Journal of Endocrine Disorders

Open Access

Austin Publishing Group

Review Article

Updates in the Treatment of Diabetic Kidney Disease - A Focus on Incretin Mimetics and Sodium Glucose Co-Transporter 2 Inhibitors

Irons BI[1]*, Minze MG[1], Chastain LM[1] and McMurry ME[2]

[1]Department of Pharmacy Practice, Texas Tech University Health Sciences Center, USA

[2]Department of Internal Medicine-Nephrology Division, Texas Tech University Heath Sciences, USA

***Corresponding author:** Irons BI, Department of Pharmacy Practice, Texas Tech University Health Sciences Center, USA

Received: March 14, 2020; **Accepted:** March 31, 2020; **Published:** April 07, 2020

Abstract

The prevalence of Diabetic Kidney Disease (DKD) continues to rise and implications on morbidity, mortality and expenditures in health care resources. Glucagon-Like Peptide 1 (GLP1) agonists, Sodium Glucose Co-Transporter 2 (SGLT2) inhibitors and Dipeptidyl peptidase 4 (DPP4) inhibitors have been evaluated to assess renal outcomes though show widely variable differences in outcomes. DPP4 inhibitors and GLP1 agonists improvements in albuminuria but have not shown to impact renal outcomes such as doubling of serum creatinine or progression in renal insufficiency. Better data exist on the benefits of SGLT2 inhibitors in improving DKD outcomes. Safety studies involving SGLT2 inhibitors have shown reductions in albuminuria, but compared to the other two class of agents have also shown reductions in progression of renal insufficiency and reductions in the development of end-stage renal disease. Canagliflozin in a trial designed to evaluate the agents use in patients with DKD, showed significant less risk in doubling of serum creatinine, progression to end-stage renal disease compared to placebo. The agent also demonstrated a reduction in cardiovascular morbidity. It can be considered the first therapeutic agent in nearly twenty years to provide substantial improvement in outcomes in the treatment of DKD.

Keywords: Diabetes; Kidney disease; Renal disease

Abbreviations

CKD: Chronic Kidney Disease; US: United States; DKD: Diabetic Kidney Disease; ESRD: End Stage Renal Disease; RAS: Renin-Angiotensin System; DPP4: Dipeptidyl Peptidase 4; CI: Confidence Interval; GLP: Glucagon-Like Peptide; SGLT2: Sodium Glucose Co-Transporter 2; FDA: Food and Drug Administration; CVOT: Cardiovascular Outcome Trial; UACR: Urine Albumin: Creatinine Ration; eGFR: Estimated Glomerular Filtration Rate; CREDENCE: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation, MI: Myocardial Infarction; SBP: Systolic Blood Pressure; CVD: Cardiovascular Disease; CrCl: Creatinine Clearance; HR: Hazard Ratio; Subcut: Subcutaneous

Introduction

The association between diabetes and Chronic Kidney Disease (CKD) has progressed into a complex multifactorial public health problem that continues to grow in spite of past advances in therapeutics and medications. CKD and subsequent development of End-Stage Renal Disease (ESRD) is associated with an increased risk of cardiovascular morbidity as well as mortality [1,2]. The increasing and often under recognized incidence of CKD corresponds to the dramatic rise in diabetes. Diabetes remains the leading cause of CKD, referred to as Diabetic Kidney Disease (DKD) and subsequently increases the risk for ESRD. With current therapeutic options the disease is often slowed but rarely completely stopped. Approximately 20-40% of patients with diabetes will progress to the development of DKD though the severity varies from increased albuminuria to significant declines in renal function and ESRD [3,4]. Early detection and appropriate management of diabetes and associated cardiovascular risk factors are essential to the reduction in DKD related morbidity, mortality and health care expenditures. Medicare expenditures for CKD patients in 2017 reached $72 billion, accounting for 25% of the total spending for all fee for service Medicare beneficiaries aged 65 and older [5]. Care of beneficiaries with CKD and concurrent diabetes mellitus required $39 billion in 2017. Leading recommendations to combat the consequences of DKD have for decades promoted the importance of glycemic and blood pressure control, the latter with the use of agents that block the Renin-Angiotensin System (RAS) [6]. The use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers has improved over the last two decades but use in patients with CKD remains suboptimal [7]. Intensive glucose control decreases the risk of microalbuminuria and microalbuminuria, but the evidence is lacking as to whether intensive glycemic control reduces the risk of significant renal outcomes such as ESRD or death from renal disease. The effects of routine blood pressure lowering and intensive glucose control are independent of one another and when combined they produce additional reduction in clinically relevant outcomes [8].

Newer treatment options in the management of type 2 diabetes have been developed that offer effective improvements in glycemic control and in some cases may improve cardiovascular morbidity or mortality based on Food and Drug Administration-required safety

Citation: Irons BI, Minze MG, Chastain LM and McMurry ME. Updates in the Treatment of Diabetic Kidney Disease - A Focus on Incretin Mimetics and Sodium Glucose Co-Transporter 2 Inhibitors. J Endocr Disord. 2020; 6(1): 1033.

Table 1: Study parameters and renal outcomes derived from GLP-1 agonist cardiovascular safety studies.

