World Journal of

Diabetes

World Journal of *Diabetes*

Contents

Contents

ORIGINAL ARTICLE

Basic Study

Observational Study

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Diabetes*, Fernando Cordido, MD, PhD, Full Professor, Department of Medicine, University A Coruña, A Coruña 15006, Spain. Cordido.Carballido@sergas.es

AIMS AND SCOPE

The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

 WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

INDEXING/ABSTRACTING

The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor (IF) for *WJD* as 3.247; IF without journal self cites: 3.222; Ranking: 70 among 143 journals in endocrinology and metabolism; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yu-Jie Ma*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jia-Ping Yan.*

Recent advances in new-onset diabetes mellitus after kidney transplantation

Tess Montada-Atin, G V Ramesh Prasad

Tess Montada-Atin, G V Ramesh Prasad, Kidney Transplant Program, St. Michael's Hospital, Toronto M5C 2T2, Ontario, Canada

G V Ramesh Prasad, Department of Medicine, University of Toronto, Toronto M5C 2T2, Canada

Corresponding author: G V Ramesh Prasad, MBBS, PhD, Professor, Kidney Transplant Program, St. Michael's Hospital, 61 Queen Street East, 9th Floor, Toronto M5C 2T2, Ontario, Canada. ramesh.prasad@unityhealth.to

Abstract

A common challenge in managing kidney transplant recipients (KTR) is post-transplant diabetes mellitus (PTDM) or diabetes mellitus (DM) newly diagnosed after transplantation, in addition to known pre-existing DM. PTDM is an important risk factor for post-transplant cardiovascular (CV) disease, which adversely affects patient survival and quality of life. CV disease in KTR may manifest as ischemic heart disease, heart failure, and/or left ventricular hypertrophy. Available therapies for PTDM include most agents currently used to treat type 2 diabetes. More recently, the use of sodium glucose co-transporter 2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1 RA), and dipeptidyl peptidase 4 inhibitors (DPP4i) has cautiously extended to KTR with PTDM, even though KTR are typically excluded from large general population clinical trials. Initial evidence from observational studies seems to indicate that SGLT2i, GLP-1 RA, and DPP4i may be safe and effective for glycemic control in KTR, but their benefit in reducing CV events in this otherwise high-risk population remains unproven. These newer drugs must still be used with care due to the increased propensity of KTR for intravascular volume depletion and acute kidney injury due to diarrhea and their single-kidney status, pre-existing burden of peripheral vascular disease, urinary tract infections due to immunosuppression and a surgically altered urinary tract, erythrocytosis from calcineurin inhibitors, and reduced kidney function from acute or chronic rejection.

Key Words: Cardiovascular disease; Glucagon-like peptide-1 receptor agonists; Kidney transplantation; Oral antihyperglycemic drugs; Post-transplant diabetes mellitus; Sodium glucose co-transporter 2 inhibitors; Dipeptidyl peptidase-4 inhibitors

Core Tip: Kidney transplant recipients commonly develop post-transplant diabetes mellitus. Sodium glucose co-transporter 2 inhibitors, glucagon-like peptide-1 receptor agonists, and dipeptidyl peptidase 4 inhibitors are now available for treating type 2 diabetes mellitus. There is increasing evidence that these classes of drugs are effective in kidney transplant recipients, but caution is still advised due to their increased propensity otherwise for intravascular volume depletion, infections, and reduced kidney function.

INTRODUCTION

Kidney transplantation (KT) is the renal replacement therapy of choice in patients with end-stage kidney disease (ESKD), improving quality of life and reducing mortality risk compared to dialysis[1]. However, an adverse effect of KT is post-transplant diabetes mellitus (PTDM). PTDM adversely affects patient survival and quality of life[2,3], leading to greater risk of graft loss, rejection, and infection, as well as diabetes-associated microvascular and macrovascular complications[4]. Graft failure for example is 50% higher in kidney transplant recipients (KTR) with diabetes than without diabetes, and recurrent diabetic kidney disease occurs in almost half of kidney allografts[5,6]. About one-third of nondiabetic KTR develop persistently impaired glucose metabolism by 6 mo post-transplantation[7-9]. Risk factors for PTDM include older recipient age, deceased donor graft, the use of calcineurin inhibitors (CNI) and corticosteroids, and adult polycystic kidney disease, in addition to traditional risks factors for type 2 diabetes (T2DM).

PTDM describes newly diagnosed T2DM after organ transplantation, regardless of timing or undetected pre-transplant presence, and is applied to clinically stable patients with persistent post-transplantation hyperglycemia[10]. Therefore, PTDM is often formally diagnosed at least 45 d post-transplant due to the high prevalence of early post-transplant hyperglycemia. The term PTDM now excludes known pre-existing diabetes mellitus (DM). Common measures to combat PTDM include early treatment with insulin, lifestyle interventions such as diet and exercise, bariatric surgery, and modified immunosuppression such as CNI and steroid avoidance. Since treatment approaches to pre-existing T2DM and PTDM do not significantly differ, the discussion of PTDM is taken throughout this review to encompass pre-existing DM.

Comprehensive reviews of PTDM have been published[11]. More recently, sodium glucose co-transporter 2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1 RA), and dipeptidyl peptidase 4 inhibitors (DPP4i) are becoming increasingly available for managing T2DM. This update reviews the role of these newer agents in managing PTDM.

Current management of PTDM

At the 2013 international consensus meeting on PTDM, committee members were unable to endorse a hierarchical approach to using antihyperglycemic agents for managing PTDM. Suggestions included altering the immunosuppressive regimen and starting antihyperglycemic agents on an individualized basis[10]. CNI and steroid doses are often reduced, dietary counseling provided, and oral agents started. Despite the plethora of pharmacotherapy options for treating T2DM and by extension PTDM, there is paucity of evidence on the efficacy and safety of SGLT2i, GLP-1 RA, and DPP4i in KTR. In addition to healthy behavior interventions, metformin remains first line therapy in T2DM-associated chronic kidney disease (CKD) as well as PTDM[12-14]. Most recently, the Kidney Disease: Improving Global Outcomes (KDIGO) 2020 guidelines recommend metformin plus SGLT2i as first-line, followed by any other antihyperglycemic agent with GLP-1 RA being preferred as second line[15]. However, the safety and efficacy of SGLT2i when estimated glomerular filtration rate (eGFR) is < 30 mL/min per 1.73 m² in KTR is limited, but further studies will clarify their kidney and cardiovascular (CV) benefits[15].

Connecting PTDM to the cardiorenal syndrome

Managing PTDM connects to managing other facets of the cardiorenal syndrome, and as will be discussed in subsequent sections, can involve using SGLT2i, GLP-1 RA, and DPP4i. CV disease (CVD) leads causes of death in KTR, accounting for 30% of all deaths with a functioning graft[16,17]. KTR also carry a burden of other CV risk factors including hypertension, dyslipidemia, and obesity, all exacerbated by immuno-suppressive medications[18]. KTR risk higher mortality than their age-matched counterparts without kidney disease[19]. This mortality risk is almost two-fold greater in PTDM[20]. For KTR with pre-existing diabetes, the risk of CVD and stroke increases threefold compared to non-diabetic recipients[21].

The most common CVD in KTR is ischemic heart disease (IHD), congestive heart failure (CHF) and left ventricular hypertrophy (LVH). IHD contributes over 50% to mortality in KTR[21]. CHF occurs 2-5 times more in KTR than the general population[22], reaching almost 20% by 3 years post-KT[23]. DM can cause heart failure (HF) independently of IHD *via* a diabetic cardiomyopathy with either preserved or reduced ejection fraction (HFpEF, HFrEF). HF is 2- to 4-fold more prevalent in DM and occurs earlier[24]. Diabetic nephropathy influences drug dosing in HF, resulting in treatment adjustments and failure to attain therapeutic targets. Risk factors for new-onset HF post-KT include DM[22,23,25]. LVH, a risk factor for sudden cardiac death in KTR, occurs in 50%-70% of this population. In non-KTR with T2DM, large CV and renal outcome trials of SGLT2i and GLP-1 RA have shown that these medications are safe, improve glycemia, and carry CV and renal benefits[26].

