KI REPORTS
KIReports.org

Renal Outcomes of Antidiabetic Treatment Options for Type 2 Diabetes—A Proposed MARE Definition

Friedrich C. Prischl[1] and Christoph Wanner[2]

[1]Department of Nephrology, 4th Department of Internal Medicine, Klinikum Wels-Grieskirchen, Wels, Austria; and [2]Division of Nephrology, University Hospital, Würzburg, Germany

One of the most critical long-term complications of type 2 diabetes is nephropathy, currently termed diabetic kidney disease. Although the prevalence is increasing, renal outcomes are heterogeneously defined. Intensive glucose control is effective for the prevention of microvascular complications, including kidney disease. However, the impact of specific drugs on renal outcome measures such as the incidence of kidney disease, albuminuria, progression to end-stage kidney disease, or death of renal cause remains unclear. Comparison of agents or drug classes is impossible, as renal outcomes are inconsistently defined in trials. Recent publications include more stringent criteria, but use only composite endpoints, which can reveal significant results driven by a single surrogate marker but not clinical events of true relevance to patients. This review discusses renal outcomes related to antidiabetic agents for type 2 diabetes, in an attempt to determine the influence of specific drugs on the incidence of diabetic kidney disease and various renal outcomes. There are marked differences among the various agents, but direct comparisons are difficult due to heterogeneous measures. Statements from Kidney Disease Improving Global Outcomes (KDIGO) or European Renal Best Practice (ERBP) highlight that "standardized outcome reporting is key to achieving evidence-based guidance and improving clinical care for patients." Renal outcome studies including a well-defined, standardized core set of patient-relevant outcomes are needed. Here, we propose to define and establish major adverse renal events (MARE) as the outcome measure for future studies.

Kidney Int Rep (2018) **3,** 1030–1038; https://doi.org/10.1016/j.ekir.2018.04.008
KEYWORDS: antidiabetic agent; diabetic kidney disease; major adverse renal event; renal endpoints; renal outcome; type 2 diabetes

Type 2 diabetes (T2D) is among the leading causes of end-stage kidney disease (ESKD) necessitating renal replacement therapy (RRT) worldwide. The high prevalence of T2D coincides with a high prevalence of diabetic kidney disease (DKD), as shown by data from the National Health and Nutrition Examination Survey.[1] A population-wide DKD increase from 2.2% to 3.3% was observed between 1988 and 2008, and DKD accounts for 24% of chronic kidney disease (CKD) cases.[2] This is likely also true in many industrialized countries, but exact numbers for CKD categories G2 to G4 are often lacking. Numbers are available for G5, and the incidence of DKD was 35.7 per million population in at least 1 example (Austria).[3]

Correspondence: Friedrich Prischl, Department of Nephrology, 4th Department of Internal Medicine, Klinikum Wels-Grieskirchen, Grieskirchnerstrasse 42, A-4600 Wels, Austria. E-mail: friedrich.prischl@klinikum-wegr.at

Received 28 February 2018; revised 10 April 2018; accepted 16 April 2018; published online 14 May 2018

The development and progression of DKD may be triggered by long-standing hyperglycemia, which can induce or deregulate various biochemical pathways and lead to an increase in reactive oxygen species, activation of protein kinase C, increased production of advanced glycation end-products, or secretion of profibrotic cytokines.[4]

The U.S. Food and Drug Administration (FDA) published guidelines for the pharmaceutical industry for the establishment of the cardiovascular safety of new glucose-lowering agents in 2008, and studies on renal endpoints were also performed as prespecified secondary outcomes in the cardiovascular safety trials. Personalized medicine in the form of individually selected antidiabetic treatment may influence cardiovascular comorbidity and have an impact on the development of DKD and its progression to ESKD in the long-term. Antidiabetic drugs have the potential for both harm and benefit to the kidneys, and clinical management of overt DKD and comorbidities must be considered along with timely preparation for RRT when appropriate.[5]

Renal Endpoints—The Practice So Far

The European Renal Best Practice guideline group recently discussed the observation that high-quality studies addressing clinically relevant questions for CKD patients are lacking, despite the frequency of CKD.[6] The definition of renal endpoints is heterogeneous; a wide range of variable outcomes are used; and reports are frequently incomplete, and heterogeneity is present or lacking when renal death, requirement of RRT, mortality, morbidity, patient-relevant and patient-centered outcomes, quality of life, pain, or costs are described.[6] This is also true for studies evaluating glucose-lowering agents and the risk of DKD development or progression.

New onset of nephropathy (incident DKD) is a commonly used renal outcome, and delaying its progression is a major goal of intervention in a clinical setting. Diabetic kidney disease is defined by diagnostic criteria[7–9] such as urinary albumin excretion (UAE) and glomerular filtration rate (GFR), acting as surrogate markers for kidney injury and loss of function. Urinary albumin excretion may be quantified using the urinary albumin−creatinine ratio (UACR) with a threshold of 30 mg/g in spot urine to discriminate between pathologic and normal values. Values ≥30 mg/g are defined as microalbuminuria or high albuminuria, and values >300 mg/g are defined as macroalbuminuria or very high albuminuria.[7] Urinary albumin–creatinine ratio-should be determined at regular intervals and requires multiple measurements (i.e., 2 or 3 times within 3−6 months) to establish a diabetic kidney injury diagnosis. Estimated GFR (eGFR) is used in parallel, as various observations have reported reduced eGFR in patients with DKD who had no albuminuria.[10,11]