Study	Lixisenatide	Liraglutide	Semaglutide (weekly subcut) [29]	Exenatide	Dulaglutide	Semaglutide (daily oral) [26]
Parameter	(daily) [25,27]	(daily) [28]		(weekly) [31,32]	(weekly) [30]	
Subjects (n)	6068	9340	3297	14752	9901	3183
Study duration (yr)	2.1	3.8	2.1	3.2	5.4	1.3
Duration of diabetes	9.3	12.8	13.9	12	10.5	14.9
h/o CVD (%)	100	81	83	73	31	85
Baseline	75	80	≥ 90 (30%)	76	77	74
eGFR (ml/min/1.73 m^2)			60 - <90 (42%)			
			30 - <60 (25%)			
			< 30 (3.3%)			
Baseline UACR (mg/g)	17	Mean not reported	Not reported	Mean not reported	16	Mean not reported
	19% subjects with UACR 30-300 mg/g	26% subjects with UACR 30-300 mg/g		15-21% subjects with microalbuminuria		33% subjects with UACR > 300 mg/g
	7% subjects with UACR > 300 mg/g	10% subjects with UACR >300 mg/g		2.6-13% subjects with macroalbuminuria*		
Patients receiving RAS therapy at baseline (%)	85	82	84	80	81	Not reported
Composite Renal Outcome	NA	New-onset persistent macroalbuminuria, doubling of serum Cr and eGFR< 45 ml/min/1.73 m^2, need for renal replacement, or renal death	New or worsening nephropathy (macroalbuminuria, doubling of serum Cr and CrCl< 45 ml/min/1.73 m^2, or need for renal replacement therapy)	Composite 1: First event of a 40% decline in eGFR, renal replacement, or renal death	New macroalbuminuria, sustained decline in eGFR≥30% from baseline, or need for renal replacement	NA
				Composite 2: Composite 1 plus incident macroalbuminuria		
Composite Renal Outcome HR (95% CI)	NA	0.78 (0.67-0.92)	0.64 (0.46-0.88)	Composite 1	0.85 (0.77-0.93)	NA
				HR 0.84 (0.67-1.04)		
				Composite 2		
				0.85 (0.74-0.98)		
Individual	% Change in UACR	Persistent macroalbuminuria	Persistent macroalbuminuria	New macroalbuminuria	New macroalbuminuria	eGFR ratio baseline to end of study
Renal Outcome(s)		HR 0.74 (0.60-0.91)	HR 0.54 (0.37-0.77)	HR 0.84 (0.70-1.07)	HR 0.77 (0.68-0.87)	
	+34% Placebo					Placebo 0.98
	+24% Lixisenatide	Doubling of serum Cr and persistent eGFR< 45 ml/min/1.73 m^2	Doubling of serum Cr and persistent CrCL< 45 ml/min/1.73 m^2	Mean change in eGFR	Sustained decline in eGFR≥30%	
	(p=0.004)	HR 0.89 (0.67-1.19)	HR 1.28 (0.64-2.58)	0.21 ml/min/1.73 m^2 (NS)	HR 0.89 (0.78-1.01)	Semaglutide
						0.98
	Persistent macroalbuminuria	Need for renal replacement therapy	Need for renal replacement therapy		Need for renal replacement	
	HR 0.84 (0.68-1.02)	HR 0.87 (0.61-1.24)	HR 0.91 (0.40-2.07)		HR 0.75 (0.39-1.44)	
	Doubling of serum Cr	Renal death				
	HR 1.16 (0.74-1.83)	HR 1.59 (0.52-4.87)				

GLP: Glucagon-Like Peptide; CVD: Cardiovascular Disease; UACR: Urine Albumin-To-Creatinine Ratio; NA: Not Assessed; NS: Not Significant; eGFR: Estimated Glomerular Filtration Rate; CrCl: Creatinine Clearance; HR: Hazard Ratio; Subcut: Subcutaneous; RAS: Renin-Angiotensin System

* Assessed by questionnaire not by UACR, % of patients with either micro- or macroalbuminuria was presented based on chronic kidney disease stage (1-3b), not collectively of the study population.

studies. These include Dipeptidyl Peptidase-4 (DPP-4) inhibitors, Glucagon-Like Peptide (GLP) 1 agonists, and Sodium Glucose Co-Transporter 2 (SGLT2) inhibitors. This review assesses each class as to potential renal benefits evaluating clinical trials in patients with

type 2 diabetes with or without DKD, large scale Cardiovascular Outcome Trials (CVOT) that also evaluated renal outcomes, and one large landmark study specifically designed to assess a SGLT2 inhibitor effects on renal outcomes in patients with DKD.

Dipeptidyl peptidase 4 inhibitors

Renal outcomes from diabetes studies: potential renal benefits of DPP4 inhibitors have been studied in a handful of trials involving patients with diabetes with or without existing CKD. The studies are mixed in patient population evaluated, length of study and specific renal outcomes explored. Sitagliptin in conjunction with a sulfonylurea was shown to reduce Urine Albumin-To-Creatinine Ratio (UACR) by 43 mg/g in 82 Japanese patients as a secondary outcome of an efficacy and safety study assessing the combination of agents for one year [9]. Alogliptin was also shown to reduced UACR mildly (5 mg/g) at 12 weeks compared to placebo in 61 Japanese patients with type 2 diabetes [10]. UACR with the use of linagliptin in combination with a RAS inhibitor was assessed in a pooled retrospective analysis of four phase III clinical trials in patients with type 2 diabetes [11]. Linagliptin showed a greater reduction in adjusted geometric mean UACR (28%) compared to placebo. In another linagliptin study the agent, when added to a RAS inhibitor in 360 patients with type 2 diabetes and residual albuminuria did not significantly reduce UACR or improve estimated glomerular filtration rate (eGFR) compared to placebo over 24 weeks [12]. In a pooled analysis of the use of saxagliptin either as monotherapy or in combination with other agents involving 20 controlled studies and including over 9000 patients found no effect, positive or negative, on renal function [13].

Renal outcomes from cardiovascular safety studies: Sitagliptin's effect on change in eGFR was analyzed as a secondary outcome in its CVOT. Sitagliptin had a very small, but statistically significant, change in eGFR from baseline compared to placebo with an estimated difference of -1.34 mL/min/1.73m^2 (95% CI, -1.76 to -0.91;p<0.001) between groups and no significant changes in eGFR were noted in patients with chronic kidney disease at baseline over the 3 year study [14,15]. Additionally in the analysis for safety in patients with CKD with an eGFR < 60 mL/min/1.73m^2 was compared to those without CKD (eGFR > 60 mL/min/1.73m^2), serious adverse events were higher in those with poorer baseline renal function but the study found no significant difference in the development of microalbuminuria or renal failure in patients receiving sitagliptin compared to placebo. An exploratory analysis of saxagliptin's renal safety and efficacy compared to placebo over 2.1 years the saxagliptin CVOT did not show a difference in the prespecified composite outcome (doubling of serum creatinine, initiation of chronic dialysis, renal transplant, or serum creatinine >6.0 mg/dL), and change in eGFR was similar between groups over the time frame analysed [16]. With regards to alogliptin, no difference in a change in eGFR or initiation of dialysis was seen in patients with type 2 diabetes in the agent's CVOT [17]. The linagliptin CVOT showed the agent did not significantly alter the composite renal outcome (sustained end-stage renal disease, renal failure death, or sustained decrease of >40% in eGFR from baseline) but did show a favorable 14% relative reduction in progression of albuminuria [18]. Thus DPP-4 inhibitors show positive to neutral effect in reducing UACR but fail to show any profound evidence that the class reduces the risk for inhibiting significant decline in renal function or attenuating the risk for the development of CKD.