SGLT2I

SGLT2i act selectively on the sodium-glucose 2 cotransporter in the proximal tubule of the nephron that reabsorbs approximately 90% of filtered glucose, to effectively prevent its reuptake and promote its urinary excretion to reduce blood levels. Glycosuria results whenever filtered glucose exceeds the maximum absorption rate by SGLT2 co-transporters. SGLT2i reduce hemoglobin A1c (HbA1c) by 0.5%-0.7% in an insulin-independent manner with minimal risk of hypoglycemia, leading to weight loss[26]. SGLT2i cause an osmotic diuretic and natriuretic effect that leads to plasma volume contraction, in turn decreasing systolic and diastolic blood pressure (BP) by 4-6 and 1-2 mmHg, respectively[27]. Since filtered glucose load depends on blood glucose, SGLT2i achieve their greatest blood glucose reduction during hyperglycemia. Glucose-lowering efficacy declines from reduced glycosuria as GFR declines. SGLT2i-induced natriuresis leads to increased sodium delivery to the macula densa, and tubular glomerular feedback results in afferent arteriolar vasoconstriction, with reduced intraglomerular hypertension, GFR and albuminuria. Natriuresis-related reductions in BP and possibly renoprotection persist even with reduced kidney function[28]. It should be remembered that KTR still have CKD; the eGFR is often 50 mL/min per 1.73 m² or less, and CKD associates with CVD. Therefore, the hypothesis that SGLT2i reduce CV risk in KTR is worth exploring.

SGLT2i are available both individually and combined with metformin and DPP4i. Sotagliflozin is a dual SGLT2/1i for treating both T2DM and T1DM. Sotagliflozin also inhibits intestinal SGLT2, delaying glucose absorption and post prandial glucose rise[29].

Adverse effects of SGLT2i

SGLT2i cause mycotic genital or yeast infections, often with candida species, in about 9%-18% of women with half this rate in men[30-32]. Urinary tract infections (UTI) are less common. Euglycemic diabetic ketoacidosis (DKA), while rare, occurs in the context of insulin deficiency, sudden reductions in insulin dose, or increased dose requirements from illness, surgery or alcohol abuse[12]. The incidence of DKA was increased with dapagliflozin[33], while increased lower limb amputations were seen with canagliflozin[32]. However, a meta-analysis of randomized clinical trials (RCT) found no class effect-based increased risk for amputation[34]. Volume depletion may worsen perfusion of an already dysfunctional vascular network, but this hypothesis remains unproven[35]. Fracture risk may be higher with canaglifozin but this risk was unconfirmed by meta-analysis[36]. SGLT2i may also affect bone metabolism and density[37].

SGLT2i and CV protection

SGLT2i reduce 3-point major adverse CV events [MACE: Death from CV causes, non-fatal myocardial infarction (MI) or non-fatal stroke], all-cause mortality and HF hospitalizations in the general population in varying combinations[31-33]. SGLT2i significantly reduced MACE in those with established CVD[38]. Potential beneficial mechanisms include naturietic diuresis, reduced inflammation, and increased hematocrit from erythropoietin production with enhanced myocardial tissue oxygen delivery[39].

Several trials specifically examined HF as a primary outcome[38,40-42]. Many patients did not have T2DM, and SGLT2i reduced CV death and HF hospitalization or progression regardless of diabetes status[43,44]. Patients with HFrEF of < 40% showed a significantly lower CV death or HF hospitalization again regardless of T2DM status[44], and a slower eGFR decline in T2DM[45]. With T2DM and recent worsening HF there was lower CV mortality and HF hospitalization.

LVH has not been studied to the same extent as CV mortality and HF. However, a substudy of the EMPA-HEART (Effects of Empagliflozin on Cardiac Structure in Patients With Type 2 Diabetes) CardioLink-6 RCT showed that empagliflozin was associated with significant reduction in LV mass index, possibly from increased red cell mass and improved myocardial tissue oxygen delivery[46].

SGLT2i and kidney protection

Empagliflozin was associated with slower CKD progression, reduced albuminuria progression, and reduced ESKD or death and maintenance[45]. The CANVAS trial using canagliflozin showed a reduced eGFR decline and reduced albuminuria in T2DM[47], while CREDENCE demonstrated both reduced kidney failure and CV events in T2DM[48]. The DAPA-CKD trial of dapagliflozin in CKD with or without T2DM demonstrated a lower composite of sustained decline in eGFR by 50%, ESKD, or death from renal or CV causes[49]. A systematic review and meta-analysis of data from EMPA-REG, CANVAS, CREDENCE, and DECLARE TIMI 58 found that SGLT2i reduced risk of dialysis, acute kidney injury (AKI), and death due to kidney disease in patients with T2DM eGFR levels down to 30 mL/min per 1.73 m^2[50].

A pre-specified meta- analysis of trials involving empagliflozin and dapagliflozin on hospitalisations for HF were consistent, suggesting that they improve renal outcomes, all-cause and CV death in patients with HFrEF[51]. Another meta-analysis showed that SGLT2i improved CV and kidney outcomes, regardless of T2DM, HF, and/or CKD status, with the greatest benefit for HF-related hospitalization and CKD progression[52].

SGLT2i use in KTR with PTDM

KTR are typically excluded from large clinical trials, including registration trials. The safety and efficacy of SGLT2i in non-KT patients with T2DM is now well-established, and so has led to attempts to extend the study of SGLT2i to KTR. A recent systematic review and meta-analysis of 8 studies in 132 KTR showed that SGLT2i were effective in lowering HbA1C and body weight, and preserved kidney function with no serious adverse events such as euglycemic ketoacidosis or acute rejection[53]. Fourteen patients had a UTI, one patient had a myocotic gential infection, one AKI, and one cellulitis. Another recent review concluded that SGLT2i are safe, along with GLP-1 RA and DPP4i, but are not as efficacious as in non-diabetic non-KTR[54].

A small RCT using empagliflozin in 22 KTR (versus 22 placebo) showed that the magnitude of HbA1c reduction depended on eGFR and baseline HbA1c, with no significant difference in adverse events, immunosuppressive drug levels, or eGFR[55]. A pilot study to replace insulin with empagliflozin in 14 stable KTR resulted in weight loss, but also significant drop-out and increased HbA1c, necessitating the reinstitution of insulin therapy in some[56]. SGLT2i were not as efficacious in KTR compared to other diabetic groups, perhaps from lower eGFR and the vasoconstrictive effect of CNI. A case series of 10 KTR demonstrated that the median HbA1c decreased from 7.3% to 7.1%[57]. An uncontrolled study of canagliflozin in 24 KTR, 23 of who were male, showed reduced body weight, BP, HbA1c, and need for other hypoglycemic agents. There were also no hypoglycemic episodes[58]. Other small series have reported similar findings[59]. Another experience using canagliflozin of 10 patients that also included 4 simultaneous pancreas-KT recipients showed that the magnitude of improvements in glycemic control, weight, and BP are similar to nontransplant patients[60]. A search of the Cochrane Kidney and Transplant Register of Studies reported that SGLT2i probably do not affect kidney graft survival compared to placebo, but may improve glycemic control without causing hypoglycemia and

affecting eGFR long-term[61].

Erythrocytosis has been noted with SGLT2i[62]. A well-described adverse event seen in KTR is post-transplant erythrocytosis[63]. Increased erythropoietin production is seen with SGLT2i and may be beneficial in the general population, but whether this is a positive effect in KTR is unknown. Posttransplant erythrocytosis (PTE) occurs in 8%-15% of KTR and affects patients with well-preserved graft function, commonly 8-24 mo post-KT[64]. PTE can cause malaise, headache, lethargy, dizziness, thromboembolic events, and a 1%-2% mortality. Endogenous erythropoietin may play a central role in PTE with a defect in normal feedback regulation, and persistent erythropoietin secretion from native kidneys. PTE is generally treated with angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and occasionally phlebotomy[64,65]. A randomized study of empagliflozin for 6 mo in non-KT patients suggested that hematocrit increase is at least partly the result of increased erythropoietin and stimulated erythropoiesis rather than hemoconcentration, based on changes in red blood cell (RBC) morphology, reduced ferritin or iron stores, differential time course of response, and reduced RBC hemoglobin concentration[46]. This safety concern regarding erythrocytosis particularly needs evaluation in KTR.

Dose adjustments of SGLT2i in CKD are recommended (Table 1). Since glucose-mediated hyperfiltration and high blood sugar levels combine to increase glucose filtration[66], the glucose-lowering effects of SGLT2i are decreased at an eGFR < 60 mL/min and almost absent with eGFR < 30 mL/min.