Studies focusing on the effect of specific antidiabetic drugs on kidney function tend to use heterogeneously defined endpoints. A relevant decline of kidney function can be defined by an eGFR decline of 30%, 40%, or 50% from baseline value, but other studies use serum-creatinine doubling (a 57% eGFR decline) as the cut-off. An evaluation of the incidence of albuminuria/proteinuria as a surrogate marker of kidney damage is another approach, and the incidence of ESKD development (eGFR <10 or <15 ml/min per 1.73 m^2) or RRT onset are only occasionally used as measures, as these require more time than typical study periods. A so-called composite of microvascular endpoints, including retinopathy requiring photocoagulation, vitreous hemorrhage, blindness, and nephropathy including the occurrence of albuminuria, proteinuria, deterioration of renal function, new onset of RRT, or death from renal cause was used as 1 set of outcomes in the United Kingdom Prospective Diabetes Study (UKPDS) study.[12]

The 2008 Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation study (ADVANCE)[13] and the 2016 Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial[14] and Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes mellitus Patients–Remove Excess Glucose (EMPA-REG OUTCOME) kidney study[15] used more uniformly defined composite renal endpoints, consisting of surrogate measures such as new onset of macroalbuminuria (UACR >300 mg/g) and doubling of serum creatinine with an eGFR ≤45 ml/min per 1.73 m^2, but also included hard renal endpoints such as initiation of RRT or death from renal cause.[15]

Using uniformly defined renal endpoints to evaluate standard therapy plus placebo versus standard therapy plus drug of interest would allow for the comparison of various antidiabetic drugs in terms of the development or progression of DKD, but this requires that the study populations be comparable.

Antidiabetic Drugs and Development of Nephropathy or Progression

Metformin

Metformin is one of the oldest antidiabetic drugs and is recommended as first-line therapy in virtually all guidelines.[16–18] The United Kingdom Prospective Diabetes Study and other studies examined microvascular endpoints including nephropathy[12] and found that albuminuria of >50 mg/l developed in 23% to 24% of patients during an observation period of 10.7 years, irrespective of intensified treatment, metformin, or conventional treatment. A trend in favor of metformin was observed after summarizing all microvascular endpoints, but it did not reach statistical significance.[12] However, a retrospective analysis of a Veterans Administration database including 93,577 T2D patients revealed that treatment with sulfonylureas (n = 30,550) resulted in a 20% higher incidence of a composite of persistent reduction of eGFR of >25% from baseline, ESKD, and/or death from renal cause in comparison to treatment with metformin (n = 60,104) or rosiglitazone (n = 1,923).[19] An overview on the results of this study, and a comparison to the studies presented subsequently, are provided in Table 1. Although the Veterans Administration analysis was not a randomized trial, these data are consistent with the United Kingdom Prospective Diabetes Study results.[12] Metformin appears to have a positive impact on the incidence of nephropathy and may delay DKD progression.

Sulfonylureas

A Cochrane Review on renal endpoints under monotherapy with sulfonylureas in comparison to other

Table 1. Antidiabetic drugs and renal outcome endpoints

Drug class	Substance	Ref	Comparator	Composite (renal/micro-vascular) endpoint	Composite endpoint outcome	New-onset DKD	UAE/UACR ≥30 mg/g	UAE/UACR >300 mg/g	Fall in GFR	ESKD RRT	Death from renal cause	Death from any cause
Biguanides	Metformin	12	Various	Y	+	–	–	–	n t	n t	–	++
		19	Sulfonyl-urea	Y	++	n t	n t	n t	++	++	n t	++
Sulfonylureas	n a	20		n t	n t	n t	n t	n t	n t	n t	n t	n t
α-Glucosidase inhibitors	Acarbose	22	Metformin	N	n a	n t	++	n a	–	n a	n t	n t
Glitazones	Pioglitazone	26	Acarbose	N	n a	n t	–	–	–	n t	n t	n t
DPP4 inhibitors	Alogliptin	29	Sitagliptine crossover	N	n a	n t	++	n t	–	n t	n t	n t
	Linagliptin	30	Placebo	N	n a	n t	++	n t	n t	n t	n t	n t
	Sitagliptin	31	None	N	n a	n t	++	n t	n t	n t	n t	n t
Incretin mimetics	Exenatide	36	Placebo, insulin	N	n a	n t	n t	n t	–	n t	n t	n t
		37	Glimepiride	N	n a	n t	++	n t	n t	n t	n t	n t
	Liraglutide	38	Placebo	Y	++	++	++	++	–	–	–	++
SGLT2 inhibitors	Empagliflozin	15	Placebo	Y	++	++	++	++	–	++	–	++
	Canagliflozin	40	Placebo	Y	++	++	n t	++	n t	n t	n t	–
	Dapagliflozin	42	Placebo	N	n a	n t	+	+	n t	n t	n t	n t
Insulin	Insulin ≥3 injections daily or pump	47	Insulin ≤2 injections daily	N	n a	++	n t	++	++	++	n t	n t
	Insulin metaanalysis	49	Various	Y	–	n t	n t	n t	–	n t	n t	–
	Insulin degludec	50	Insulin glargine	N	n a	n t	n t	n t	–	n t	n t	–
	Insulin detemir/glargine	51	Pioglitazone	N	n a	n t	n t	n t	–	n t	n t	n t

DKD, diabetic kidney disease; DPP4, dipeptidyl-peptidase-4; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; N, no; n a = not applicable; n t, not tested (and/or not reported); Ref, reference; RRT, renal replacement therapy; SGLT2, sodium-glucose-co-transporter 2; UACR, urinary albumin–creatinine ratio; UAE, urinary albumin excretion; Y, yes; –, no effect (or even negative effect); +, positive trend, not significant; ++, significant positive outcome (P at least <0.05). A "positive" (+) outcome meant improvement of a parameter (or a composite), or delay in progression, or a reduction of an event rate.

antidiabetic drugs was published in 2013.[20] The authors concluded that meta-analysis is not possible, as studies addressing this issue are lacking; therefore, no statement on sulfonylureas can be made. Notably, this review was withdrawn by July29, 2015 for formal reasons, and 1 of the coauthors was identified as an employee of a pharmaceutical company. However, the study's conclusion is unchanged following this withdrawal, in our opinion.