Glucagon-like Peptide 1 Receptor Agonists

Renal outcomes from diabetes studies: There are a handful of studies that directly assess the use of GLP-1 agonists on renal outcomes. The outcomes assessed in these studies, the populations evaluated, and duration of study vary significantly. In a twelve-week study of 55 overweight patients with type 2 diabetes with no history of chronic kidney disease, neither liraglutide or sitagliptin showed an effect on eGFR or UACR [19]. In a study involving 31 subjects with type 2 diabetes and baseline microalbuminuria, exenatide twice daily by subcutaneous administration showed a reduction in 24-hour urinary albumin compared to subjects taking glimepiride after 16 weeks of treatment [20]. After 12 months of therapy with liraglutide in 84 patients with Type 2 diabetes another study found an improvement in eGFR in subjects with a baseline eGFR < 90 ml/min/1.73 m^2 (absolute change 5-6 ml/min) but no change in those with a baseline eGFR > 90 ml/min/1.73 m^2 [21]. Urine albumin excretion in twenty-four hours improved mildly in both groups. No changes compared to placebo in eGFR or UACR were noted in 277 subjects with type 2 diabetes and moderate renal impairment (30-59 ml/min/1.73 m^2) in a 26-week trial designed to assess efficacy and safety of liraglutide in this population [22]. Oral semaglutide has also been evaluated for safety and efficacy in 324 patients with type 2 diabetes and moderate renal impairment (30-59 ml/min/1.73 m^2) [23]. After 26 weeks of treatment, the study found no difference between semaglutide or placebo in changes in eGFR or urine albumin:creatinine ratio. Once-weekly dulaglutide was compared to insulin glargine for efficacy and safety in 577 patients with type 2 diabetes and moderate-to-severe chronic kidney disease (baseline eGFR at randomization 38 ml/min/1.73 m^2) [24]. While the primary outcome of this study was the evaluation of changes in A1c, prespecified secondary outcomes included changes in eGFR and UACR. After one year of treatment, eGFR in subjects receiving dulaglutide was 2.7 ml/min/1.73 m^2 higher than in subjects receiving insulin therapy despite similar reductions in A1c. Changes in UACR were not statistically different between the two groups however dulaglutide did reduce the ratio more than insulin treated subjects in those with macroalbuminuria (>300 mg/g) at baseline. The latter three studies discussed were not designed to assess renal benefit but rather to assess A1c reduction in subjects with renal insufficiency. Together, the above studies provide some insight into improvements in urinary albumin excretion within this class of agent and variable, limited improvement in eGFR. As in the case of DPP4 inhibitors, the studies do not provide sufficient insight into reducing more robust renal outcomes such as decreasing the likelihood of significant renal insufficiency or progression to end stage renal disease.

Renal outcomes from cardiovascular safety studies: Some of the GLP1 agonist CVOT studies performed pre-specified secondary outcome or post-hoc exploratory assessment of renal outcomes in patients with or at high risk for cardiovascular disease. Table 1 describes some of these differences in these studies. The trials differ in many ways including baseline cardiorenal risk, duration of study and hence drug exposure time, duration of diabetes, and type of renal outcomes assessed. Some studies included a specific composite renal outcome while others made no general renal outcome assessment. However, these trials are significantly larger in scope and length than the trials described above. Baseline subject renal insufficiency is mild in each of the studies. UACR are inconsistently reported among the

Table 2: Study parameters and renal outcomes derived from SGLT2 inhibitor cardiovascular safety studies.

Study / Parameter	Empagliflozin [40]	Canagliflozin [41,42]	Dapagliflozin [43]
Subjects (n)	7020	10,142	17,160
Study duration (yr)	2.6	3.6	4.2
Duration of diabetes	57% of subjects > 10 years	14	10.5
h/o CVD (%)	100	65	41
Baseline eGFR (ml/min/1.73 m^2)	74	77	85
Baseline UACR (mg/g)	NR ^	12	NR ^
	<30 mg/g: 59%	< 30 mg/g: 70%	<30 mg/g: 56-71%
	30-300 mg/g: 29%	30-300 mg/g: 23%	30-300 mg/g: 23-31%
	> 300 mg/g: 11%	> 300 mg/g: 8%	> 300 mg/g: 6-14%
Patients receiving RAS therapy at baseline (%)	81	80	81
Composite Renal Outcome	Progression to UACR > 300 mg/g, doubling of serum Cr and decline in eGFR≤ 45 ml/min/1.73m^2, initiation of renal replacement, or renal death	40% reduction in eGFR, renal replacement initiation, or renal death	Sustained decrease of 40% or greater in eGFR and < 60 ml/min/1.73 m^2, new end-stage renal disease, or death due to cardiovascular or renal cause
Composite Renal Outcome HR (95% CI)	0.61 (0.53-0.70)	0.60 (0.47-0.77)	0.76 (0.67-0.87)
Individual	Progression to UACR > 300 mg/g	Progression of albuminuria*	Sustained decrease of 40% or greater in eGFR and < 60 ml/min/1.73 m^2, new end-stage renal disease, or death due to renal cause
Renal Outcome(s)	HR 0.62 (0.54-0.72)	HR 0.73 (0.67-0.79)	HR 0.53 (0.43-0.66)
	Doubling of serum Cr and decline in eGFR≤ 45 ml/min/1.73 m^2	Regression of albuminuria**	Sustained 40+% decrease in eGFR and eGFR< 60 ml/min/1.73 m^2
	HR 0.56 (0.39-0.79)	HR 1.70 (1.51-1.91)	HR 0.54 (0.43-0.67)
	Initiation of renal replacement therapy	40% reduction in eGFR	End-stage renal disease
	HF 0.45 (0.21-0.97)	HR 0.60 (0.47-0.78)	HR 0.31 (0.13-0.79)
		Doubling of serum creatinine	
		HR 0.50 (0.30-0.84)	

CVD: Cardiovascular Disease; NR: Not Reported; UACR: Urine Albumin-To-Creatinine Ratio; Egfr: Estimated Glomerular Filtration Rate; HR: Hazard Ratio; N: Number Of Subjects; RAS: Renin-Angiotensin System.

^ Levels of albuminuria reported based on baseline eGFR range, mean baseline not reported

* Defined as a 30% increase in albuminuria and a change from normoalbuminuria to microalbuminuria (30-300 mg/g) or macroalbuminuria (> 300 mg/g) or microalbuminuria to macroalbuminuria.