KDIGO guidelines do not currently recommend using SGLT2i in KTR[15]. When used, however, proper patient education is key in reducing the risk of SGLT2i-related complications. Patients should be counseled on sick day management that includes temporarily stopping SGLT2i during periods of illness with vomiting, diarrhea or other states that risk dehydration or intravascular volume depletion. as well as around planned surgical procedures. These illnesses are common early after KT. The eGFR is in a state of flux, with frequent change in kidney function from acute rejection, infections, and CNI-induced vasoconstriction. CNI dose adjustments are frequent. Transplant renal artery stenosis may occur from edema at the anastomotic site, and there is often surgical manipulation of the urinary tract, including stent removal. KTR may also have a pre-existing burden of peripheral vascular disease or recurrent UTI. Peripheral arterial disease may be worsened due to the anastomosis of the kidney allograft to the external iliac artery, further reducing lower extremity arterial perfusion. Peri-transplant ischemic CV events may occur, further affecting effective circulating volume. Post-KT hyperglycemia also commonly improves with routine corticosteroid dose reduction in the first few months after KT, and so new antihyperglycemic medication introduction is often delayed. Diuretics are commonly prescribed early after KT for volume expanded states, especially if heart function is reduced or there is significant peripheral edema. Some patients experience difficulty in unlearning the salt-restricted diet imposed by dialysis. SGLT2 inhibition is natriuretic[66] and may theoretically potentiate the natriuretic action of prescribed diuretics.

In summary, despite the prevalence of meticulously studied endpoints in large clinical trials in the general population, as well as small clinical trials and observational studies in KTR, it remains unclear if the cardiorenal benefits associated with SGLT2i in the general population (with or without DM) will more generally translate to PTDM. There is also presently no reason to use SGLT2i in non-diabetic KTR. Nonetheless, SGLT2i appear to be well-tolerated, but should preferably be avoided in the early post-surgical phase of KT.

GLP-1 RA

The incretin system has become an essential target for managing T2DM. Incretins are hormones produced by the intestinal mucosa in response to oral food intake, and enhance insulin while suppressing glucagon secretion in a glucose dependent manner to lower blood glucose[67-70]. Thus, incretins reduce insulin release when glucose levels are near-normal. Incretin hormones include glucose-dependent insulinotropic polypeptide (GIP) and GLP-1. GLP-1 also slows gastric emptying and increases satiety, leading in-turn to weight loss. Insulin secretion is greater in response to oral than intravenous glucose intake, the so-called "the incretin effect", but this effect decreases in T2DM[70]. The GLP-1 effect declines with impaired insulin secretion, insulin resistance, and hyperglycemia, all leading to decrease in GLP-1 receptor expression and increased GLP-1 resistance[70-72]. GLP-1 RA are eliminated by proteolytic degradation and glomerular filtration, so their metabolism does not involve CYP- or

Table 1 Newer antihyperglycemic agents and chronic kidney disease

CKD stage	1	2	3a	3b	4	5
eGFR (mL/min per 1.73 m^2)	≥ 90	60-89	45-59	30-44	15-29	≤ 15
SGLT2 inhibitors						
Canagliflozin (Invokana)	300 mg OD	Dose adjustment not required	Reduce dose to 100 mg OD if < 60 mL/min	Reduce dose to 100 mg OD in previously treated patients with albuminuria > 33.9 mg/mol. Do not initiate if < 30 mL/min		
Dapagliflozin (Forxiga)	10 mg OD	Dose adjustment not required		Not recommended	Contraindicated	
Empagliflozin (Jardiance)	25 mg OD	Dose adjustment not required			Contraindicated	
Ertugliflozin (Steglatro)	15 mg OD	Dose adjustment not required	Not recommended for initiation of therapy. Discontinue if persistently < 45 mL/min		Contraindicated	
Sotogliflozin (Zynquista)	400 mg OD	Dose adjustment not required	Not recommended for initiation of therapy. Discontinue if persistently < 45 mL/min		Contraindicated; safety not established	
GLP-1R agonists						
Dulaglutide (Trulicity)	1.5 mg weekly	Dose adjustment not required				Caution as safety not established
Exenatide (Byetta)	10 μg BID	Dose adjustment not required	Caution if 30-50 ml/min		Not recommended due to risk of accumulation	
Liraglutide (Victoza)	1.8 mg OD	Dose adjustment not required				Safety not established
Lixisenatide (Adlyxine)	20 μg OD	Dose adjustment not required			Safety not established	
Semaglutide (Ozempic)	1 mg weekly	Dose adjustment not required			Limited experience	Not recommended
Semaglutide (Rybelsus)	14 mg OD	Dose adjustment not required			Limited experience	Not recommended
DPP4 inhibitors						
Alogliptin (Nesina)	25 mg OD	Dose adjustment not required	Reduce dose to 12.5 mg		Reduce dose to 6.25 mg	
Linagliptin (Trajenta)	5 mg OD	Dose adjustment not required				Limited experience
Saxagliptin (Onglyza)	5 mg OD	Dose adjustment not required	Reduce dose to 2.5 mg if < 50 mL/min			Not recommended
Sitagliptin (Januvia)	100 mg OD	Dose adjustment not required	Reduce dose to 50 mg if < 50 mL/min		Reduce dose to 25 mg	
Vildaglitin (Galvus)	50 mg BID	Dose adjustment not required	Reduce dose to 50 mg OD if < 50 mL/min			

CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; SGLT2: Sodium glucose co-transporter 2; GLP-1R: Glucagon-like peptide-1 receptor; DPP4: Dipeptidyl peptidase 4.

transported-mediated drug-drug interactions. GLP-1 RA are incretin mimetics.

Hypoglycemia may occur if GLP-1 RA is given concomitantly with an insulin secretagogue. Most GLP-1 RA are administered subcutaneously, but there is one oral GLP-1 RA available (Table 1). Common adverse effects include nausea, vomiting, diarrhea, and injection-site reactions. GLP-1 RA are contraindicated for patients with a history of medullary thyroid cancer, multiple endocrine neoplasia 2, or pancreatitis. Oral intake must be adequate for GLP-1 RA to be given.

GLP-1 RA, CV, and kidney protection
GLP-1 RA studies were generally conducted in individuals with established atherosclerotic CVD. Except lixisenatide[72], all current GLP-1 RA are associated with a reduction in risk of MACE in patients with T2DM and established CVD. Lixisenatide, liraglutide, and dulaglutide all demonstrated CV safety[72-75].

The LEADER trial using liraglutide that included individuals with eGFR 15-30 mL/min per 1.73 m², demonstrated a greater benefit to MACE reduction with eGFR < 60 mL/min[73]. Liraglutide added to standard care resulted in lower new-onset and slower progression of diabetic CKD, driven primarily by persistent macroalbuminuria, with a similar rate of renal adverse events including AKI to placebo. The REWIND trial using dulaglutide showed, besides reduced MACE, a reduction in new severely increased albuminuria, sustained eGFR decline of 30% from baseline, or renal replacement therapy[76]. The AWARD 7 trial of once-weekly dulaglutide in moderate-to-severe CKD produced glycaemic control similar to insulin, with reduced eGFR decline[77]. SUSTAIN 6 CVOT using weekly semaglutide also demonstrated safety and significantly reduced MACE in posthoc analysis for superiority[78]. A systematic review and meta-analysis showed that GLP-1 RA are cardioprotective across many population subgroups, and reduce HF hospitalization and all-cause mortality[79]. In summary therefore, besides CVD risk reduction with GLP-1 RA, there is also risk reduction in new-onset albuminuria, eGFR decline, and progression to ESKD or kidney death.

GLP-1 RA use in KTR with PTDM

GLP-1 RA are recommended by most guidelines as second line as an alternate to an SGLT2i after metformin in managing T2DM especially with CVD, CV risk factors, or CKD. Small case series using GLP-1 RA in KTR do exist, showing no serious adverse effects or immunosuppressive drug interactions[80]. However, the evidence for use in KTR remains very limited. A review of the Cochrane Kidney and Transplant Register found no randomized, quasi-RCT and cross-over studies examining the effects of GLP-1 RA on safety and efficacy for treating pre-existing and new onset diabetes in KTR[61].

