Review

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Heterogeneity in renal end points of cardiovascular outcomes trials in Type 2 diabetes

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Composite renal end points and end stage renal disease (ESRD) are frequently included as prespecified secondary end points in the cardiovascular outcomes trials (CVOTs) of diabetes medications. We examined the heterogeneity in the definitions of composite renal end point and ESRD in CVOTs. Five criteria (macroalbuminuria, doubling of serum creatinine, estimated glomerular filtration rate [GFR], ESRD and renal death), were considered for the renal composite end point across the trials. Only three of the 12 trials included all five criteria, whereas the other trials included different combinations of four, three and two criteria. ESRD definition also showed considerable heterogeneity across the trials. Heterogeneity exists in the definitions of renal composite and ESRD end points in CVOTs making it challenging to assess comparative efficacy of the active treatments for reimbursement purposes.

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Diabetic kidney disease (DKD) is one of the most common complications for people living with Type 2 diabetes mellitus (T2DM) and is associated with an increased risk of mortality [1]. According to a previous study that linked baseline data from the Third National Health and Nutrition Examination Survey (NHANES III) with the National Death Index, the absolute risk difference of 10-year standardized all-cause mortality was 23.4% for participants with both diabetes and kidney disease when compared with participants who did not have both the conditions [2]. End stage renal disease (ESRD) is the most advanced stage of kidney disease, nearly 40% of the cases of ESRD in the USA are caused due to the diabetes according to the Centers for Disease Control and Prevention, treatment for ESRD typically includes renal replacement therapy [3–5]. While treatments focusing on the renin-angiotensin-aldosterone system remain the mainstay of treatment in diabetic patients at risk of developing DKD or ESRD, the recent introduction of new classes of antidiabetic medications, such as SGLT-2 inhibitors and GLP-1 analogues, have demonstrated promising results for renal outcomes [6,7]. In March 2020, the US FDA published draft guidelines for establishing safety in the treatment of diabetes with newer classes of diabetes medications, replacing the 2008 guidelines [8]. These guidelines acknowledge the importance of cardiovascular (CV) events as a significant source of morbidity and mortality in patients with Type 2 diabetes and call for the use of rigorous methods to collect adverse CV event data [8]. Although cardiovascular safety outcomes are considered primary end points, renal end points are also frequently included as prespecified secondary end points in the cardiovascular outcomes trials (CVOTs) of diabetes medications. Composite renal end points and ESRD are two commonly reported outcomes in CVOTs, given their utility in facilitating comparison between different classes of diabetes medications with respect to their relative efficacies in the prevention or delay of DKD. There is considerable debate about the choice of the renal end points in clinical trials, particularly because some individual components that measure ESRD may not be optimal and might occur when the kidney function is deteriorated [9,10]. As shown previously by Weldegiorgis *et al.*, end points such as initiation of renal replacement therapy not only depends on

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Table 1. Criteria considered for renal composite end point.

Trial	Active treatment	Macroalbuminuria	Serum creatinine	eGFR	ESRD	Renal death	Ref.
SAVOR-TIMI	Saxagliptin	No	Doubling or >6.0 mg/dl (530 μmol/l)	No	Need for renal dialysis, transplant or serum creatinine >530 μmol/l	No	[17]
CARMELINA	Linagliptin	No	No	Sustained ≥40% decrease in eGFR and eGFR ≤60 ml/min/1.73 m^2	Need for renal dialysis ≥30 days or renal transplant	Yes	[21]
LEADER	Liraglutide	New macroalbuminuria (urinary ACR >300 mg/g or urinary albumin >300 mg in 24 h)	Doubling	≤45 ml/min/1.73 m^2	Need for continuous renal replacement therapy	Yes	[14]
SUSTAIN-6	Semaglutide	New macroalbuminuria (urinary ACR >300 mg/g or urinary albumin >300 mg in 24 h)	Doubling	≤45 ml/min/1.73 m^2	Need for continuous renal replacement therapy	Yes	[15]
EXSCEL	Exenatide	New macroalbuminuria	No	Sustained ≥40% decrease in eGFR	Need for renal replacement therapy	Yes	[11]
REWIND	Dulaglutide	New macroalbuminuria (urinary ACR >33.9 mg/mmol)	No	Sustained ≥30% decrease in eGFR	Need for continuous renal replacement therapy	No	[13]
EMPA-REG OUTCOME	Empagliflozin	Progression to macroalbuminuria (urinary ACR >300 mg/g)	Doubling	≤45 ml/min/1.73 m^2	Need for renal replacement therapy	Yes	[22]
CANVAS	Canagliflozin	No	No	≥40% decrease in eGFR	Sustained eGFR <15 ml/min/1.73 m^2 for >30 days, dialysis ≥30 days or renal transplant	Yes	[19]
CREDENCE	Canagliflozin	No	Doubling	No	Sustained eGFR <15 ml/min/1.73 m^2 for >30 days or need for dialysis ≥30 days or renal transplant	Yes†	[20]
DECLARE-TIMI 58	Dapagliflozin	No	No	Sustained ≥40% decrease in eGFR to eGFR ≤60 ml/min/1.73 m^2	Sustained eGFR <15 ml/min/1.73 m^2 or dialysis ≥90 days or renal transplant	Yes†	[18]
DAPA-HF	Dapagliflozin	No	No	Sustained ≥50% decrease in eGFR	Sustained eGFR <15 ml/min/1.73 m^2 for ≥28 days or need for continuous renal replacement therapy	Yes	[16]
VERTIS-CV	Ertugliflozin	No	Doubling	No	Renal dialysis or need for renal transplant	Yes	[12]