** Defined as development of normoalbuminuria if baseline was micro- or macroalbuminuria or development of microalbuminuria if baseline was macroalbuminuria.

studies but doesn't appear a significant issue in the subjects in these trials. The use of RAS inhibitors was high (80+%) and consistent between studies that reported the use of these agents.

The studies evaluating once daily lixisentide or once daily oral semaglutide did not assess a composite renal outcome in their CVOT studies [25,26]. However lixisentide demonstrated a smaller increase in urine albumin excretion compared to subjects receiving placebo but found no difference in the development of macroalbuminuria or the doubling of serum creatinine [27]. The CVOT of oral semaglutide did not evaluate changes in UACR and found no difference in the ratio of baseline and end of study eGFR between those receiving the GLP-1 agonist or placebo. In comparison, once daily liraglutide, once weekly semaglutide and dulaglutide showed significant reductions (15-36%) in the composite renal outcome evaluated in their respective CVOT studies (Table 1) [28-30]. When the individual outcomes making up the composite renal outcome are further assessed, it appears reducing the development of persistent macroalbuminuria likely drives the composite outcome reduction in those receiving the GLP-1 agonist compared to placebo. Once weekly exenatide did not show a reduction in the main renal composite outcome (which didn't include change in albuminuria status) but their secondary renal composite outcome, which included macroalbuminuria, did show a significant 15% relative reduction [31,32]. However the risk for the development of macroalbuminuria was not found to improve with the use of exenatide compared to placebo when evaluated separately. None of the studies demonstrated a significant reduction in the decline of eGFR or development of ESRD.

Renal outcomes were also assessed in a systematic review and meta-analysis of the GLP-1 agonist CVOTs that reported such data at the time of their analysis [33]. This study found a 17% relative

reduction over a median follow-up of 3.2 years in the composite outcome defined as the development of macroalbuminuria, worsening of kidney function (doubling of serum creatinine or a >40% decline in eGFR), ESRD, or renal death). As in the above individual CVOT data, this composite outcome was primarily due to a reduction in albuminuria. When assessed separately, a worsening of renal function was not found to be significantly affected.

Sodium glucose co-transporter 2 inhibitors

Renal outcomes from diabetes studies: Trials assessing SGLT2 inhibitors have the same limitations as discussed above in terms of not being designed to specifically assess the renal benefit of this class of agent on preventing progression of renal impairment, are typically short in duration, and evaluate rather small groups of patients. A 26-week study designed to evaluate canagliflozin in terms of A1c reduction in 269 patients with type 2 diabetes and stage 3 CKD found a larger decrease in overall eGFR in subjects receiving canagliflozin compared to those receiving placebo [34]. The decrease in renal function occurred during the first few weeks of the study and trended toward baseline at the study's end. Subjects receiving canagliflozin showed a 21-30% reduction in UACR compared to those receiving placebo, 7.5% reduction. A secondary analysis of a previously published study of 1450 patients with type 2 diabetes evaluated two-year data of canagliflozin compared to glimepiride [35]. Subjects receiving canagliflozin showed a modest slowing in eGFR decline compared to those receiving the sulfonylurea. Despite similar decreases in A1c, the canagliflozin group also showed a slightly larger reduction in UACR compared to the glimepiride group in those with a baseline ratio >30 mg/g. A 52-week study evaluating the use of empagliflozin in 290 patients with diabetes and CKD showed improvements in UACR in those receiving the SGLT2 inhibitor compared to placebo [36]. The effect of empagliflozin in those subjects with baseline elevated UACR (> 30 mg/g) was evaluated in a pooled assessment of five phase five studies [37]. The investigators found a 32% reduction in UACR compared to placebo in those with baseline UACR 30-300 mg/g and a 41% reduction in those with baseline UACR > 300 mg/g. A two-year study pooling two controlled trials evaluating ertugliflozin to glimepiride or placebo in patients without significant baseline CKD found ertugliflozin was associated with smaller decreases in eGFR at the study's end compared to placebo or sulfonylurea treated subjects [38]. The investigators also found ertugliflozin treated subjects had between a 29 to 33% reduction in UACR compared to subjects not receiving the SGLT2 inhibitor. Dapagliflozin was assessed in a post-hoc analysis of the effects of the agent in 166 subjects with diabetes and both chronic kidney disease (eGFR >30-60 ml/min/1.73m^2) and increased albuminuria (>30 mg/g) [39]. The investigators noted at the end of the two-year study a larger reduction in UACR in subjects receiving the SGLT-2 inhibitor compared to placebo (-44-57% placebo-corrected).

Renal outcomes from cardiovascular safety studies: Three of the four currently approved SGLT2 inhibitors have completed and reported their required CVOT data and, like many of the CVOT studies evaluating the other two classes of agents, had prespecified renal outcomes included in their analysis [40-43]. The three CVOTs in this class, as with the GLP1 agonist and DPP4 inhibitor studies, are much larger than the above discussed studies and typically of much longer duration. They also vary in study duration, size, and baseline cardiorenal risk and are placebo-controlled rather than comparative between agents or across class of agent. (Table 2) As in the GLP1 agonist studies, baseline renal function was not significantly impaired and most subjects had normal albuminuria concentrations. Use of RAS inhibitors in study subjects was high at 80% or greater. While the prespecified renal outcome differed between studies, a significant reduction (24-40%) in their composite renal outcome were noted. Some important differences in the renal results of the SGLT2 inhibitor CVOT compared to the GLP1 agonist studies are noteworthy. First, in the case of both the dapagliflozin and canagliflozin composite outcomes, changes in degree of albuminuria was not part of the assessed outcome so this composite outcome cannot be said to be driven primarily by changes in UACR. Second, both the empagliflozin and dapagliflozin studies showed a greater than 40% significant reductions in worsening of renal function as well as a 55-69% relative reduction in progression to ESRD. However, the latter absolute difference between those receiving a SGLT2 inhibitor

Table 3: Baseline characteristics and outcome results of the CREDENCE study [45].