Although it is not the focus of this review, it should be emphasized that sulfonylureas represent the second highest risk factor for relevant hypoglycemia.[21] Hypoglycemia is an exceedingly harmful event for patients with CKD, as they are highly susceptible to hypoglycemia-triggered arrhythmias and other threats. Therefore, sulfonylureas should be avoided in CKD patients.[17]

Alpha-Glucosidase Inhibitors

In a study from Beijing, China, 762 patients with newly diagnosed T2D randomly received 300 mg daily acarbose or 1500 mg daily metformin and were followed up for UACR.[22] All patients received initial instructions on lifestyle modification during a 4-week run-in period, and 20.4% and 23.9% of patients randomized to acarbose and metformin respectively had an elevated UACR at baseline. Both drugs were able to reduce UACR significantly (acarbose: 10.9%, $P < 0.01$; metformin: 15.1%, $P < 0.01$) within 48 weeks of observation. Similar effects were observed for fasting glucose, postprandial glucose levels, and HbA1c levels, whereas the initially normal eGFR remained unchanged during the observation period.[22]

The results on metformin are consistent with the previously discussed studies[19] but could also be interpreted as a retardation of kidney disease progression. The acarbose results may be the consequence of better glucose control, but also the lowering of diastolic blood pressure and the influence on insulin resistance may add to the result.[22] The authors conclude that the mechanisms of lowering UACR with acarbose are poorly understood.

Glitazones (Thiazolidinediones)

Currently, pioglitazone is the only clinically available peroxisome-proliferator-activator-receptor-γ-ligand (PPARγ). This drug is able to prevent the development of DKD in animal models.[23,24] Glitazone binding leads to apoptosis of large insulin-resistant fat cells and reduces liberation of free fatty acids by small fat cells. Because cellular uptake of glucose is preferred over fatty acids, this results in increased insulin sensitivity.[25] Pioglitazone may be used without dose modification in CKD, but the risk of fluid retention and other side effects must be considered.[8]

There is only 1 small study assessing pioglitazone and renal endpoints, from Taiwan.[26] Thirty patients with T2D received 30 mg daily pioglitazone or 150 mg

daily acarbose in addition to metformin and sulfonylureas in a prospective, randomized, but open-label study. Baseline HbA1c was 8.26% and follow-up was 6 months. Pioglitazone led to a 0.72% reduction of HbA1c ($P < 0.001$), a 1.3-kg increase in body weight ($P < 0.02$), and a 7−ml/min per 1.73 m^2 reduction in eGFR ($P = 0.03$), whereas the increase in UACR was not significant (+12 mg/g; $P = 0.46$). The only difference between the 2 treatments was the increase in body weight.[26] Limitations of this study include a sex imbalance (73% women) and a 26.7% use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in the pioglitazone group only. A 2010 meta-analysis including 10 studies with pioglitazone, 5 studies with rosiglitazone, and 2,860 patients overall revealed different results.[27] The authors pointed to a rather heterogeneous set of data, but were able to show a reduction of 64.8% and 24.8% of UAE and UACR, respectively, with thiazolidinediones compared to controls.[27] The authors conclude that further and larger trials using hard renal endpoints are warranted to clarify a potential benefit of glitazones for DKD.

Dipeptidyl-Peptidase−4 Inhibitors (DPP4-I, Gliptines)

There are 2 ways to increase the activity of glucagon-like peptide−1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP): the use of DPP4-resistant GLP-1 analogues and the inhibition of DPP4.[28] Both GLP-1 and GIP are key incretins for the regulation of plasma glucose levels. DPP4-I has shown antidiabetic effectiveness and a low risk of hypoglycemia in many studies.[28] Studies including renal endpoints are available for alogliptin[29], linagliptin,[30] and sitagliptin,[31] although these were focused on surrogate parameters (UAE and eGFR) rather than hard renal outcomes. A UACR reduction was seen in all 3 studies within 3 to 6 months, whereas eGFR remained stable over the observation period. Measurements of markers of oxidative stress indicated a potential nephroprotective effect regardless of the level of glucose lowering,[29] and a review of sitagliptin described the pleiotropic effects of this drug and DPP4-I in general.[32] Pointing to DeFronzo's "ominous octet" for the pathophysiology of T2D,[33] the authors suggest that the high DPP4 expression levels in the mammalian kidney are targeted for inhibition even when upregulated in DKD, thereby ameliorating diabetic dysmetabolism, restoring GLP-1 action, and leading to UAE reduction.[32] The results of the Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients With Type 2 Diabetes (CARMELINA) study (linagliptin) are expected later in 2018 and may help to clarify this issue, as the study includes a prespecified secondary renal composite endpoint defined as a sustained 40% eGFR reduction, sustained ESKD, and death from renal cause.[34]

A recent meta-analysis of 13 randomized controlled studies evaluated safety for CKD patients.[35] Although HbA1c was effectively lowered and hypoglycemia occurred rarely, data on mortality, cardiovascular events, or ESKD showed a high variability as indicated by the 95% confidence intervals. Therefore, no definite conclusion can be drawn.[35]

Incretin Mimetics

This class of drugs includes analogues of endogenous GLP-1 and GIP, which are resistant to DPP4.[28] The incidence of gastrointestinal and other side effects seems to be somewhat elevated in CKD, a common feature of all incretin mimetics.[28] Several agents are available (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide). They are eliminated via glomerular filtration and/or tubular reabsorption and/or proteolytic degradation.

