Cardiometabolic and Kidney Protection in Kidney Transplant Recipients with Diabetes

Sridhar, Vikas S; Ambinathan, Jaya Prakash N; Gillard, Pieter; Mathieu, Chantal; Cherney, David Z I; Lytvyn, Yuliya; Singh, Sunita K

Published in:
Transplantation

DOI:
10.1097/TP.0000000000003919

Publication date:
2022

License:
Unspecified

Document Version:
Accepted author manuscript

Transplantation Publish Ahead of Print

DOI: 10.1097/TP.0000000000003919

Cardiometabolic and Kidney Protection in Kidney Transplant Recipients with Diabetes: Mechanisms, Clinical Applications, and Summary of Clinical Trials

Vikas S. Sridhar, MD,[1,2,3]* Jaya Prakash N. Ambinathan, MD,[1,2,3]* Pieter Gillard, MD, PhD,[4] Chantal Mathieu, MD, PhD,[4] David Z.I. Cherney, MD, PhD,[1,2] Yuliya Lytvyn, PhD,[1†] Sunita K. Singh, MD, MSc[1,2,3†]

[1] Division of Nephrology, Toronto General Hospital, University Health Network, Toronto, ON, Canada.

[2] Department of Medicine, University of Toronto, Toronto, ON, Canada.

[3] The Kidney Transplant Program and the Multi-Organ Transplant Program, Toronto General Hospital, University Health Network, Toronto, ON, Canada.

[4] Department of Endocrinology, University Hospitals Leuven, Catholic University Leuven, Leuven, Belgium.

* Co–first authors

† Co–senior authors

Funding The authors declare no funding was received for this review.

Disclosures J.P.N.A., P.G., Y.L., and S.K.S. have no conflicts of interest to declare. V.S.S. is supported by the Department of Medicine Eliot Phillipson Clinician Scientist Training Program and a Banting and Best Diabetes Centre Postdoctoral fellowship at the University of Toronto. C.M. serves or has served on the advisory panel for Novo Nordisk, Sanofi, Merck Sharpe, and Dohme Ltd., Eli Lilly and Company, Novartis, AstraZeneca, Boehringer Ingelheim, Hanmi Pharmaceuticals, Roche, Medtronic, Actobio Therapeutics, Pfizer, and UCB. Financial

compensation for these activities has been received by KU Leuven; KU Leuven has received research support for C.M. from Medtronic, Novo Nordisk, Sanofi, Merck Sharpe and Dohme ltd., Eli Lilly and Company, Novartis, Abbott, Roche, and Actobio Therapeutics; C.M. serves or has served on the speakers bureau for Novo Nordisk, Sanofi, Merck Sharpe and Dohme ltd., Eli Lilly and Company, AstraZeneca, Boehringer Ingelheim and Novartis. Financial compensation for these activities has been received by KU Leuven. D.Z.I.C. has received consulting fees or speaking honorarium or both from Janssen, Bayer, Boehringer Ingelheim-Eli, Lilly, AstraZeneca, Merck & Co Inc, Prometic and Sanofi, and has received operating funds from Janssen, Boehringer Ingelheim-Eli, Lilly, Sanofi, AstraZeneca and Merck & Co Inc. D.Z.I.C. is supported by a Department of Medicine, University of Toronto Merit Award and receives support from the CIHR, Diabetes Canada and the Heart and Stroke Richard Lewar Centre of Excellence.

Authorship

All authors participated in the literature review and the writing of the manuscript.

Correspondence: Sunita Singh, MD, MSc, FRCPC Toronto General Hospital 585 University Avenue, 11-PMB-176 Toronto, ON, Canada M5G 2N2 Office: 416-340-3240 Fax: 647-689-2738 E-mail: sunita.singh@uhn.ca

ABSTRACT

Kidney transplantation is the therapy of choice for patients with end-stage renal disease. Preexisting diabetes mellitus is highly prevalent in kidney transplant recipients (KTR), and the development of posttransplant diabetes mellitus is common due to a number of transplant-specific risk factors such as the use of diabetogenic immunosuppressive medications and posttransplant weight gain. The presence of pretransplant and posttransplant diabetes in KTR significantly and variably affect the risk of graft failure, cardiovascular disease (CVD) and death. Among the many available therapies for diabetes, there is little data to determine the glucose-lowering agent(s) of choice in KTR. Furthermore, despite the high burden of graft loss and CVD among KTR with diabetes, evidence for strategies offering cardiovascular and kidney protection is lacking. Recent accumulating evidence convincingly shows glucose-independent cardiorenal protective effects in non-KTR with glucose lowering agents, such as sodium glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists. Therefore, our aim is to review cardiorenal protective strategies, including the evidence, mechanisms and rationale for the use of these glucose lowering agents in KTR with diabetes mellitus.