Baseline Characteristic	
Age (years)	63
Female sex (%)	34
Ethnicity or Race (%)	
White	67
Black	5
Asian	20
Other	8.4
Duration of diabetes (years)	15.8
Existing cardiovascular disease (%)	50
A1c (%)	8.3
eGFR (ml/min/1.73 m^2)	56
Urinary albumin:creatinine (Median, mg/g)	927
Study Outcome	Hazard Ratio (95% Confidence Interval)
Primary composite outcome *	0.70 (0.59-0.82)
Doubling of serum creatinine	0.60 (0.48-0.76)
End stage kidney disease **	0.68 (0.54-0.86)
eGFR < 15 ml/min/1.73m^2	0.60 (0.45-0.80)
Initiation of dialysis or renal transplantation	0.74 (0.55-1.00)
Cardiovascular death	0.78 (0.61-1.00)
Cardiovascular death, MI, or stroke	0.80 (0.67-0.95)
Hospitalization for heart failure	0.61 (0.47-0.80)
End of study difference in A1c compared to placebo (%)	-0.11
End of study difference in A1c compared to placebo (%)	-2.38
End of study difference in A1c compared to placebo (%)	-0.88

Egfr: Estimated Glomerular Filtration Rate; MI: Myocardial Infarction; SBP: Systolic Blood Pressure

* Defined as dialysis for at least 30 days, renal transplantation, eGFR of < 15 ml/min/1.73 m^2 for at least 30 days, doubling of serum creatinine concentration from baseline, or death from cardiovascular or renal disease.

** Defined as eGFR < 15 ml/min/1.73 m^2, initiation of dialysis, or renal transplantation.

versus placebo is quite small, 0.1-0.3%. The canagliflozin CVOT showed a 40% relative reduction in having a 40% reduction in eGFR and a 50% reduction in a doubling of serum creatinine, the latter also having a very small absolute reduction. Secondary renal outcomes of limiting progression of albuminuria were positively impacted with the use of canagliflozin and empagliflozin. Both the dapagliflozin and canagliflozin studies showed a reduction in their composite outcome regardless of baseline eGFR or cardiovascular risk. Results of the effects of ertugliflozin on cardiovascular safety are pending but perhaps could shed additional light on any potential renal benefit in patients with diabetes and established vascular disease. The CVOT with this agent concluded late in 2019 and results should be available in 2020.

A meta-analysis of the current three CVOTs evaluating more than 34,000 patients found a significant 45% relative risk reduction in the composite renal outcome of worsening renal function, ESRD, or renal death. [44] This analysis did not assess the changes in the individual endpoints making up the composite outcome. The reduction in the composite renal outcome was independent of baseline atherosclerotic risk however the risk reduction was lower in subjects with poorer baseline eGFR compared to those with higher eGFR.

Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE)

As with the previous classes of agents reviewed, the effect of an SGLT2 inhibitor used for the treatment of type 2 diabetes had not been studied specifically to reduce the risk of end stage renal disease. The landmark CREDENCE study reported in 2019 has changed this [45]. A multicentered, multinational study, CREDENCE included 4401 patients with diabetes and established albuminuric CKD. At baseline the average eGFR was less than 60 ml/min/1.73 m^2 and median UACR was greater than 900 mg/g. (Table 3) Patients were randomly assigned to either 100 mg daily of canagliflozin or placebo and all subjects were receiving stable doses of RAS inhibitors. The primary composite outcome was the development of end stage kidney disease. A third of the subjects evaluated were female, the average age of subjects was greater than 60 years of age, most were white, the average duration of diabetes was nearly 16 years, and half had established cardiovascular disease. The study was stopped early after an interim analysis met prespecified efficacy criteria. The median duration of the study was 2.62 years. The investigators found a 30% relative reduction in the primary composite outcome. (Table 3) Results evaluating components of the primary outcome showed a 40% in the risk for doubling of serum creatinine and a 32% reduction in progression to ESRD. The risk of the composite of myocardial infarction, stroke or death due to cardiovascular disease was also reduced by 20% as was the risk for hospitalization for heart failure (39% reduction). Renal death, cardiovascular death, and all-cause mortality were not significantly reduced. There were small improvements at the study's conclusion in A1c, systolic blood pressure, and body weight in those receiving the SGLT2 inhibitor. Prespecified safety outcomes assessment found no increased risk for fracture, cancer, or amputation. The latter a concern from the CVOT of canagliflozin that found a small but concerning and statistically significant increase in the high-risk patients assessed for that outcome [46]. Subjects receiving canagliflozin showed a significant early decrease in eGFR but thereafter had a slower decline in renal function the remainder of the study compared to subjects receiving placebo.

A meta-analysis that included all three existing CVOT studies plus the data from CREDENCE comprising nearly 39,000 subjects assessed the composite renal outcome of dialysis, renal transplantation, or renal death. [47]. The analysis found a significant 33% relative risk reduction in this composite outcome and also found a significant 35% reduction in the development of ESRD. While all groups assessed based on baseline eGFR benefited with SGLT2 inhibitor therapy compared to placebo, there again appeared to be a lower risk reduction in the composite endpoint in those with worse baseline renal function.

Proposed mechanisms of renal benefit

The small changes in A1c in the CVOT and Credence study is likely not significant enough to be the sole cause of the renal benefits seen with these agents. GLP1 agonists and SGLT2 inhibitors may have direct and indirect effects on the vascular system. Each of these drug types have some common effects and class-specific effects that may explain, at least in part, the improvement in cardiorenal benefits. Some of the non-glycemic effects of the SGLT2 inhibitors and GLP1 agonists are decreases in body weight, blood pressure, improvements in lipid profile, and reduction in visceral fat [48,49]. However, it appears that these effects alone, many of which are quite small, are not the only root cause eliciting renal benefits when using such agents.

With regards to GLP agonists, GLP receptors are expressed in the human kidney with functional receptors in proximal tubular cells and in the renal vasculature. Proposed mechanism for inducing renal benefits is GLP-1 induced natriuresis and diuresis, mediated by inhibition of sodium-hydrogen exchanger isoform 3 activity in the renal proximal tubule [48-51]. GLP1 agonists may inhibit the activity of this isoform, thereby enhancing natriuresis and diuresis. These changes may contribute to reducing albuminuria and possibly some blood pressure reduction, although the summative hemodynamic changes associated with this natriuretic effect is not completely elucidated. GLP-1 activity may also have a direct vasodilatory effect on the afferent arteriole, which is in part dependent on increased production of nitric oxide [51,52]. Experimental data indicate GLP-1 agonists are able to indirectly suppress other factors known to contribute to efferent arteriole vasoconstriction, such as suppression of angiotensin-II and reduced production of reactive oxygen species [49]. The net effect of these changes could possibly result in a reduction in diabetes-related glomerular hyperfiltration [51,52]. While there is no definitive answer at this time, it seems that the net effect of vasodilatory activity, inhibition of glomerular hyperfiltration and possible anti-atherosclerotic potential provide some cursory explanation for renal benefits seen with GLP1 agonists [49].