An analysis of 19 studies on the safety and tolerability of exenatide, including 5,549 patients, revealed an incidence rate of 1.56 for kidney-related adverse events, including acute kidney injury, which was similar to the (combined) comparators.[36] A small comparison of exenatide and glimepiride for 16 weeks showed a numerically higher reduction in UAE with exenatide.[37]

Liraglutide is another member of this drug class that was evaluated for renal outcomes[38] in addition to cardiovascular endpoints[14] in the LEADER trial. Liraglutide led to a significant reduction of the composite renal endpoint at 22%. However, this study shows the bias of a composite endpoint, as the effect was driven predominantly by a 26% reduction of persistent macroalbuminuria whereas the other endpoints studied showed only minor effects.[38] The risk for renal adverse events was not elevated.

Sodium-Glucose-Cotransporter−2 Inhibitors (SGLT2I)

The EMPA-REG OUTCOME study was initially designed[15,39] to follow the U.S. Food and Drug Administration (FDA) regulation for the necessity of cardiovascular safety studies for newer antidiabetic drugs. The surprising results found for cardioprotection[39] drew attention to what could follow for renal outcomes. Empagliflozin treatment was shown to reduce new onset or worsening of nephropathy by 39%, progression to macroalbuminuria by 38%, doubling of serum creatinine accompanied by eGFR ≤45 ml/min per 1.73 m^2 by 44%, and initiation of RRT by 55%.[15] An initial drop in eGFR was observed, followed by stabilization, as seen previously

for the blockade of the renin–angiotensin–aldosterone system.

The Canagliflozin Cardiovascular Assessment Study (CANVAS) program included 2 studies with canagliflozin and 10.142 patients followed for a mean of 43.3 months.[40] Kidney disease was initially present in 17.5%, mean eGFR was 76.5 ml/min per 1.73 m^2, and mean UACR was 12.3 mg/g with 69.8% of normoalbuminuric patients. Almost 30% of the canagliflozin and placebo treatment arms stopped drug intake early, and the composite cardiovascular endpoint (3-point major adverse cardiovascular events; MACE) was significantly reduced ($P < 0.001$ for noninferiority and $P = 0.02$ for superiority). Although on the basis of the prespecified hypothesis testing sequence the renal endpoints were not viewed as statistically significant, the results showed a possible benefit with respect to albuminuria progression (27% reduction) with canagliflozin, and UAE regression was seen more frequently (293.4 vs. 187.5 patients with regression per 1000 patient-years). The composite of a 40% reduction of eGFR, need for RRT, or death from renal causes was reduced by 40%.[40]

Dapagliflozin also showed a reduction of UAE. From a previous study of 252 patients,[41] 166 patients with stage 3 CKD were included in a *post hoc* analysis.[42] In all, 39.6% and 33.9% of patients treated with 5 and 10 mg of dapagliflozin, respectively, moved to lower categories of UACR when compared with placebo (15.8%). An increase in UACR occurred in 4.3% and 14.7% of the 5- and 10-mg dapagliflozin patients only, whereas 27.3% of placebo patients showed an increase in UACR. It is noteworthy that there were only 29, 20, and 25 evaluable patients at 104 weeks in the 10-mg and 5-mg dapagliflozin and placebo-treated groups.[42]

The UACR reduction seen with canagliflozin,[40] dapagliflozin,[41] and empagliflozin[15] point to a potential hemodynamic and therefore nephroprotective effect of this drug class. In the CANVAS program, however, nearly twice as many lower extremity amputations (hazard ratio [HR] = 1.97, 95% confidence interval [CI] = 1.41–2.75) were observed,[40] not seen with empagliflozin[15,39] or other SGLT-2 inhibitors. This led to a black box warning for canagliflozin in many countries worldwide.[43] Until March 2017, 66 SGLT2I-associated amputations were reported to the FDA Adverse Event Reporting System (FAERS), 57% or 86% of which were related to canagliflozin.[44] Approximately one-third of affected patients had pre-existing diabetic foot syndrome. Two further analyses of the FAERS investigated the occurrence of ketoacidosis with SGLT2I treatment.[45,46] A total of 21,636 reports of adverse events were found, with SGLT2I suspected as the cause or given as a co-medication. Of these, 2018 events (9.4%) reported acidosis, metabolic acidosis, or ketoacidosis with SGLT2I used for the indication of diabetes.[45] The calculated proportional reporting ratio was 13.9% in diabetic patients with SGLT2I versus 0.54% in patients with other antidiabetic drugs. This listing included patients with type 1 diabetes (T1D) as well as patients receiving metformin or insulin,[45] and women were affected more frequently.[46] The number of reports of ketoacidosis differed across the various drugs (canagliflozin: n = 450; dapagliflozin: n = 144; empagliflozin: n = 46).[46] The authors of both analyses note that that the FAERS data are vague, are heterogeneous, and lack accuracy.[45,46] The cause for ketoacidosis could be related to hypokalemia, which suppresses insulin secretion and may be induced by co-medication with SGLT2I and thiazide diuretics.[45]