The rationale for using GLP-1 RA in KTR is that incretin therapies are able to counterbalance the interference of immunosuppressive drugs on insulin secretion. Corticosteroids are commonly used in anti-rejection regimens for KTR along with CNI (tacrolimus and cyclosporine), all of which affect glucose metabolism by decreasing glucose utilization and enhancing hepatic gluconeogenesis. Corticosteroids also directly decrease insulin secretion and increase insulin resistance. CNI impair α-cell and β-cell function and the incretin effect. The mechanism of action of GLP-1 RA may be ideal in this situation due to their insulinotropic, glucagonostatic and glucose-lowering effects that directly target defects linked to immunosuppressive-induced hyperglycemia[81], although drug interactions such as CNI resulting in increased drug exposure remain a concern[82]. Weight loss is another benefit of GLP-1 RA since weight gain is a common consequence of both hyperglycemia and KT more generally, making GLP-1 RA especially appealing for PTDM.

A study examining the role of hyperglucagonemia in PTDM, and the insulinotropic and glucagonostatic effects of GLP-1 during fasting and hyperglycemic states, concluded that PTDM is characterized by reduced glucose-induced insulin secretion and attenuated glucagon suppression. Moreover, similar to T2DM, GLP-1 infusion reduced glucagon concentration and increased first- and second-phase insulin secretion[82]. A major concern of GLP-1 RA in KTR is delayed gastric emptying, potentially affecting absorption of co-administered narrow therapeutic index medications such as CNI[83]. Although GLP-1 RA are not metabolized by the liver or involved in cytochrome or transporter mediated drug-drug interaction, there may be a delay in drug concentration, but it appears drug exposure may not be affected. Thus GLP-1 RA are theoretically safe, but close monitoring of tacrolimus and cyclosporine concentrations and potential side effects is required. A case series on safety of coadministration of liraglutide and tacrolimus found that tacrolimus AUC_{0-12h} reduced but trough levels were not affected[80], and there was no evidence of acute rejection.

A chart review of KTR who received liraglutide for glycemic control showed significant improvement in A1C, FBS, eGFR and body weight with minimal side effects[84]. Another retrospective study that included 7 KTR with PTDM receiving GLP-1 RA for 12 mo found no significant changes in tacrolimus concentration or kidney function[85]. A large experience of 63 KTR with PTDM using dulaglutide found sustained reduction in body mass index and insulin requirement for up to 24 mo, without increased risk of cancer, CV events, graft-failure, or all-cause mortality. Gastrointestinal side effects were infrequent and there was no requirement for change in immunosuppressive therapy[86]. A recent study however did not demonstrate weight loss, but did show reduced total daily insulin dose and a low risk of hypoglycemia with no adverse effect on kidney allograft outcomes[87].

DPP4I

DPP4i, otherwise known as gliptins, prevent the inactivation of GLP-1 and GIP. They are once daily drugs with the exception of vildagliptin[88]. Higher levels of endogenous GLP-1 enhance incretin action including glucose-dependent insulin secretion. They slow gastric emptying, increase satiety, and reduce postprandial glucagon secretion. DPP4i are generally well tolerated, have a low risk for hypoglycemia, and are weight neutral, but can cause acute pancreatitis[88].

DPP4i, CV, and kidney protection

All major CV trials of DPP4i including linagliptin[89], sitagliptin[90], saxagliptin[91], and alogliptin[92] revealed non-inferiority compared to placebo for the risk of major events. Non-inferiority was also evident when linagliptin was compared to glimepiride[93]. However, in the SAVOR-TIMI 53 trial, saxaliptin was associated with an increased risk of hospitalization for HF in patients with elevated N-terminal pro B-type natriuretic peptide levels, a history of HF, or CKD with eGFR < 60 mL/min[94]. Linaglipitin and saxagliptin reduce the risk for albuminuria progression, or even improve albuminuria, regardless of baseline eGFR[95,96]. This benefit was not demonstrated with sitagliptin[97]. The KDIGO 2020 guidelines highlight the role of DPP4i in T2DM and CKD. Therefore, while DPP4i may be useful adjuncts to control blood glucose and favorably affect albuminuria at best, their effect on CVD outcomes and CKD progression remains uncertain.

DPP4i use in KTR with PTDM

Most diabetes practice guidelines such as those of Diabetes Canada and KDIGO recommend DPP4i as add-on therapy for patients without CVD in whom glycemic targets are not achieved, especially if a lower risk of hypoglycemia and/or weight gain are priorities. A systematic review and meta-analysis of 5 studies in KTR with PTDM found that DPP4i improved glycemic control compared to either placebo or other oral anti-hyperglycemic agents, but did not significantly affect eGFR or tacrolimus concentration[98]. A meta-analysis including eight DPP4i studies showed both efficacy and safety[99]. A search of the Cochrane Kidney and Transplant Register[61] described the evidence concerning DPP4i as being of low to very low certainty. A study of 65 KTR demonstrated increased cyclosporine concentrations with sitagliptin but not linagliptin[100].

CONCLUSION

Safety data for SGLT2i, GLP-1 RA, and DPP4i are reassuring, and the CV and kidney risk reduction benefits are certainly substantial for SGLT2i and GLP-1 RA in non-KTR with T2DM. GLP-1 RA do not share benefits similar to SGLT2i with respect to preventing HF. GLP-1 RA are a potential treatment option for PTDM to help offset the increased CV risk associated with KT. Incretin therapy uniquely counteracts the interference of immunosuppressants on insulin secretion. DPP4i are useful for glycemic control. The first priority in managing KTR is achieving glycemic control; any CV and kidney benefits should be considered incidental at this time.

More RCT are needed to support using all three drugs in KTR. The UTI risk with SGLT2i may be especially concerning for KTR. With a single kidney, volume sensitivity may theoretically risk AKI, and so sick day management education is critical. SGLT2i, GLP-1 RA, and DPP4i may eventually prove to be ideal choices for both glycemic control and cardiorenal protection in KTR, but the evidence in KTR for now remains limited. The risk of intravascular volume depletion, brought on by the use of diuretics, renal artery stenosis, and diarrhea due to mycophenolic acid may compound the concern for AKI. Sick day management of other drugs is already prescribed to KTR. Dialysis patients also need to unlearn their salt restricted diet. Other potential concerns in KTR include worsening post-transplant osteoporosis, with most bone loss occurring early after KT. KTR may also carry a burden of peripheral vascular disease, occasionally worsened by the anastomosis of the kidney allograft to the external iliac arterial system. The hemoglobin should be monitored. These special considerations are described in Table 2. However, there is no reason that any of the newer antihyperglycemic drugs cannot be used in KTR as long as patients are carefully monitored. The early studies involving KTR are all generally favorable.

Table 2 Special considerations in prescribing newer antihyperglycemic agents to kidney transplant recipients

Clinical evidence	Largely observational
Kidney function	Reduced glomerular filtration rate
	Fluctuating glomerular filtration rate
	Post-transplant diuresis
Surgically altered urinary tract	Urinary tract infections
Graft arterial anastomosis	Peripheral vascular disease
Immunosuppression	Fluctuating glucose control
	Interaction with calcineurin inhibitors
	Urinary tract infections
Gastrointestinal upset	Intravascular volume depletion
	Dehydration
Others	Post-transplant erythrocytosis

In summary, initial evidence seems to indicate that newer antihyperglycemic agents can be used in KTR. It may be preferable to avoid these drugs in the first 6 mo after KT due to the increased frequency of infections typically seen from enhanced immunosuppression coupled with an anatomically altered urinary tract, as well as susceptibility to intravascular volume depletion and the volume sensitivity of a solitary kidney. These drugs should not be considered first-line agents, but can be prescribed cautiously in the context of poor glycemic control after other suitable measures specific to KTR have already been undertaken.