†Includes renal or cardiovascular death.
ACR: Albumin creatinine ratio; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease.

the serum creatinine level or estimated glomerular filtration rate (eGFR) but also other factors. Therefore, any heterogeneity in the inclusion of components such as initiation of renal replacement therapy in renal composite outcome of clinical trials might lead to biased estimates when the comparative efficacy of potential treatments is assessed, and it is important to assess any such heterogeneity. In this review, we examine heterogeneity in the definitions of composite renal end point and ESRD in CVOTs conducted in patients with T2DM.

Review

We conducted a targeted literature review to identify both published and unpublished CVOTs conducted in Type 2 diabetes patients. Our study included a total of 12 trials [11–22]. Two trials (SAVOR-TIMI and CARMELINA) included DPP-4, four trials (LEADER, SUSTAIN-6, EXSCEL and REWIND) included GLP-1 analogues and six trials (EMPA-REG OUTCOME, CANVAS, CREDENCE, DECLARE-TIMI 58, DAPA-HF and VERTIS-CV) evaluated SGLT-2 inhibitors.

With the exception of the LEADER and SUSTAIN-6 trials, each study described a unique renal composite outcome (Table 1). Five criteria (macroalbuminuria, doubling of serum creatinine, eGFR, ESRD and renal death), were considered for the renal composite end point in the CVOT included in this review and renal composite was defined as the first occurrence of any one of the criteria. However, these five criteria were not present in every renal composite definition. Indeed, only three trials (EMPA-REG OUTCOME, LEADER and SUSTAIN-6) included

all the five criteria, with the EXSCEL trial including four (macroalbuminuria, eGFR, ESRD and renal death). VERTIS-CV and CREDENCE trials included doubling of serum creatinine, ESRD and renal death in their definition of renal composite end point. While, DAPA-HF, DECLARE-TIMI 58, CANVAS and CARMELINA trials included eGFR, ESRD and renal death in their definition of renal composite. The REWIND trial included macroalbuminuria, eGFR, ESRD in the definition of renal composite end point. Meanwhile, the SAVOR-TIMI trial included only doubling of serum creatinine (>6.0 mg/dl [530 µmol/l]) or ESRD to define renal composite end point. Between trials, clinical criteria within renal composite end points varied, with ESRD used most frequently compared with onset of macroalbuminuria which was the least frequently used criteria.

Beyond the inclusion of outcome components, we also observed substantial heterogeneity in the definitions of the criteria themselves. For instance, the definition of ESRD in the LEADER, SUSTAIN-6, EXSCEL, REWIND and EMPA-REG OUTCOME trials was restricted to the 'need for continuous renal replacement therapy', whereas investigators for CANVAS and CREDENCE defined ESRD as 'sustained eGFR <15 ml/min/1.73 m^2 for >30 days or dialysis ≥30 days or renal transplant'. The remaining five trials were all unique with respect to their respective definitions of ESRD. This trend was also present in definitions of eGFR declines. In CARMELINA, EXSCEL and DECLARE-TIMI 58, a sustained decrease of ≥40% in eGFR was established as a threshold whereas investigators for REWIND and DAPA-HF considered ≥30% and ≥50% sustained decreases in eGFR as thresholds, respectively. Although, onset of macroalbuminuria was chosen as criteria to define renal composite in only five of the 12 trials, the definition of macroalbuminuria was largely inconsistent. Furthermore, CREDENCE and DECLARE-TIMI trials also included death from renal or cardiovascular causes under renal death.