Insulin

The search for renal endpoints for insulin is complicated. Obviously, insulin deficiency requires treatment with insulin substitution. The question of renal outcomes following insulin treatment has a definite answer in the case of T1D, not for specific insulin preparations or specific insulin analogues but rather for the effect of intensified treatment. Intensified insulin therapy with at least 3 injections per day or continuous insulin administration resulted in a reduction of the development of nephropathy over conventional therapy (1–2 insulin injections per day), from 25% to only 9%.[47] Less than 1% of patients needed RRT or lost vision over an observation period of 30 years. Measurable differences in microvascular endpoints were observed after 15 to 20 years of treatment, but were accompanied by a markedly higher rate of hypoglycemia requiring assistance (61.2 vs. 18.7 events per 100 patient-years with intensified versus conventional insulin administration).[47]

Intensified glucose control is also effective in T2D, lessening the risk for microalbuminuria by 14% (risk ratio = 0.86, 95% CI = 0.76–0.96) and for macroalbuminuria by 26% (risk ratio 0.74, 95% CI = 0.65–0.85), whereas serum creatinine doubling, ESKD, or death from renal cause are unaffected.[48] The studies included in this analysis predominantly used oral antidiabetics (United Kingdom Prospective Diabetes Study, Action to Control Cardiovascular Risk in Diabetes [ACCORD], ADVANCE, and others).

A French meta-analysis, focusing on the incidence of endpoints following treatment with insulin, other antidiabetic drugs, diet, or placebo found rather disappointing results.[49] Data from 20 randomized controlled trials including 18,599 patients were included, and the secondary endpoints of renal insufficiency or serum creatinine doubling were not significantly influenced by insulin regimens (risk ratio = 0.68, 95% CI = 0.43–1.06), and only a trend toward renoprotection was

seen.[49] A positive effect was found only for development of retinopathy and need for photocoagulation.

The newer ultra–long acting insulin analogue degludec was compared to insulin glargine in 6,509 randomized patients with a relatively short observation period of 2 years in the DEVOTE study.[50] Cardiovascular safety as the primary endpoint was confirmed in this noninferiority study. The renal endpoint was eGFR only, which showed a comparable decrease of 2.4 and 2.6 ml/min per 1.73 m^2 with degludec and glargine, respectively. Acute kidney injury was analyzed as a serious adverse event only, and occurred at a rate of 1.04 and 1.46 per 100 patient-years.[50] We note that no difference in renal outcome is expected within a median observation of 1.99 years and a median duration of treatment of 1.83 years.

An additional study of interest compared pioglitazone with insulin detemir or glargine.[51] Overall, 1002 patients who showed inadequate responses to sulfonylurea or metformin received treatment escalation with 1 of the 3 medications. To ensure similar patient characteristics, 105 patients in each group were analyzed finally. Patients with pioglitazone had the greatest reduction in HbA1c after 3.5 years of treatment. The probability of CKD progression was elevated in the detemir (HR = 2.63, 95% CI = 1.79–3.88) and glargine (HR = 3.13, 95% CI = 2.01–4.87) groups compared to pioglitazone, as determined by Cox regression.[51]

In general, specific insulin preparations or analogues are either not studied for renal outcomes, are not studied long enough,[50] or are not able to show significant nephroprotective effects.[49]

The Future of Renal Endpoints

A variety of initiatives have begun to discuss the challenges in conducting clinical trials in nephrology.[6,52] There are many studies without the power and duration to observe the changes required. Endpoint definitions are frequently heterogeneous, and outcome measures are often surrogate markers only, without or with minor relevance to patients. This does little to guide the care of patients with DKD or CKD from other causes.[6]

The SONG initiative represents an attempt at improvement, and aims to define a "Standardized Outcomes in Nephrology" dataset.[53] First, numerous methodological items were clarified and are outlined in the SONG Handbook.[54] Differences must be observed with regard to the treatment modality under evaluation. First considerations are available regarding hemodialysis,[55,56] peritoneal dialysis,[57] and kidney transplantation,[58] and more are underway.

Appropriate outcome measures for drug trials of patients with DKD as well as general CKD are also required. We propose to develop and define Major Adverse Renal Events as "MARE" (Figure 1), comparable to the term "MACE" for major adverse cardiovascular events. MARE (to be pronounced like "mare," the Italian word for "sea") may include a set of major morbidity events such as the development of new-onset DKD, reaching ESKD, starting RRT, or receiving a kidney transplant, and mortality