REFERENCES

1   **Wolfe RA**, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, Held PJ, Port FK. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999; **341**: 1725-1730 [PMID: 10580071 DOI: 10.1056/NEJM199912023412303]

2   **Miles AM**, Sumrani N, Horowitz R, Homel P, Maursky V, Markell MS, Distant DA, Hong JH, Sommer BG, Friedman EA. Diabetes mellitus after renal transplantation: as deleterious as non-transplant-associated diabetes? *Transplantation* 1998; **65**: 380-384 [PMID: 9484755 DOI: 10.1097/00007890-199802150-00014]

3   **Jindal RM**, Hjelmesaeth J. Impact and management of posttransplant diabetes mellitus. *Transplantation* 2000; **70**: SS58-SS63 [PMID: 11152233]

4   **Davidson J**, Wilkinson A, Dantal J, Dotta F, Haller H, Hernández D, Kasiske BL, Kiberd B, Krentz A, Legendre C, Marchetti P, Markell M, van der Woude FJ, Wheeler DC; International Expert Panel. New-onset diabetes after transplantation: 2003 International consensus guidelines. Proceedings of an international expert panel meeting. Barcelona, Spain, 19 February 2003. *Transplantation* 2003; **75**: SS3-S24 [PMID: 12775942 DOI: 10.1097/01.TP.0000069952.49242.3E]

5   **Taber DJ**, Meadows HB, Pilch NA, Chavin KD, Baliga PK, Egede LE. Pre-existing diabetes significantly increases the risk of graft failure and mortality following renal transplantation. *Clin Transplant* 2013; **27**: 274-282 [PMID: 23383719 DOI: 10.1111/ctr.12080]

6   **Ponticelli C**, Moroni G, Glassock RJ. Recurrence of secondary glomerular disease after renal transplantation. *Clin J Am Soc Nephrol* 2011; **6**: 1214-1221 [PMID: 21493742 DOI: 10.2215/CJN.09381010]

7   **Valderhaug TG**, Jenssen T, Hartmann A, Midtvedt K, Holdaas H, Reisaeter AV, Hjelmesaeth J. Fasting plasma glucose and glycosylated hemoglobin in the screening for diabetes mellitus after renal transplantation. *Transplantation* 2009; **88**: 429-434 [PMID: 19667949 DOI: 10.1097/TP.0b013e3181af1f53]

8   **David-Neto E**, Lemos FC, Fadel LM, Agena F, Sato MY, Coccuza C, Pereira LM, de Castro MC, Lando VS, Nahas WC, Ianhez LE. The dynamics of glucose metabolism under calcineurin inhibitors in the first year after renal transplantation in nonobese patients. *Transplantation* 2007; **84**: 50-55 [PMID: 17627237 DOI: 10.1097/01.tp.0000267647.03550.22]

9   **Porrini E**, Moreno JM, Osuna A, Benitez R, Lampreabe I, Diaz JM, Silva I, Domínguez R, Gonzalez-Cotorruelo J, Bayes B, Lauzurica R, Ibernon M, Moreso F, Delgado P, Torres A. Prediabetes in patients receiving tacrolimus in the first year after kidney transplantation: a prospective and multicenter study. *Transplantation* 2008; **85**: 1133-1138 [PMID: 18431233 DOI:

10.1097/TP.0b013e31816b16bd]

10   **Sharif A**, Hecking M, de Vries AP, Porrini E, Hornum M, Rasoul-Rockenschaub S, Berlakovich G, Krebs M, Kautzky-Willer A, Schernthaner G, Marchetti P, Pacini G, Ojo A, Takahara S, Larsen JL, Budde K, Eller K, Pascual J, Jardine A, Bakker SJ, Valderhaug TG, Jenssen TG, Cohney S, Säemann MD. Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. *Am J Transplant* 2014; **14**: 1992-2000 [PMID: 25307034 DOI: 10.1111/ajt.12850]

11   **Palepu S**, Prasad GV. New-onset diabetes mellitus after kidney transplantation: Current status and future directions. *World J Diabetes* 2015; **6**: 445-455 [PMID: 25897355 DOI: 10.4239/wjd.v6.i3.445]

12   **Diabetes Canada Clinical Practice Guidelines Expert Committee**, Lipscombe L, Butalia S, Dasgupta K, Eurich DT, MacCallum L, Shah BR, Simpson S, Senior PA. Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update. *Can J Diabetes* 2020; **44**: 575-591 [PMID: 32972640 DOI: 10.1016/j.jcjd.2020.08.001]

13   **American Diabetes Association**. 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes-2020*. *Diabetes Care* 2020; **43**: S98-S110 [PMID: 31862752 DOI: 10.2337/dc20-S009]

14   **Cosentino F**, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Jüni P, Lettino M, Marx N, Mellbin LG, Östgren CJ, Rocca B, Roffi M, Sattar N, Seferović PM, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020; **41**: 255-323 [PMID: 31497854 DOI: 10.1093/eurheartj/ehz486]

15   **Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group**. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int* 2020; **98**: S1-S115 [PMID: 32998798 DOI: 10.1016/j.kint.2020.06.019]

16   **Saran R**, Li Y, Robinson B, Ayanian J, Balkrishnan R, Bragg-Gresham J, Chen JT, Cope E, Gipson D, He K, Herman W, Heung M, Hirth RA, Jacobsen SS, Kalantar-Zadeh K, Kovesdy CP, Leichtman AB, Lu Y, Molnar MZ, Morgenstern H, Nallamothu B, O'Hare AM, Pisoni R, Plattner B, Port FK, Rao P, Rhee CM, Schaubel DE, Selewski DT, Shahinian V, Sim JJ, Song P, Streja E, Kurella Tamura M, Tentori F, Eggers PW, Agodoa LY, Abbott KC. US Renal Data System 2014 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis* 2015; **66**: Svii, S1-305 [PMID: 26111994 DOI: 10.1053/j.ajkd.2015.05.001]

17   **Lam NN**, Kim SJ, Knoll GA, McArthur E, Lentine KL, Naylor KL, Li AH, Shariff SZ, Ribic CM, Garg AX. The Risk of Cardiovascular Disease Is Not Increasing Over Time Despite Aging and Higher Comorbidity Burden of Kidney Transplant Recipients. *Transplantation* 2017; **101**: 588-596 [PMID: 26985745 DOI: 10.1097/TP.0000000000001155]

18   **Devine PA**, Courtney AE, Maxwell AP. Cardiovascular risk in renal transplant recipients. *J Nephrol* 2019; **32**: 389-399 [PMID: 30406606 DOI: 10.1007/s40620-018-0549-4]

19   **Foster BJ**, Mitsnefes MM, Dahhou M, Zhang X, Laskin BL. Changes in Excess Mortality from End Stage Renal Disease in the United States from 1995 to 2013. *Clin J Am Soc Nephrol* 2018; **13**: 91-99 [PMID: 29242373 DOI: 10.2215/CJN.04330417]

20   **Ojo AO**, Hanson JA, Wolfe RA, Leichtman AB, Agodoa LY, Port FK. Long-term survival in renal transplant recipients with graft function. *Kidney Int* 2000; **57**: 307-313 [PMID: 10620213 DOI: 10.1046/j.1523-1755.2000.00816.x]

21   **Kasiske BL**, Guijarro C, Massy ZA, Wiederkehr MR, Ma JZ. Cardiovascular disease after renal transplantation. *J Am Soc Nephrol* 1996; **7**: 158-165 [PMID: 8808124]

22   **Rigatto C**, Parfrey P, Foley R, Negrijn C, Tribula C, Jeffery J. Congestive heart failure in renal transplant recipients: risk factors, outcomes, and relationship with ischemic heart disease. *J Am Soc Nephrol* 2002; **13**: 1084-1090 [PMID: 11912270]

23   **Lentine KL**, Schnitzler MA, Abbott KC, Li L, Burroughs TE, Irish W, Brennan DC. De novo congestive heart failure after kidney transplantation: a common condition with poor prognostic implications. *Am J Kidney Dis* 2005; **46**: 720-733 [PMID: 16183428 DOI: 10.1053/j.ajkd.2005.06.019]

24   **Kenny HC**, Abel ED. Heart Failure in Type 2 Diabetes Mellitus. *Circ Res* 2019; **124**: 121-141 [PMID: 30605420 DOI: 10.1161/CIRCRESAHA.118.311371]

25   **Lentine KL**, Rocca-Rey LA, Bacchi G, Wasi N, Schmitz L, Salvalaggio PR, Abbott KC, Schnitzler MA, Neri L, Brennan DC. Obesity and cardiac risk after kidney transplantation: experience at one center and comprehensive literature review. *Transplantation* 2008; **86**: 303-312 [PMID: 18645495 DOI: 10.1097/TP.0b013e31817ef0f9]