Discussion

Through this targeted literature review, we observed substantial heterogeneity in the criteria selected to define renal composite end points in CVOTs in T2DM. This observation extended to the definitions of component criteria. Only three of the 12 included trials considered the inclusion of all the five criteria identified across the trials in the definition of renal composite. Although ESRD was the most commonly cited component, it was also the most heterogeneously defined across studies. The heterogeneity in renal outcomes in clinical trials and the need for a uniform definition of renal end points has been discussed previously [23,24]. Weldegiorgis *et al.* in their review of renal end points suggested that although all the components of the renal composite end point measure the functions of a kidney and are correlated each component might have a different interpretation of the drug effect [9]. Prischl *et al.* proposed the use of major adverse renal events as an outcome, including both hard and soft end points (initiation of renal replacement therapy, quality of life measures, histological changes in the kidney tissue, death from renal cause) and surrogate markers such as eGFR and Urine Albumin-to-Creatinine Ratio (UACR) [24]. Initiatives such as the Standardized Outcomes in Nephrology have also begun to improve and define standardized renal outcomes [25].

Having common renal outcome definitions across trials is not only important to inform clinical practice, such as through treatment guidelines, but is also critical in the assessment of the comparative effectiveness of different classes of antidiabetic treatments. Although indirect treatment comparisons have demonstrated differences in renal protection effects between various interventions based on hard clinical end points, the underlying heterogeneity in definitions of composite renal outcomes across trials cannot and should not be ignored. The results of analyses conducted based on such evidence should be interpreted with caution [26].

Conclusion

Heterogeneity persists in the definitions of composite renal end points in CVOTs in T2DM. The standardization of such composite and other renal end points is a necessary and timely exercise, as the usage of such end points is recommended for future trials. We recommend that investigators conducting indirect comparisons of antidiabetic medications make explicit, the heterogeneity of the renal outcome definitions in the evidence base being evaluated.

Future perspective

As the number of newer classes of diabetes medications are expected to increase over next 10 years, it is imperative to construct homogenous definitions to evaluate renal composite outcomes and ESRD across future CVOTs and implement standardized guidelines for assessing renal outcomes in clinical trials. Having homogenous definitions for end points will help in establishing relative efficacy when indirect treatment comparisons are made between the treatments that lack direct head-to-head comparison.

Summary points

- Composite renal end points and end stage renal disease (ESRD) are two commonly reported outcomes in cardiovascular outcomes trials and can be used to assess relative efficacies in the prevention or delay of diabetic kidney disease.
- This review outlined the heterogeneous definitions of composite renal end point and ESRD in cardiovascular outcomes trials conducted in patients with Type 2 diabetes mellitus.
- Our review included two trials evaluating DPP-4 inhibitors, four trials evaluated GLP-1 analogues and six trials evaluated sodium-glucose cotransporter-2 inhibitors.
- Five criteria (macroalbuminuria, serum creatinine, estimated glomerular filtration rate, ESRD and renal death), were considered for the renal composite end point across the trials.
- Between trials, clinical criteria within renal composite end points varied, with ESRD used most frequently and onset of macroalbuminuria used least frequently.
- Beyond the inclusion of outcome components, we also observed substantial heterogeneity in the definitions of the criteria themselves.
- Only three of the 12 included trials considered the inclusion of all the five criteria identified across the trials in the definition of renal composite.
- Having common renal outcome definitions across trials is necessary to inform clinical practice and is also significant in the context of health technology assessments, where decision makers evaluate competing candidate treatments for reimbursement purposes.

Author contributions

C Balijepalli designed the study and wrote the first draft of the manuscript. K Yan and M Zoratti extracted data and supported in writing the first draft. M Franklin and E Druyts critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

Financial & competing interests disclosure

C Balijepalli and E Druyts are the founding partners of Pharmalytics Group, Vancouver BC, Canada. K Yan is an employee of Pharmalytics Group. M Zoratti is a PhD candidate at McMaster University, Hamilton, ON, Canada. M Franklin is the owner of Franklin Pharmaceutical Consulting LLC, Rock Hill, SC, USA. No funding was received to conduct this study. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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