2021 Database lock (estimated): Dec 2021 Primary completion (estimated): Jun 2022
Statistical analysis plan	• Descriptive statistics will be used to report baseline clinical characteristics • Matching will be performed by PSM with 1:1 or 1:2 or 1:3 ratio according to the final numbers of unmatched patients in the two groups. Good balance between groups will be defined when absolute standardized mean difference are <10%. Matching variables will include the pre-index date eGFR slope. • The primary outcome will be analysed using the mixed model for repeated measures. eGFR slope will be calculated with or without the acute phase. • For categorical endpoints, the proportion of patients in the two groups will be compared by chi-squared test or logistic regression models. • Missing data will be handled by multiple imputation. • Subgroup analyses will be performed by age, sex, diabetes duration, HbA1c, baseline eGFR category and KDIGO categories of CKD,[62] history of other microangiopathies (including albuminuria categories), cardiovascular disease, concomitant therapies.

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GLM, glucose-lowering medication; HbA1c, glycated haemoglobin.

providing additional clinically relevant information from data collected during routine practice. Table 1 shows some key challenges and possible solutions to overcome, at least in part, such limitations.

7 | DESIGN AND OBJECTIVES OF THE DARWIN-RENAL STUDY

To address some of the shortcomings of prior RWSs on the renal effectiveness of SGLT2 inhibitors, the Italian Diabetes Society has designed the DApagliflozin Real-World EvIdeNce (DARWIN)-Renal study. DARWIN-Renal will retrospectively collect data on patients newly prescribed with dapagliflozin from 2015 to 2020 to expand our knowledge on the implications of the use of SGLT2 inhibitors in clinical practice, with special regard to the long-term effects on renal function in a wide cohort of individuals with T2D. DARWIN-Renal will specifically address response to therapy according to patient phenotype, with appropriate calculation of updated eGFR slopes and an expected longer follow-up (~2.5-3.0 years).

In Italy, the widespread use of SGLT2 inhibitors as second-line agents is still contended by other oral GLMs that are perceived to be safe, namely, DPP-4 inhibitors.[52] DPP-4 inhibitors as a class lower glycated haemoglobin by 0.5% to 0.7% and exert minor or no effects on body weight, blood pressure, and lipid profile.[53] In addition, CVOTs showed no benefit of sitagliptin, saxagliptin, linagliptin or alogliptin on cardiovascular outcomes,[54] with a signal that saxagliptin may increase the risk of hHF.[54] DPP-4 inhibitors can be safely used in CKD patients, with or without dose adjustment, but they did not exert major nephroprotective effects. Repaglinide is another drug still used in patients with T2D and CKD because it does not require dose adjustment. However, there are concerns that repaglinide may worsen cardiac ischaemia, as reported in the drug's label. GLP-1RAs can be used in patients with CKD stage III to IV, and they have been shown to reduce the rate of new-onset macroalbuminuria but, according to CVOTs, they exert no consistent effects on the progressive decline of eGFR in T2D, with the possible exception of dulaglutide.[55] The ongoing FLOW trial on the renal effects of semaglutide in patients with DKD will clarify whether GLP-1RAs may slow DKD progression, thereby complementing the beneficial metabolic and cardiovascular effects.[56] Finally, in Italy, a relatively high proportion of patients with stage III CKD are still treated with sulphonylureas, with no expected cardio-renal protection and high risk of hypoglycaemia.[57] DARWIN-Renal (Table 2) aims to provide data on the comparative effectiveness of dapagliflozin versus non-SGLT2 inhibitor GLMs (with the exclusion of insulin) on multiple renal-related endpoints, including change in eGFR, albuminuria, and blood pressure. DARWIN-Renal has the potential to overcome some of the limitations observed in prior RWSs on this topic. The study will include at least 1130 patients in each matched group from an expected 50 diabetes specialist outpatient clinics, thereby providing a view on the effectiveness of SGLT2 inhibitors in the best setting for the assessment of chronic diabetic complications. Enrolment criteria will impose no restriction on renal function, except that eGFR will have to be greater than 15 mL/min/1.73 m^2. Therefore, we expect the population of the DARWIN-Renal study to be representative of patients with T2D seen in routine specialist care in Italy,[58] with most patients having eGFR values greater than 60 mL/min/1.73 m^2 and normal albumin excretion. In the prior DARWIN study editions, 0% to 10% of patients had CKD stage III or higher and 13% to 22% had micro-/macroalbuminuria.[59,60] Confounding by indication will be addressed in a new-user design by the gold standard methodology of propensity score matching (PSM) without group interdependency. There will be no conditioning on the future on post-index date eGFR availability. Similarly, there will be no constraint on the number of post-index date eGFR values but, based on the structure of the chart database, we expect to collect an equal number (~8) of pre-index date and post-index date eGFR measures for all patients during a mean observation time of 2.5 to 3.0 years after drug initiation. This will allow solid estimations of eGFR slopes.