26   **North EJ**, Newman JD. Review of cardiovascular outcomes trials of sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists. *Curr Opin Cardiol* 2019; **34**: 687-692 [PMID: 31436559 DOI: 10.1097/HCO.0000000000000673]

27   **Heerspink HJ**, 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**: 368-375 [PMID: 27539604 DOI: 10.1681/ASN.2016030278]

28   **Cherney DZI**, Cooper ME, Tikkanen I, Pfarr E, Johansen OE, Woerle HJ, Broedl UC, Lund SS. Pooled analysis of Phase III trials indicate contrasting influences of renal function on blood pressure, body weight, and HbA1c reductions with empagliflozin. *Kidney Int* 2018; **93**: 231-244 [PMID:

28860019 DOI: 10.1016/j.kint.2017.06.017]

29   **Cefalo CMA**, Cinti F, Moffa S, Impronta F, Sorice GP, Mezza T, Pontecorvi A, Giaccari A. Sotagliflozin, the first dual SGLT inhibitor: current outlook and perspectives. *Cardiovasc Diabetol* 2019; **18**: 20 [PMID: 30819210 DOI: 10.1186/s12933-019-0828-y]

30   **Zelniker TA**, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine MS. 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 [PMID: 30424892 DOI: 10.1016/S0140-6736(18)32590-X]

31   **Zinman B**, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015; **373**: 2117-2128 [PMID: 26378978 DOI: 10.1056/NEJMoa1504720]

32   **Neal B**, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 2017; **377**: 644-657 [PMID: 28605608 DOI: 10.1056/NEJMoa1611925]

33   **Wiviott SD**, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS; DECLARE–TIMI 58 Investigators. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2019; **380**: 347-357 [PMID: 30415602 DOI: 10.1056/NEJMoa1812389]

34   **Li D**, Yang JY, Wang T, Shen S, Tang H. Risks of diabetic foot syndrome and amputation associated with sodium glucose co-transporter 2 inhibitors: A Meta-analysis of Randomized Controlled Trials. *Diabetes Metab* 2018; **44**: 410-414 [PMID: 29506779 DOI: 10.1016/j.diabet.2018.02.001]

35   **Katsiki N**, Dimitriadis G, Hahalis G, Papanas N, Tentolouris N, Triposkiadis F, Tsimihodimos V, Tsioufis C, Mikhailidis DP, Mantzoros C. Sodium-glucose co-transporter-2 inhibitors (SGLT2i) use and risk of amputation: an expert panel overview of the evidence. *Metabolism* 2019; **96**: 92-100 [PMID: 30980838 DOI: 10.1016/j.metabol.2019.04.008]

36   **Azharuddin M**, Adil M, Ghosh P, Sharma M. Sodium-glucose cotransporter 2 inhibitors and fracture risk in patients with type 2 diabetes mellitus: A systematic literature review and Bayesian network meta-analysis of randomized controlled trials. *Diabetes Res Clin Pract* 2018; **146**: 180-190 [PMID: 30389620 DOI: 10.1016/j.diabres.2018.10.019]

37   **Meier C**, Schwartz AV, Egger A, Lecka-Czernik B. Effects of diabetes drugs on the skeleton. *Bone* 2016; **82**: 93-100 [PMID: 25913633 DOI: 10.1016/j.bone.2015.04.026]

38   **Packer M**, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F; EMPEROR-Reduced Trial Investigators. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med* 2020; **383**: 1413-1424 [PMID: 32865377 DOI: 10.1056/NEJMoa2022190]

39   **Lopaschuk GD**, Verma S. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: A State-of-the-Art Review. *JACC Basic Transl Sci* 2020; **5**: 632-644 [PMID: 32613148 DOI: 10.1016/j.jacbts.2020.02.004]

40   **McMurray JJV**, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde AM; DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2019; **381**: 1995-2008 [PMID: 31535829 DOI: 10.1056/NEJMoa1911303]

41   **Bhatt DL**, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Voors AA, Metra M, Lund LH, Komajda M, Testani JM, Wilcox CS, Ponikowski P, Lopes RD, Verma S, Lapuerta P, Pitt B; SOLOIST-WHF Trial Investigators. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *N Engl J Med* 2021; **384**: 117-128 [PMID: 33200892 DOI: 10.1056/NEJMoa2030183]

42   **Butler J**, Zannad F, Filippatos G, Anker SD, Packer M. Totality of evidence in trials of sodium-glucose co-transporter-2 inhibitors in the patients with heart failure with reduced ejection fraction: implications for clinical practice. *Eur Heart J* 2020; **41**: 3398-3401 [PMID: 32935133 DOI: 10.1093/eurheartj/ehaa731]

43   **Nassif ME**, Windsor SL, Tang F, Khariton Y, Husain M, Inzucchi SE, McGuire DK, Pitt B, Scirica BM, Austin B, Drazner MH, Fong MW, Givertz MM, Gordon RA, Jermyn R, Katz SD, Lamba S, Lanfear DE, LaRue SJ, Lindenfeld J, Malone M, Margulies K, Mentz RJ, Mutharasan RK, Pursley M, Umpierrez G, Kosiborod M. Dapagliflozin Effects on Biomarkers, Symptoms, and Functional Status in Patients With Heart Failure With Reduced Ejection Fraction: The DEFINE-HF Trial. *Circulation* 2019; **140**: 1463-1476 [PMID: 31524498 DOI: 10.1161/CIRCULATIONAHA.119.042929]

44   **Packer M**. Lessons learned from the DAPA-HF trial concerning the mechanisms of benefit of SGLT2 inhibitors on heart failure events in the context of other large-scale trials nearing completion. *Cardiovasc Diabetol* 2019; **18**: 129 [PMID: 31585532 DOI: 10.1186/s12933-019-0938-6]

45   **Wanner C**, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, Johansen OE, Woerle HJ, Broedl UC, Zinman B; EMPA-REG OUTCOME Investigators. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med* 2016; **375**: 323-334 [PMID: 27299675 DOI: 10.1056/NEJMoa1515920]

46   **Mazer CD**, Hare GMT, Connelly PW, Gilbert RE, Shehata N, Quan A, Teoh H, Leiter LA, Zinman B, Jüni P, Zuo F, Mistry N, Thorpe KE, Goldenberg RM, Yan AT, Connelly KA, Verma S. Effect of Empagliflozin on Erythropoietin Levels, Iron Stores, and Red Blood Cell Morphology in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease. *Circulation* 2020; **141**: 704-707 [PMID: 31707794 DOI: 10.1161/CIRCULATIONAHA.119.044235]

47   **Perkovic V**, de Zeeuw D, Mahaffey KW, Fulcher G, Erondu N, Shaw W, Barrett TD, Weidner-Wells M, Deng H, Matthews DR, Neal B. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. *Lancet Diabetes Endocrinol* 2018; **6**: 691-704 [PMID: 29937267 DOI: 10.1016/S2213-8587(18)30141-4]

48   **Perkovic V**, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW; CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med* 2019; **380**: 2295-2306 [PMID: 30990260 DOI: 10.1056/NEJMoa1811744]

49   **Heerspink HJL**, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JFE, McMurray JJV, Lindberg M, Rossing P, Sjöström CD, Toto RD, Langkilde AM, Wheeler DC; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med* 2020; **383**: 1436-1446 [PMID: 32970396 DOI: 10.1056/NEJMoa2024816]

50   **Neuen BL**, Young T, Heerspink HJL, Neal B, Perkovic V, Billot L, Mahaffey KW, Charytan DM, Wheeler DC, Arnott C, Bompoint S, Levin A, Jardine MJ. 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**: 845-854 [PMID: 31495651 DOI: 10.1016/S2213-8587(19)30256-6]

51   **Zannad F**, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, Brueckmann M, Ofstad AP, Pfarr E, Jamal W, Packer M. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet* 2020; **396**: 819-829 [PMID: 32877652 DOI: 10.1016/S0140-6736(20)31824-9]

52   **Salah HM**, Al'Aref SJ, Khan MS, Al-Hawwas M, Vallurupalli S, Mehta JL, Mounsey JP, Greene SJ, McGuire DK, Lopes RD, Fudim M. Effect of sodium-glucose cotransporter 2 inhibitors on cardiovascular and kidney outcomes-Systematic review and meta-analysis of randomized placebo-controlled trials. *Am Heart J* 2021; **232**: 10-22 [PMID: 33214130 DOI: 10.1016/j.ahj.2020.10.064]