The case for renal protection with SGLT2 inhibitors is slightly clearer than with the GLP1 agonists. SGLT2 inhibition induces acute osmotic and natriuretic effects that impact both systemic and renal hemodynamic parameters [53,54]. The known benefit of systemic hemodynamic changes associated with SGLT2 inhibitors is generally reflected in a small reduction of systolic blood pressure. There is some evidence to suggest that SGLT2 inhibition also provides very modest RAS activation in response to contraction of plasma volume related to osmotic diuresis, which may lead to vasodilation [54,55]. Secondly, in the diabetic kidney, SGLT2 is upregulated causing a distortion in

the tubular glomerular feedback system resulting in hyperfiltration. This feedback system, in the presence of SGLT2 inhibition, results in afferent arteriole vasoconstriction, which in turn decreases intraglomerular pressure, thereby normalizing the GFR. The net effect of these modulations is seen with the typical reduction in albuminuria when employing this class of drugs [54]. Furthermore, SGLT2 inhibition theoretically mitigates renal hypoxia and may even improve oxygenation to the kidney through several mechanisms. The preservation of cardiac function and cardiac output seen with SGLT2 inhibitors would result in increased renal perfusion, which is also enhanced by the increased hematocrit, and resultant oxygen carrying capacity, seen with SGLT2 inhibitors [53,54].

Lastly, SGLT2 inhibitors have been shown to reduce production of interleukin-6 and other pro-inflammatory markers in the presence of hyperglycemic conditions. Also, some experimental models have linked SGLT2 inhibition with reduction in fibrosis. This, in part, leads to the hypothesis that the anti-inflammatory and anti-fibrotic activities associated with SGLT2 inhibitors could protect against progression of DKD [53,54].

Conclusion

While all three drug classes discussed have at least some potential for benefit in reducing the impact of diabetes on renal outcomes, the SGLT2 inhibitors appear best poised to help in this key therapeutic area based on current data. While the DPP4 inhibitors and GLP1 agonists may provide some benefit in reducing albuminuria, they have not been shown to reduce more key renal outcomes, in particular, significant decline in renal function, end stage renal disease, or renal death. While UACR is strongly associated with the risk for renal insufficiency, improved changes in albuminuria do not necessarily suggest it will decrease the risk for such [56,57]. The positive effects of SGLT2 inhibitors, in particular canagliflozin, on renal outcomes surpass those with the other two class of agents. In addition to decreasing UACR, the CVOTs in this class have shown more significant reductions in robust renal outcomes including the attenuation of renal function decline and small reductions in the risk for ESRD in patients with or at high risk for cardiovascular events. The landmark CREDENCE study with canagliflozin showed in patients with diabetes along with existing renal insufficiency and significant albuminuria, a marked reduction in worsening renal function and a risk reduction in proceeding toward ESRD compared to placebo. The study also found a reduction in heart failure admissions and cardiovascular events in this population.

As a result of the CREDENCE study, the manufacturer of canagliflozin was granted a change in their product's approved indications. In addition to the indication to improve glycemic control in patients with type 2 diabetes, the agent as of the fall of 2019 is now also indicated to reduce the risk of end stage kidney disease, doubling of serum creatinine, cardiovascular death, and admissions for heart failure in patients with both type 2 diabetes and existing kidney disease and albuminuria. This is the first new indication for a drug to reduce the risk for diabetic kidney disease in nearly two decades. Whether the benefits seen with the use of canagliflozin in the CREDENCE study can be applied to the other three agents in this class is yet to be determined. Until such time that the renal benefits are convincingly a class effect, canagliflozin should be considered the best option within the class. An ongoing study evaluating dapagliflozin's effects on the progression of chronic kidney disease is expected to be completed in late 2020. Empagliflozin's effects on renal outcomes is also being evaluated but the study with this agent is not expected to conclude until the middle of 2022.

Recent changes in national guidelines have also occurred as a result of the newer renal outcomes trial data. Previous ADA recommendations stated to consider either a SGLT2 inhibitor or GLP1 agonist shown to reduce the risk of progression of chronic kidney disease in patients with type 2 diabetes and chronic kidney disease. [58,59]. This recommendation is primarily based on the composite renal outcome data from the CVOT studies in both classes. The 2020 ADA Standards of Medical Care in Diabetes now recommend the use of SGLT2 inhibitors to reduce the risk of chronic kidney disease progression , cardiovascular events, or both in patients with type 2 diabetes and kidney disease in patients with eGFRs at least 30 ml/min/1.73m^2 and some degree of albuminuria, especially those with UACR greater than 300 mg/g [4]. They recommend a GLP1 agonist in patients with chronic kidney disease to reduce the risk of albuminuria progression, cardiovascular events, or both in patients at an increased risk for cardiovascular events but the recommendation is not as strong as the one for use of SGLT2 inhibitors. The 2020 executive summary by the American Association of Clinical Endocrinologists and American College of Endocrinology are less specific on class of agent stating either class should be considered, regardless of glycemic control, in those with established or high cardiovascular risk and/or CKD [60].

Thus it appears we are entering a new era in attempting to curb the progression of CKD in patients with diabetes, one that has been too long in coming. In addition to obtaining optimal blood pressure control with agents known to affect the RAS and optimizing glycemic control, clinicians should consider adding a SGLT2 inhibitor in patients with type 2 diabetes and chronic kidney disease as long as the eGFR is greater than 30 ml/min/1.73 m^2. An early reduction in eGFR should be expected with the use of this class of agent but data with the use of canagliflozin in this patient population suggests the decrease in eGFR over time is slower than that in subjects receiving placebo and should not be a deterrent in their use as the benefits appear to outweigh the risks in the long run. The use of DPP4 inhibitors in such patients is not likely to provide more than a reduction in albuminuria. The same can be expected with the use of GLP1 agonists in high-risk patients but this class may provide some degree of cardiovascular benefit in such patients [60]. Specifically how these agents work to minimize renal outcomes may not be fully understood. With appropriate use of these agents, in particular SGLT2 inhibitors, in the right patient population, the clinical burden to patients and the economic burden to society of diabetic chronic kidney disease could likely be lessened. Perhaps future cost-effectiveness will shed light on the latter. It is unknown if any class of agent reviewed above could have an effect on robust renal outcomes in patients with type 1 diabetes or in patients with CKD without diabetes. It is also unknown if these agents would slow progression of diabetic kidney disease in those with moderate loss of kidney function but in the absence of albuminuria, a patient population often undertreated [61].