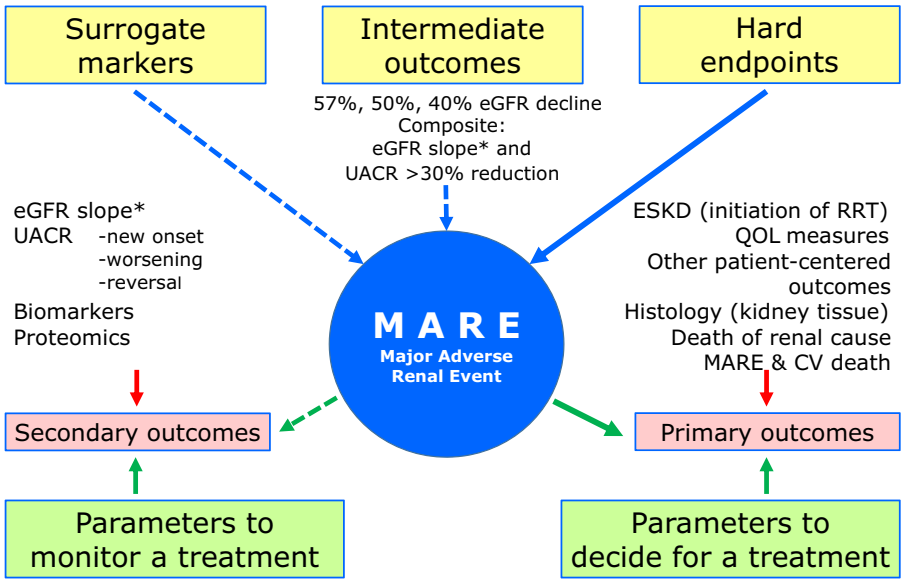

Figure 1. Renal outcome measures in drug studies of diabetic (chronic) kidney disease. CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; MARE, major adverse renal events (that is, a core set of renal outcome measures, yet to be defined exactly); QOL, quality of life; RRT, renal replacement therapy (hemodialysis, peritoneal dialysis, kidney transplantation); UACR, urinary albumin/creatinine ratio. *The magnitude of a slope, connected to a hard outcome, requires further research (i.e., an eGFR decline of 8 ml/min per year over 2 years of follow-up, based on 7 creatinine/cystatine C measurements). Solid-line arrows indicate a "hard" impact on MARE; dotted-line arrows indicate a markedly lower impact or markers should be used as additional secondary endpoints only.

from renal cause. Trials may use MARE and add intermediate endpoints and surrogate endpoints where appropriate (Figure 1). We are aware that MARE may also have drawbacks, as is the case with all composite endpoints. Composites may be driven mainly by a singular response to one item included but leaving unaffected all others. Nevertheless, a uniformly agreed-upon definition for MARE would make meta-analyses easier and would facilitate the comparison of different studies. Trial reporting statutory has to include analyses of each item of MARE, too. It is obvious that one always would have to remain cognizant of the effects of a certain drug on the various components of a MARE composite, and would have to choose and administer the drug accordingly.

New efforts to identify diabetic patients at high risk for developing endpoints such as ESKD have been made by introducing new disease progression biomarkers, such as serum tumor necrosis factor receptor 1, to better identify patients who should be enrolled in studies.[59] However, whether high-risk DKD patients are representative of all DKD patients in the long term, allowing for the generalization of study results to all DKD patients, remains to be seen.

Surviving the "burden of disease" is not the only patient concern, but carrying the "burden of treatment" also matters to patients. Therefore, patient-centered outcomes such as quality of life require consideration for inclusion in composite outcomes. Attempts are currently made by the regulatory agencies (FDA and European Medicines Agency) and the U.S. National Kidney Foundation to develop surrogate markers such as slopes derived from eGFR, UAE, and UACR into valid and accepted endpoints, and results will be seen shortly.

Conclusion

Studies of drug-specific effects on renal outcomes have been performed or are in progress within the FDA's mandate to perform studies on cardiovascular safety issues. Numerous studies have shown that more intense glucose control and adequate blood pressure control lead to a reduction of microvascular complications including nephropathy. However, studies of a drug-specific effect on renal outcomes are missing for older antidiabetic agents. No data are available for sulfonylureas, whereas a trend toward potential nephroprotection or delayed progression is seen with metformin, α-glucosidase inhibitors, pioglitazone, and DPP4-inhibitors. Positive data on hard renal outcomes have been published with liraglutide and empagliflozin, and nephroprotection has been shown (reduced albuminuria) for incretin mimetics and SGLT-2 inhibitors. Data are missing for specific insulin preparations or analogues, and meta-analyses of insulin in type-2 diabetes do not show a kidney benefit. Unfortunately, trial protocols are heterogeneous or are based on surrogates but not hard endpoints, therefore not allowing comparison of drug classes or individual drugs. Therefore, a better-defined and uniform core set of hard, patient-relevant renal outcome measures rather than surrogate parameters is urgently needed for drug intervention studies.

We propose to develop and define major adverse renal events as "MARE," which should include major morbidity and mortality events. Patient-centered outcomes such as quality of life and others should be considered to be included as outcomes of interest. Surrogate markers such as slopes derived from eGFR, UAE, and UACR are currently reconsidered as endpoints under well-defined conditions, but are still seen as surrogate or secondary endpoints. Using well defined "MARE" as a primary outcome in drug studies of DKD and CKD in general could generate more comparable study results, could enable meta-analyses, and would produce better evidence for individual treatment selection. All trialists in nephrology should work toward this development in the near future.

DISCLOSURE

FCP (during working lifetime) has received honoraria for lectures, travel funding, or membership of advisory board from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen-Cilag, Novartis, Roche, and Takeda. CW has received honoraria for steering committee membership and lecturing from Boehringer Ingelheim, Janssen, Novo-Nordisk, and Sanofi-Genzyme.