53   **Chewcharat A**, Prasitlumkum N, Thongprayoon C, Bathini T, Medaura J, Vallabhajosyula S, Cheungpasitporn W. Efficacy and Safety of SGLT-2 Inhibitors for Treatment of Diabetes Mellitus among Kidney Transplant Patients: A Systematic Review and Meta-Analysis. *Med Sci (Basel)* 2020; **8** [PMID: 33213078 DOI: 10.3390/medsci8040047]

54   **Anderson S**, Cotiguala L, Tischer S, Park JM, McMurry K. Review of Newer Antidiabetic Agents for Diabetes Management in Kidney Transplant Recipients. *Ann Pharmacother* 2021; **55**: 496-508 [PMID: 32795145 DOI: 10.1177/1060028020951955]

55   **Halden TAS**, Kvitne KE, Midtvedt K, Rajakumar L, Robertsen I, Brox J, Bollerslev J, Hartmann A, Åsberg A, Jenssen T. Efficacy and Safety of Empagliflozin in Renal Transplant Recipients With Posttransplant Diabetes Mellitus. *Diabetes Care* 2019; **42**: 1067-1074 [PMID: 30862658 DOI: 10.2337/dc19-0093]

56   **Schwaiger E**, Burghart L, Signorini L, Ristl R, Kopecky C, Tura A, Pacini G, Wrba T, Antlanger M, Schmaldienst S, Werzowa J, Säemann MD, Hecking M. Empagliflozin in posttransplantation diabetes mellitus: A prospective, interventional pilot study on glucose metabolism, fluid volume, and patient safety. *Am J Transplant* 2019; **19**: 907-919 [PMID: 30585690 DOI: 10.1111/ajt.15223]

57   **Mahling M**, Schork A, Nadalin S, Fritsche A, Heyne N, Guthoff M. Sodium-Glucose Cotransporter 2 (SGLT2) Inhibition in Kidney Transplant Recipients with Diabetes Mellitus. *Kidney Blood Press Res* 2019; **44**: 984-992 [PMID: 31437852 DOI: 10.1159/000501854]

58   **Shah M**, Virani Z, Rajput P, Shah B. Efficacy and Safety of Canagliflozin in Kidney Transplant Patients. *Indian J Nephrol* 2019; **29**: 278-281 [PMID: 31423063 DOI: 10.4103/ijn.IJN_2_18]

59   **AlKindi F**, Al-Omary HL, Hussain Q, Al Hakim M, Chaaban A, Boobes Y. Outcomes of SGLT2 Inhibitors Use in Diabetic Renal Transplant Patients. *Transplant Proc* 2020; **52**: 175-178 [PMID: 31924404 DOI: 10.1016/j.transproceed.2019.11.007]

60   **Rajasekeran H**, Kim SJ, Cardella CJ, Schiff J, Cattral M, Cherney DZI, Singh SKS. Use of Canagliflozin in Kidney Transplant Recipients for the Treatment of Type 2 Diabetes: A Case Series. *Diabetes Care* 2017; **40**: e75-e76 [PMID: 28416475 DOI: 10.2337/dc17-0237]

61   **Lo C**, Toyama T, Oshima M, Jun M, Chin KL, Hawley CM, Zoungas S. Glucose-lowering agents for treating pre-existing and new-onset diabetes in kidney transplant recipients. *Cochrane Database Syst Rev* 2020; **8**: CD009966 [PMID: 32803882 DOI: 10.1002/14651858.CD009966.pub3]

62   **Chin-Yee B**, Solh Z, Hsia C. Erythrocytosis induced by sodium-glucose cotransporter-2 inhibitors. *CMAJ* 2020; **192**: E1271 [PMID: 33077524 DOI: 10.1503/cmaj.76686]

63   **Vlahakos DV**, Marathias KP, Agroyannis B, Madias NE. Posttransplant erythrocytosis. *Kidney Int* 2003; **63**: 1187-1194 [PMID: 12631334 DOI: 10.1046/j.1523-1755.2003.00850.x]

64   **Vishnu P**, Moreno Vanegas Y, Wadei HM, Rivera CE. Post-transplant erythrocytosis refractory to ACE inhibitors and angiotensin receptor blockers. *BMJ Case Rep* 2018; **2018** [PMID: 29954763 DOI: 10.1136/bcr-2018-224622]

65   **Mithoowani S**, Laureano M, Crowther MA, Hillis CM. Investigation and management of erythrocytosis. *CMAJ* 2020; **192**: E913-E918 [PMID: 32778603 DOI: 10.1503/cmaj.191587]

66   **Thomas MC**, Cherney DZI. The actions of SGLT2 inhibitors on metabolism, renal function and blood pressure. *Diabetologia* 2018; **61**: 2098-2107 [PMID: 30132034 DOI: 10.1007/s00125-018-4669-0]

67   **Hinnen D**. Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes. *Diabetes Spectr* 2017; **30**: 202-210 [PMID: 28848315 DOI: 10.2337/ds16-0026]

68   **Trujillo JM**, Nuffer W, Ellis SL. GLP-1 receptor agonists: a review of head-to-head clinical studies. *Ther Adv Endocrinol Metab* 2015; **6**: 19-28 [PMID: 25678953 DOI: 10.1177/2042018814559725]

69   **Drucker DJ**, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006; **368**: 1696-1705 [PMID: 17098089 DOI: 10.1016/S0140-6736(06)69705-5]

70   **Nauck M**, Stöckmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia* 1986; **29**: 46-52 [PMID: 3514343 DOI: 10.1007/BF02427280]

71   **Calanna S**, Christensen M, Holst JJ, Laferrère B, Gluud LL, Vilsbøll T, Knop FK. Secretion of glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes: systematic review and meta-analysis of clinical studies. *Diabetes Care* 2013; **36**: 3346-3352 [PMID: 24065842 DOI: 10.2337/dc13-0465]

72   **Pfeffer MA**, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, Lawson FC, Ping L, Wei X, Lewis EF, Maggioni AP, McMurray JJ, Probstfield JL, Riddle MC, Solomon SD, Tardif JC; ELIXA Investigators. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med* 2015; **373**: 2247-2257 [PMID: 26630143 DOI: 10.1056/NEJMoa1509225]

73   **Marso SP**, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2016; **375**: 311-322 [PMID: 27295427 DOI: 10.1056/NEJMoa1603827]

74   **Mann JFE**, Ørsted DD, Brown-Frandsen K, Marso SP, Poulter NR, Rasmussen S, Tornøe K, Zinman B, Buse JB; LEADER Steering Committee and Investigators. Liraglutide and Renal Outcomes in Type 2 Diabetes. *N Engl J Med* 2017; **377**: 839-848 [PMID: 28854085 DOI: 10.1056/NEJMoa1616011]

75   **Gerstein HC**, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, Probstfield J, Riesmeyer JS, Riddle MC, Rydén L, Xavier D, Atisso CM, Dyal L, Hall S, Rao-Melacini P, Wong G, Avezum A, Basile J, Chung N, Conget I, Cushman WC, Franek E, Hancu N, Hanefeld M, Holt S, Jansky P, Keltai M, Lanas F, Leiter LA, Lopez-Jaramillo P, Cardona Munoz EG, Pirags V, Pogosova N, Raubenheimer PJ, Shaw JE, Sheu WH, Temelkova-Kurktschiev T; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019; **394**: 121-130 [PMID: 31189511 DOI: 10.1016/S0140-6736(19)31149-3]

76   **Gerstein HC**, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, Probstfield J, Botros FT, Riddle MC, Rydén L, Xavier D, Atisso CM, Dyal L, Hall S, Rao-Melacini P, Wong G, Avezum A, Basile J, Chung N, Conget I, Cushman WC, Franek E, Hancu N, Hanefeld M, Holt S, Jansky P, Keltai M, Lanas F, Leiter LA, Lopez-Jaramillo P, Cardona Munoz EG, Pirags V, Pogosova N, Raubenheimer PJ, Shaw JE, Sheu WH, Temelkova-Kurktschiev T; REWIND Investigators. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. *Lancet* 2019; **394**: 131-138 [PMID: 31189509 DOI: 10.1016/S0140-6736(19)31150-X]