References

1. Palsson R, Patel U. Cardiovascular complications of diabetic kidney disease

Adv Chronic Kidney Dis 2014; 21: 273-80.

2. Afkarian M, Sachs M, Kestenbaum B, Hirsch I, Tuttle K, Himmelfarb J, et al. Kidney disease and increased mortality risk in type 2 diabetes J Am Soc Nephrol. 2013; 24: 302-8.

3. Alicic R, Rooney M, Tuttle K. Diabetic kidney disease-challenges, progress, and possibilities Clin J Am Soc Nephrol .2017; 12: 2032-45.

4. American Diabetes Association. Microvascular complications and foot care. Standards of medical care in diabetes. Diabetes Care. 2020; 43: 135-51.

5. United States Renal Data Sheet. US Renal data system 2019 annual data report. epidemiology of kidney disease in the United States Am J Kidney Dis. 2020; 75: 1-64.

6. American Diabetes Association. Diabetic nephropathy Diabetes Care. 2020; 23: 69-72.

7. Murphy D, Drawz P, Foley R. Trends in angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker use among those with impaired kidney function in the United States. JASN 2019; 30: 1314-21.

8. Zoungas S, deGalan B, Ninomiva T, Grobbee D, Hamet P, Heller S, et al. Combined Effects of Routine Blood Pressure Lowering and Intensive Glucose Control on Macrovascular and Microvascular Outcomes in Patients with Type 2 Diabetes. Diabetes Care. 2009; 32: 2068-74.

9. Harashima SI, Ogura M, Tanaka D, Fukushima T, Wang Y, Koizumi T, et al. Sitagliptin add-on to low dosage sulphonylureas: efficacy and safety of combination therapy on glycaemic control and insulin secretion capacity in type 2 diabetes. Int J Clin Pract. 2012; 66: 465-76.

10. Sakata K, Hayakawa M, Yano Y, Tamaki N, Yokota N, Eto T, et al. Efficacy of alogliptin, a dipeptidyl peptidase-4 inhibitor, on glucose parameters, the activigy of the Advanced Glycation End product (AGE) Receptor for AGE (RAGE) axis and albuminuria in Japanese type 2 diabetes. Diabetes Metab Res Rev. 2013; 29: 624-30.

11. Groop PH, Cooper ME, Perkovic V, Emser A, Woerle JJ, Von Eynatten M. Linagliptin lowers albuminuria on top of recommended standard treatment in patients with type 2 diabetes and renal dysfunction. Diabetes Care. 2013; 36: 3460-8.

12. Groop PH, Cooper ME, Perkovic V, Hocher B, Kanasaki K, Haneda M, et al. Linagliptin and its effects on hyperglycemia and albuminuria in patients with type 2 diabetes and renal dysfunction.the randomized MARLINA-T2D trial. Diabetes Obes Metab. 2017; 19: 1610-19.

13. Hirshberg B, Parker A, Edelberg H, Donovan M, Iqbal N. Safety of saxagliptin. events of special interest in 9156 patients with type 2 diabetes mellitus. Diabetes Metab Res Rev 2014; 30: 556-69.

14. Green J, Bethel A, Armstrong PW, Buse JB, Engel S, Garg J, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015; 373: 232-42.

15. Engel SS, Suryawanshi S, Stevens SR, Josse RG, Cornel J, Jakuboniene N, et al. Safety of sitagliptin in patients with type 2 diabetes and chronic kidney disease. outcomes from TECOS. Diabetes Obes Metab. 2017; 19: 1587-93.

16. Mosenzon O, Leibowitz G, Bhatt DL, Cahn A, Hirshberg B, Wi C, et al. Effect of saxagliptin on renal outcomes in the SAVOR-TIMI 53 trial. Diabetes Care. 2017; 40: 69-76.

17. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal R, Bakris G, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013; 369: 1327-35.

18. Rosenstock J, Perkovic V, Johansen O, Cooper M, Kahn S, Marx N, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk-The CARMELINA randomized clinical trial JAMA . 2019; 321: 69-79.

19. Tonneijck L, Smits M, Muskiet M, Hoekstra T, Kramer M, Danser A, et al. Renal effects of DPP-4 inhibitor sitagliptin or GLP-1 receptor agonist liraglutide in overweight patients with type 2 diabetes. a 12-week, randomized, double-blind, placebo-controlled trial. Diabetes Care. 2016; 39: 2042-50.

20. Zhang H, Zhang X, Hu C, Lu W. Exenatide reduces urinary transforming growth factor-β1 and Type IV collagen excretion in patients with type 2 diabetes and microalbuminuria. Kidney Blood Press Res 2012; 35: 483-8.

21. Zavattaro M, Caputo M, Sama M, Mele C, Chasseur L, Marzullo, et al. One-year treatment with liraglutide improved renal function in patients with type 2 diabetes: a pilot prospective study. Endocrine. 2015; 50: 620-6.

22. Davies M, Bain S, Atkin S, Rossing P, Scott D, Shamkhalova M, et al. Efficacy and safety of liraglutide versus placebo as ad-on to glucose-lowering therapy in patients with type 2 diabetes and moderate renal impairment (LIRA-RENAL). a randomized clinical trial. Diabetes Care. 2016; 39: 222-30.

23. Mosenzon O, Blicher T, Rosenlund S, Eriksson J, Heller S, Hels O, et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment. a placebo-controlled randomized, phase 3a trial. Lancet Diabetes Endocrinol. 2019; 7: 515-27.

24. Tuttle K, Lakshmanan M, Rayner B, Busch R, Zimmermann A, Woodward D, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney diseasea multicenter, open-label, randomized trial. Lancet Diabetes Endocrinol. 2018; 6: 605-17.

25. Pfeffer M, Claggett B, Diaz R, Dickstein K, Gerstein H, Kober L, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med. 2015; 373: 2247-57.

26. Husain M, Birkenfeld A, Donsmark M, Dungan K, Eliaschewitz F, Franco D, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019; 381: 841-51.

27. Muskiet M, Tonneijck L, Huang Y, Liu M, Saremi A, Heerspink H, et al. Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: an exploratory analysis of the ELIA randomized, placebo-controlled trial. Lancet Diabetes Endocrinol. 2018; 6: 859-69.

28. Mann J, Orsted D, Brown-Frandsen K, Marso S, Poulter N, Rasmussen S, et al. Liraglutide and renal outcomes in type 2 diabetes. N Engl J Med. 2017; 377: 839-48.