REFERENCES

1. deBoer IH, Rue TC, Hall YN, et al. Temporal trends in the prevalence of diabetic kidney disease in the United States. *JAMA*. 2011;305:2532–2639.
2. Zelnick LR, Weiss NS, Kestenbaum BR, et al. Diabetes and CKD in the United States population, 2009-2014. *Clin J Am Soc Nephrol*. 2017;12:1984–1990.
3. Prischl FC, Auinger M, Säemann M, et al. Diabetes-related end stage renal disease in Austria 1965-2013. *Nephrol Dial Transplant*. 2015;30:1920–1927.
4. Badal SS, Danesh FR. New insights into molecular mechanisms of diabetic kidney disease. *Am J Kidney Dis*. 2014;63: S63–S83.
5. Schernthaner G, Prischl FC. Management of overt diabetic kidney disease and uremia. In: Bakris GL, Hahr A, Khardori R, et al, eds. *Managing Diabetic Nephropathies in Clinical Practice*. Adis: Springer International Publishing Switzerland; 2017:77–115.
6. Nistor I, Bolignano D, Haller MC, et al. Why creating standardized core outcome sets for chronic kidney disease will improve clinical practice. *Nephrol Dial Transplant*. 2017;32: 1268–1273.

7. American Diabetes Association. Microvascular complications and foot care. Section 10. Standards of medical care in diabetes—2018. *Diabetes Care*. 2018;41(suppl 1):S105–S118.
8. National Kidney Foundation. KDOQI Clinical practice guidelines for diabetes and chronic kidney disease: 2012 update. *Am J Kidney Dis*. 2012;60:850–886.
9. Sourij H, Edlinger R, Prischl F, et al. Diabetic kidney disease—update 2016. Position paper of the Austrian Diabetes Society and the Austrian Society of Nephrology. *Wien Klin Wochenschr*. 2016;128(suppl 2):85–96.
10. Caramori ML, Fioretto P, Mauer M. Low glomerular filtration rate in normoalbuminuric type 1 diabetic patients: an indicator of more advanced glomerular lesions. *Diabetes*. 2003;52:1036–1040.
11. Kramer HJ, Nguyen QD, Curhan G, Hsu CY. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. *JAMA*. 2003;289:3273–3277.
12. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352:854–865.
13. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358:2560–2572.
14. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311–322.
15. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes et al. *N Engl J Med*. 2016;375:323–334.
16. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2018 executive summary. *Endocr Pract*. 2018;24:91–110.
17. Guideline Development Group. Clinical practice guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR<45mL/min). *Nephrol Dial Transplant*. 2015;30:ii1–ii142.
18. Clodi M, Abrahamian H, Drexel H, et al. Antihyperglykämische Therapie bei Diabetes mellitus Typ 2 (Grundsatzstatement). *Wien Klin Wochenschr*. 2016;128(suppl 2):S45–S53.
19. Hung AM, Roumie CL, Greevy RA, et al. Comparative effectiveness of incident oral antidiabetic drugs on kidney function. *Kidney Int*. 2012;81:698–706.
20. Hemmingsen B, Schroll JB, Lund SS, et al. Sulphonylurea monotherapy for patients with type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2013;4:CD009008.
21. Ben-Ami H, Nagachandran P, Mendelson A, Edoute Y. Drug-induced hypoglycemic coma in 102 diabetic patients. *Arch Intern Med*. 1999;159:281–274.
22. Pan Q, Xu Y, Yang N, et al. Comparison of acarbose and metformin on albumin excretion in patients with newly diagnosed type 2 diabetes. *Medicine*. 2016;95:e3247.
23. Guan Y, Breyer M. Peroxisome proliferator-activated receptors (PPARs). Novel therapeutic targets in renal disease. *Kidney Int*. 2001;60:14–30.
24. Isshiki K, Haneda M, Koya D, et al. Thiazolidinedione compounds ameliorate glomerular dysfunction independent of their insulinsensitizing action in diabetic rats. *Diabetes*. 2000;49:1022–1032.
25. Seer C, Lehmann R. Antidiabetika bei niereninsuffizienz und nierentransplantation. *Praxis*. 2016;105:69–76.
26. Chen YH, Tarng DC, Chen HS. Renal outcomes of pioglitazone compared with acarbose in diabetic patients: a randomized controlled study. *PLoS One*. 2016;11:e0165750.
27. Sarafidis PA, Stafylas PC, Georgianos PI, et al. Effect of thiazolidinediones on albuminuria and proteinuria in diabetes: a meta-analysis. *Am J Kidney Dis*. 2010;55:835–847.
28. Agarwal V, Giri C, Solomon RJ. The effect of glucose-lowering therapies on diabetic kidney disease. *Curr Diabetes Rev*. 2015;11:191–200.
29. Fujita H, Taniai H, Murayama H, et al. DPP-4 inhibition with alogliptin on top of angiotensin II type 1 receptor blockade ameliorates albuminuria via up-regulation of SDF-1alpha in type 2 diabetic patients with incipient nephropathy. *Endocr J*. 2014;61:159–166.
30. Groop PH, Cooper ME, Perkovic V, et al. Linagliptin lowers albuminuria on top of recommended standard treatment in patients with type 2 diabetes and renal dysfunction. *Diabetes Care*. 2013;36:3460–3468.
31. Hattori S. Sitagliptin reduces albuminuria in patients with type 2 diabetes. *Endocr J*. 2011;58:69–73.
32. Mega C, Teixeira-Lemos E, Fernandes R, Reis F. Renoprotective effects of the dipeptidyl peptidase-4 inhibitor sitagliptin: a review in type 2 diabetes. *J Diabetes Res*. https://doi.org/10.1155/2017/5164292.
33. DeFronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;58:773–795.
34. Rosenstock J, Perkovic V, Alexander JH, et al. Rationale, design, and baseline characteristics of the CArdiovascular safety and Renal Microvascular outcomE study with LINAgliptin (CARMELINA®): a randomized, double-blind, placebo-controlled clinical trial in patients with type 2 diabetes and high cardio-renal risk. *Cardiovasc Diabetol*. 2018;17:39.
35. Howse PM, Chibrikova LN, Twells LK, et al. Safety and efficacy of incretin-based therapies in patients with type 2 diabetes and CKD: a systematic review and meta-analysis. *Am J Kidney Dis*. 2016;68:733–742.
36. MacConell L, Brown C, Gurney K, et al. Safety and tolerability of exenatide twice daily in patients with type 2 diabetes: integrated analysis of 5594 patients from 19 placebo-controlled and comparator-controlled clinical trials. *Diab Metab Syndr Obes*. 2012;5:29–41.
37. Zhang H, Zhang X, Hu C, Lu W. Exenatide reduces urinary transforming growth factor-beta1 and type IV collagen excretion in patients with type 2 diabetes and microalbuminuria. *Kidney Blood Press Res*. 2012;35:483–488.
38. Mann JFE, Ørsted DD, Brown-Frandsen K, et al. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med*. 2017;377:839–848.
39. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128.

40. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644–657.
41. Kohan DE, Fioretto P, Tang W, List JF. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. *Kidney Int*. 2014;85:962–971.
42. Fioretto P, Stefansson BV, Johnsson E, et al. Dapagliflozin reduces albuminuria over 2 years in patients with type 2 diabetes and renal impairment. *Diabetologia*. 2016;59:2036–2039.
43. Food and Drug Administration. FDA Drug Safety Communication: FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR) Available at: https://www.fda.gov/Drugs/DrugSafety/ucm557507.htm. Accessed April 2, 2018.
44. Fadini GP, Avogaro A. SGLT2 inhibitors and amputation in the US FDA Adverse Event Reporting System. *Lancet Diabetes Endocrinol*. 2017;5:680–681.
45. Fadini GP, Bonora BM, Avogaro A. SGLT2 inhibitors and diabetic ketoacidosis: data from the FDA Adverse Event Reporting System. *Diabetologia*. 2017;60:1385–1389.
46. D'Elia JA, Segal AR, Bayliss GP, Weinrauch LA. Sodium-glucose cotransporter-2 inhibition and acidosis in patients with type 2 diabetes: a review of US FDA data and possible conclusions. *Int J Nephrol Renovasc Dis*. 2017;10:153–158.
47. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group, Nathan DM, Zinman B, et al. Modern-day clinical course of type 1 diabetes mellitus after 30 years duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburg epidemiology of diabetes complications experience (1983-2005). *Arch Intern Med*. 2009;169:1307–1316.
48. Coca SG, Ismail-Beigi F, Haq N, et al. Role of intensive glucose control in development of renal endpoints in type 2 diabetes: systematic review and meta-analysis. *Arch Intern Med*. 2012;172:761–769.
49. Erpeldinger S, Rehman MB, Berkhout C, et al. Efficacy and safety of insulin in type 2 diabetes: meta-analysis of randomized controlled trials. *BMC Endocrine Disord*. 2016;16:39.
50. Marso SP, McGuire DK, Zinman B, et al. Efficacy and safety of degludec versus glargine in type 2 diabetes. *N Engl J Med*. 2017;377:723–732.
51. Chang YH, Hwu DW, Chang DM, et al. Renal function preservation with pioglitazone or with basal insulin as an add-on therapy for patients with type 2 diabetes mellitus. *Acta Diabetol*. 2017;54:561–568.
52. Baigent C, Herrington WG, Voresj J, et al. Challenges in conducting clinical trials in nephrology: conclusions from a Kidney Disease–Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2017;92:297–305.
53. Tong A, Craig JC, Nagler EV, Van Biesen W. Composing a new song for trials: the Standardized Outcomes in Nephrology (SONG) initiative. *Nephrol Dial Transplant*. 2017;32:1963–1966.
54. SONG Initiative. *The SONG Handbook* (Version 1.0). Available at: http://songinitiative.org/reports-and-publications/. Accessed April 2, 2018.
55. Wetmore JB, Gilbertson DT, Liu J, Collins AJ. Improving outcomes in patients receiving dialysis: the Peer Kidney Care Initiative. *Clin J Am Soc Nephrol*. 2016;11:1297–1304.
56. Tong A, Manns B, Hemmelgarn B, et al. Establishing core outcome domains in hemodialysis: report of the Standardized Outcomes in Nephrology–Hemodialysis (SONG-HD) consensus workshop. *Am J Kidney Dis*. 2017;69:97–107.
57. Manera KE, Tong A, Craig JC, et al. Standardized Outcomes in Nephrology–Peritoneal Dialysis (SONG-PD): study protocol for establishing a core outcome set in PD. *Perit Dial Int*. 2017;37:639–647.
58. Tong A, Gill J, Budde K, et al. Towards establishing core outcome domains for trials in kidney transplantation: report of the Standardized Outcomes in Nephrology–Kidney Transplantation consensus workshops. *Transplantation*. 2017;101:1887–1896.
59. Yamanouchi M, Skuoien J, Niewczas MA, et al. Improved clinical trial enrollment criterion to identify patients with diabetes at risk of end-stage renal disease. *Kidney Int*. 2017;93:258–266.