77   **Tuttle KR**, Lakshmanan MC, Rayner B, Busch RS, Zimmermann AG, Woodward DB, Botros FT. Dulaglutide *vs* insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol* 2018; **6**: 605-617 [PMID: 29910024 DOI: 10.1016/S2213-8587(18)30104-9]

78   **Marso SP**, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T; SUSTAIN-6 Investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2016; **375**: 1834-1844 [PMID: 27633186 DOI: 10.1056/NEJMoa1607141]

79   **Kristensen SL**, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, Køber L, Petrie MC, McMurray JJV. 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**: 776-785 [PMID: 31422062 DOI: 10.1016/S2213-8587(19)30249-9]

80   **Pinelli NR**, Patel A, Salinitri FD. Coadministration of liraglutide with tacrolimus in kidney transplant recipients: a case series. *Diabetes Care* 2013; **36**: e171-e172 [PMID: 24065848 DOI: 10.2337/dc13-1066]

81   **Halden TA**, Egeland EJ, Åsberg A, Hartmann A, Midtvedt K, Khiabani HZ, Holst JJ, Knop FK,

Hornum M, Feldt-Rasmussen B, Jenssen T. GLP-1 Restores Altered Insulin and Glucagon Secretion in Posttransplantation Diabetes. *Diabetes Care* 2016; **39**: 617-624 [PMID: 26908914 DOI: 10.2337/dc15-2383]

82   **Vanhove T**, Remijsen Q, Kuypers D, Gillard P. Drug-drug interactions between immunosuppressants and antidiabetic drugs in the treatment of post-transplant diabetes mellitus. *Transplant Rev (Orlando)* 2017; **31**: 69-77 [PMID: 27665059 DOI: 10.1016/j.trre.2016.09.001]

83   **Tsai SF**, Chen CH. Management of Diabetes Mellitus in Normal Renal Function, Renal Dysfunction and Renal Transplant Recipients, Focusing on Glucagon-Like Peptide-1 Agonist: A Review Based upon Current Evidence. *Int J Mol Sci* 2019; **20** [PMID: 31261624 DOI: 10.3390/ijms20133152]

84   **Thangavelu T**, Lyden E, Shivaswamy V. A Retrospective Study of Glucagon-Like Peptide 1 Receptor Agonists for the Management of Diabetes After Transplantation. *Diabetes Ther* 2020; **11**: 987-994 [PMID: 32072430 DOI: 10.1007/s13300-020-00786-1]

85   **Liou JH**, Liu YM, Chen CH. Management of Diabetes Mellitus With Glucagonlike Peptide-1 Agonist Liraglutide in Renal Transplant Recipients: A Retrospective Study. *Transplant Proc* 2018; **50**: 2502-2505 [PMID: 30316386 DOI: 10.1016/j.transproceed.2018.03.087]

86   **Singh P**, Pesavento TE, Washburn K, Walsh D, Meng S. Largest single-centre experience of dulaglutide for management of diabetes mellitus in solid organ transplant recipients. *Diabetes Obes Metab* 2019; **21**: 1061-1065 [PMID: 30565376 DOI: 10.1111/dom.13619]

87   **Kukla A**, Hill J, Merzkani M, Bentall A, Lorenz EC, Park WD, D'Costa M, Kudva YC, Stegall MD, Shah P. The Use of GLP1R Agonists for the Treatment of Type 2 Diabetes in Kidney Transplant Recipients. *Transplant Direct* 2020; **6**: e524 [PMID: 32095510 DOI: 10.1097/TXD.0000000000000971]

88   **Makrilakis K**. The Role of DPP-4 Inhibitors in the Treatment Algorithm of Type 2 Diabetes Mellitus: When to Select, What to Expect. *Int J Environ Res Public Health* 2019; **16** [PMID: 31366085 DOI: 10.3390/ijerph16152720]

89   **Rosenstock J**, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, Alexander JH, Pencina M, Toto RD, Wanner C, Zinman B, Woerle HJ, Baanstra D, Pfarr E, Schnaidt S, Meinicke T, George JT, von Eynatten M, McGuire DK; CARMELINA Investigators. 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 [PMID: 30418475 DOI: 10.1001/jama.2018.18269]

90   **Green JB**, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F, Peterson ED, Holman RR; TECOS Study Group. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2015; **373**: 232-242 [PMID: 26052984 DOI: 10.1056/NEJMoa1501352]

91   **Scirica BM**, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013; **369**: 1317-1326 [PMID: 23992601 DOI: 10.1056/NEJMoa1307684]

92   **White WB**, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013; **369**: 1327-1335 [PMID: 23992602 DOI: 10.1056/NEJMoa1305889]

93   **Rosenstock J**, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, Pfarr E, Keller A, Mattheus M, Baanstra D, Meinicke T, George JT, von Eynatten M, McGuire DK, Marx N; CAROLINA Investigators. Effect of Linagliptin *vs* Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes: The CAROLINA Randomized Clinical Trial. *JAMA* 2019 [PMID: 31536101 DOI: 10.1001/jama.2019.13772]

94   **Scirica BM**, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, Udell JA, Mosenzon O, Im K, Umez-Eronini AA, Pollack PS, Hirshberg B, Frederich R, Lewis BS, McGuire DK, Davidson J, Steg PG, Bhatt DL; SAVOR-TIMI 53 Steering Committee and Investigators*. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. *Circulation* 2014; **130**: 1579-1588 [PMID: 25189213 DOI: 10.1161/CIRCULATIONAHA.114.010389]

95   **Perkovic V**, Toto R, Cooper ME, Mann JFE, Rosenstock J, McGuire DK, Kahn SE, Marx N, Alexander JH, Zinman B, Pfarr E, Schnaidt S, Meinicke T, von Eynatten M, George JT, Johansen OE, Wanner C; CARMELINA investigators. Effects of Linagliptin on Cardiovascular and Kidney Outcomes in People With Normal and Reduced Kidney Function: Secondary Analysis of the CARMELINA Randomized Trial. *Diabetes Care* 2020; **43**: 1803-1812 [PMID: 32444457 DOI: 10.2337/dc20-0279]

96   **Mosenzon O**, Leibowitz G, Bhatt DL, Cahn A, Hirshberg B, Wei C, Im K, Rozenberg A, Yanuv I, Stahre C, Ray KK, Iqbal N, Braunwald E, Scirica BM, Raz I. Effect of Saxagliptin on Renal Outcomes in the SAVOR-TIMI 53 Trial. *Diabetes Care* 2017; **40**: 69-76 [PMID: 27797925 DOI: 10.2337/dc16-0621]

97   **Cornel JH**, Bakris GL, Stevens SR, Alvarsson M, Bax WA, Chuang LM, Engel SS, Lopes RD, McGuire DK, Riefflin A, Rodbard HW, Sinay I, Tankova T, Wainstein J, Peterson ED, Holman RR; TECOS Study Group. Effect of Sitagliptin on Kidney Function and Respective Cardiovascular

Outcomes in Type 2 Diabetes: Outcomes From TECOS. *Diabetes Care* 2016; **39**: 2304-2310 [PMID: 27742728 DOI: 10.2337/dc16-1415]

98   **Abdelaziz TS**, Ali AY, Fatthy M. Efficacy and Safety of Dipeptidyl Peptidase-4 Inhibitors in Kidney Transplant Recipients with Post-transplant Diabetes Mellitus (PTDM)- a Systematic Review and Meta-Analysis. *Curr Diabetes Rev* 2020; **16**: 580-585 [PMID: 30907326 DOI: 10.2174/1573399815666190321144310]

99   **Oikonomaki D**, Dounousi E, Duni A, Roumeliotis S, Liakopoulos V. Incretin based therapies and SGLT-2 inhibitors in kidney transplant recipients with diabetes: A systematic review and meta-analysis. *Diabetes Res Clin Pract* 2021; **172**: 108604 [PMID: 33338553 DOI: 10.1016/j.diabres.2020.108604]

100   **Bae J**, Lee MJ, Choe EY, Jung CH, Wang HJ, Kim MS, Kim YS, Park JY, Kang ES. Effects of Dipeptidyl Peptidase-4 Inhibitors on Hyperglycemia and Blood Cyclosporine Levels in Renal Transplant Patients with Diabetes: A Pilot Study. *Endocrinol Metab (Seoul)* 2016; **31**: 161-167 [PMID: 26754588 DOI: 10.3803/EnM.2016.31.1.161]