29. Marso S, Bain S, Consoli A, Eliaschewitz F, Jodar E, Leiter L, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes N Engl J Med. 2016; 375: 1834-44.

30. Gerstein H, Colhoun H, Dagenais G, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and renal outcomes in type 2 diabetes. an exploratory analysis of the REWIND randomized, placebo-controlled trial. Lancet. 2019; 394: 131-8.

31. Holman R, Bethel M, Mentz R, Thompson V, Lokhnyhina Y, Buse J, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017; 377: 1228-39.

32. Bethel M, Mentz R, Merrill P, Buse J, Chan J, Goodman S, et al. Microvascular and cardiovascular outcomes according to renal function in patients treated with once-weekly exenatide: insights from the EXSCEL trial. Diabetes Care. 2020; 43: 446-52.

33. Kristensen S, Rorth R, Jhund P, Docherty K, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes. a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol. 2019; 7: 776-85.

34. Yale J, NBakris G, Cariou B, Yue D, David-Neto E, Xi L, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes, Obesity, and Metabolism. 2013; 15: 463-73.

35. Heerspink H, Desai M, Jardine M, Balis D, Meininger G, Perkovic V. Canagliflozin slows progression of renal function decline independently of glycemic effects. J Am Soc Nephrol. 2017; 28: 368-75.

36. Barnett A, Mithal A, Manassie J, Jones R, Rattunde H, Woerle H, et al. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2014; 7: 369-84.

37. Cherney D, Lund S, Perkins B, Groop P, . Cooper M, Kaspers S, et al. The effect of sodium glucose cotransporter 2 inhibition with empagliflozin on microalbuminuria and macroalbuminuria in patients with type 2 diabetes. Diabetologia. 2016; 59: 1860-70.

38. Cherney D, Heerspink H, Frederich R. Two-year effects of ertugliflozin on renal function. Presented at. American Diabetes Association 79th Scientific Sessions San Francisco CA. 2019; 42: 1921-29.

39. Fioretto P, Stefansson B, Johnsson E, Cain V, Sjostrom C. Dapagliflozin reduces albuminuria over 2 years in patients with type 2 diabetes mellitus and renal impairment Diabetologia. 2016; 59: 2036-39.

40. Wanner C, Inzucchi S, Lachin J, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and progression of kidney disease in type 2 diabetes N Engl J Med. 2016; 375: 323-34.

41. Neal B, Perkovic V, Mahaffey K, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes N Engl J Med. 2017; 377: 644-657.

42. Perkovic V, De Zeeuw D, Mahaffey K, Fulcher G, Erondu N, Shaw W, et al. Canagliflozin and renal outcomes in type 2 diabetes. results from the CANVAS Program randomised clinical trials Lancet Diabetes Endocrinol. 2018; 6: 691-704.

43. Mosenzon O, Wiviott S, Cahn A, Rozenberg A, Yanuv I, Goodrich E, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes an analysis from the DECLARE-TIMI 58 randomised trial Lancet Diabetes Endocrinol. 2019; 7: 606-17.

44. Zelniker T, Wiviott S, Raz I, Im K, Goodrich E, Bonaca M, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019; 393: 31-39.

45. Perkovic V, Jardine M, Bompoint S, Bompoint S, Heerspink H, Charytan D, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019; 380: 2295-306.

46. Neal B, Perkovic V, Mahaffey K, de Zeeuw D, Fulcher G, erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017; 377: 644-57.

47. Neuen B, Young T, Heerspink H, Neal B, Perkovic V, Billot L, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes.a systematic review and meta-analysis Lancet Diabetes Endocrinol. 2019; 7: 845-54.

48. Nagahisa T, Saisho Y. Cardiorenal protection: potential of SGLT2 inhibitors and GLP-1 receptor agonists in the treatment of type 2 diabetes. Diabetes. 2019; 10: 1733-1752.

49. Thomas M. The potential and pitfalls of GLP-1 receptor agonists for renal protection in type 2 diabetes. Diabetes & Metabolism. 2017; 42: 20-7.

50. Nincevic V, Kolaric T, Roguljic H, Kizivat T, Smolic M, Curcic I. Renal benefits of SGLT2 inhibitors and GLP-1 receptor agonists. Evidence supporting a paradigm shift in the medical management of type 2 diabetes. Int J Mol Sci. 2019; 20: 5831-51.

51. Muskiet M, Tonneijck L, Smits M, Van Baar M, Kramer M, Hoorn E, et al. GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes. Nat Rev Nephrol. 2017; 13: 60528.

52. Greco E, Russo G, Giadalia A, Viazzi F, Pontremoli R, De Cosmo S. GLP-1 receptor agonists and kidney function. Medicina. 2019; 55: 223-37.

53. Heerspink H, Perkins B, Fitchett D, Husain M, Cherney D. Sodium Glucose Cotransporter 2 inhibitors in the treatment of diabetes mellitus. Cardiovascular and kidney effects, potential mechanisms and clinical applications. Circulation.2016; 134: 752-72.

54. Cherney DZ, Odutayo A, DPhil A, Aronson R, Ezekowitz J, Parker J. Sodium Glucose Cotransporter-2 inhibition and cardiorenal protection. J Am Coll Cardiol. 2019; 74: 2511-24.

55. Heerspink H, Kosiborod M, Inzucchi S, Cherney D. Renoprotective effects of sodium-glucose cotransporter-2 inhibitors. Kidney International. 2018; 94: 26-39.

56. James M, Grams M, Woodward M, Elley C, Green J, Wheeler D, et al. A meta-analysis of the association of estimated GFR, albuminuria, diabetes mellitus, and hypertension with acute kidney injury. Am J Kidney Dis. 2015; 66: 602-12.

57. Parving H, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med. 2001; 345: 870-8.

58. American Diabetes Association. Microvascular complications and foot care. Standards of medical care in diabetes – 2019. Diabetes Care. 2019; 42: 124-38.

59. American Diabetes Association. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Diabetes Care. 2020; 43: 487-93.

60. Garber A, Handelsman Y, Grunberger G, Einhorn D, Abrahamson Barzilay J, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm-2020 executive summary. Endocrine Practice. 2020; 26: 107-39.

61. Vistisen D, Andersen G, Hulman A, Persson F, Rossing P, Jorgensen M. Progressive decline in estimated glomerular filtration rate in patients with diabetes after moderate loss in kidney function- even without albuminuria Diabetes Care. 2019; 42: 1886-94.