In parallel to these expected advancements over state of the art, the DARWIN-Renal trial poses some challenges. The power calculation for detecting a between-group difference in the eGFR slope greater than 0.8 mL/min/1.73 m^2/year, yielded a sample size of 1130 patients per group after matching. However, matching patients who initiated dapagliflozin (and SGLT2 inhibitors in general) to those initiating other GLMs is challenging because of the limited common support between groups.[60] Therefore, we will need to collect data on a twice-as-large number of patients. Based on historical accrual from 50 centres,[59] we expect a final sample size of approximately 3000 patients/matched group, thus going far beyond the minimum required. By imposing no restriction on the number of post-index date eGFR measures, we may not see any early drop in eGFR if eGFR values at 1 to 3 months will not be available for a substantial number of patients.[39] This may limit our ability to evaluate the early transient eGFR drop, but at the same time pose fewer problems in the calculation of chronic eGFR slopes. Finally, data missingness for some covariates always occurs when dealing with routinely accumulated clinical data.[38] We will address this challenge by multiple imputation, which introduces complexity in data analysis due to the need to pool effects estimated in many different imputed datasets.

8 | CONCLUSION

The efficacy of SGLT2 inhibitors against the progression of DKD should be considered indisputable based on the results of RCTs carried out in the T2D population. This beneficial effect has been strengthened by results of the DAPA-CKD trial in patients with CKD with or without diabetes. However, these trials have been conducted mostly in patients with high cardiovascular or renal risk. Retrospective RWSs conducted so far have confirmed that patients who initiated SGLT2 inhibitors in routine care had better renal outcomes than matched patients with T2D who received other treatments. Yet, the duration of observation was relatively short, and the analysis of surrogate endpoints was subject to inherent bias. To allocate the available resources, it is of interest to understand which patients would benefit the most from the renal protection offered by therapy with SGLT2 inhibitors. So far, there is no evidence that patient phenotypes influence the response to SGLT2 inhibitors, but it remains unclear if and to

what extent SGLT2 inhibitors slow the decline in eGFR also in patients with normal albuminuria and with preserved eGFR at baseline. We acknowledge that results of RCTs, even when coming from post-hoc analyses, always generate a level of evidence that is greater than that obtained from RWSs. Nonetheless, continuous monitoring of patients treated with SGLT2 inhibitors in real-world clinical practice and comparison with other treatment strategies will provide us with long-term evidence of effectiveness under the free-living of routine care and in low-risk patients. Therefore, RWSs may add valuable information to the evolving discussion regarding the place of SGLT2 inhibitors in treatment algorithms of T2D in different stages of DKD. Fine-tuning the methodological approach to bias in comparative observational research will improve the quality of evidence derived from such studies. Under the auspices of the Italian Diabetes Society, the DARWIN-Renal study has the potential to extend our current knowledge on this topic.

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CONFLICT OF INTEREST

G.P.F. received lecture fees or grant support from Abbott, AstraZeneca, Boehringer, Daichi-Sankyo, Lilly, Merck-Sharp-Dome, Mundipharma, Novartis, Novo Nordisk, Sanofi, Servier. S.D.P. consulted for Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD, Novartis, Novo Nordisk, and Sanofi, received grant support from AstraZeneca and Boehringer Ingelheim, and speaker fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD, Novartis, Novo Nordisk and Sanofi. A.A. received research grants, lecture or advisory board fees from Merck Sharp & Dome, AstraZeneca, Novartis, Boeringher-Ingelheim, Sanofi, Mediolanum, Janssen, Novo Nordisk, Lilly, Servier and Takeda. A.S. received lecture fees or grant support from AstraZeneca, Boehringer, Lilly, Mundipharma, Novo Nordisk, Sankyo and Sanofi.

AUTHOR CONTRIBUTIONS

G.P.F., S.D.P., A.A. and A.S. contributed to study design, collection of literature data, analysis and interpretation, manuscript writing or revision. All authors approved the final version of the manuscript. G.P.F. is the guarantor of this work.

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DATA AVAILABILITY STATEMENT

No original data were used for this study.

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