INTRODUCTION

Diabetes mellitus (DM) is a significant comorbidity in kidney transplant recipients (KTR).[1] Approximately one quarter of KTR have preexisting DM as the cause of end-stage kidney disease (ESKD).[2] The incidence of posttransplantation diabetes mellitus (PTDM) in KTR varies from 2 to 53% [3,4] depending on the definition used, diagnostic method, testing frequency, transplant era, immunosuppression, and recipient risk profile.[5,6] The largest cohort studied was from a US registry where the cumulative incidence of PTDM in 11 659 KTR was 16% by 12 months and 24% by 36 months posttransplant.[7] In addition to traditional risk factors, transplant-specific factors such as the use of immunosuppression which can induce gene-level changes in insulin signaling, viral infections including hepatitis C and potentially cytomegalovirus (CMV), as well as hypomagnesemia contribute to development of DM in the kidney transplant recipient population.[8-10] Possibly due to increased awareness, changes in immunosuppression practices, rejection rates and/or changing testing patterns, the incidence of PTDM may be declining. Valderhaug and colleagues reported a significant decrease in the incidence of PTDM 10 weeks posttransplant from 20% to 13% in 2004-2005 compared to 1995-1996, accompanied by lower rates of impaired fasting glucose, mean daily oral prednisolone use and allograft rejection.[11]

Although evidence is conflicting regarding the acceleration of microvascular complications in the setting of PTDM,[12] preexisting DM and PTDM have been shown to increase the risk of cardiovascular events including heart failure (HF) in several observational studies.[13,14] Furthermore, DM also adversely affects kidney transplant outcomes such as graft failure, patient survival, and death with a functioning graft, highlighting the need for disease modifying therapies.[15-18] Pharmacological treatment for DM in KTR is influenced by several factors including kidney function and immunosuppression, with limited data on efficacy and safety, and few

comparative trials to guide therapeutic approaches. [3,19,20] In nontransplant patients with DM (and without DM), sodium glucose cotransporter-2 (SGLT2) inhibitors represent an important therapeutic advancement, with multiple trials demonstrating significant cardiovascular (CV) and/or kidney benefits.[21-28] Glucose-independent CV benefits have also been demonstrated with glucagon-like peptide-1 (GLP-1) receptor agonists.[29,30] These novel glycemic agents with glucose-independent cardiorenal effects have the potential to yield analogous benefits in KTR. In this review, we discuss the evidence surrounding cardiorenal protective strategies and the potential for glucose-lowering agents in modifying diabetes related outcomes in KTR (**Figure 1**).

CLINICAL OUTCOMES AND NATURAL HISTORY OF DIABETES IN KIDNEY TRANSPLANT RECIPIENTS

Diabetes in KTR is associated with several adverse outcomes. In a study by Kuo and colleagues of 37 000 KTR with a functioning transplant for more than a year, pretransplant DM but not PTDM was associated with a significantly increased risk of all-cause mortality and cardiovascular mortality, though with a median follow up of only 548 days.[31] Lim et al. conducted a population cohort study of over 10 000 KTR from Australia and New Zealand with a median follow up of 6.5 years which showed that all-cause mortality and death with a functioning graft was significantly higher in KTR with pretransplant DM as compared to KTR without DM, and recipients <40 years of age were at the highest risk of these adverse events.[32] In another registry study by Kasiske et al, an adjusted model showed that PTDM was associated with increased mortality in KTR, though this was not adjusted for acute rejection.[7] Several studies have also demonstrated that both PTDM and pretransplant diabetes in KTR are associated with significantly increased rates of CV events.[33,34] The link between diabetes and graft survival in KTR requires a closer look. In the previously mentioned study by Kuo et al, pretransplant DM was associated with

worse total graft survival. Similar findings were also noted by Cole and Dienemann, where PTDM was associated with an increased risk of death with a functioning graft, but not death-censored graft failure.[35,36]

It is important to acknowledge the potential regional differences in disease incidences and outcomes, as well as the importance of transplant era on clinical outcomes in KTR. Many large registry studies in KTR are conducted using US data and therefore, the results may not be generalizable to transplant populations in different parts of the world.[37] Furthermore, in some populations, transplant outcomes have changed over time. As an example, in an ANZDATA registry analysis of KTR in 2010, a significant fall in CV death rates from 1980 to 2007 was observed despite rising rates of DM as a cause of ESKD during this period.[38] A more recent cohort study of 23 000 KTR, which also used the ANZDATA registry, demonstrated reductions in death with a functioning graft over 40 years at both early and late time points posttransplant.[39] These geographical and chronological differences are important considerations when reviewing clinical outcome data in KTR.

The natural disease course of diabetic nephropathy (DN) involves glomerular hemodynamic changes including hyperfiltration and glomerular hypertension, followed by structural changes such as glomerular basement membrane thickening and mesangial expansion, eventually leading to clinical manifestations such as albuminuria and decreased kidney function. In this review diabetic kidney disease (DKD) is clinically defined by the presence of chronic kidney disease (CKD) and/or albuminuria in the presence of DM, with the recognition that DKD may or may not include DN.[40] The role of hyperfiltration injury in KTR with diabetes is unclear, particularly considering the vasoconstrictive effects of calcineurin inhibitors widely used for immunosuppression. In a multicenter cohort study of 202 KTR without diabetes classified as

normo-insulinemic or hyperinsulinemic, Porrini demonstrated increases in estimated glomerular filtration rates (eGFR) from 3 to 12 months among KTR with persistent hyperinsulinemia.[41] Hyperinsulinemia, accompanying metabolic syndrome and diabetes, may thus predispose to future graft dysfunction and hyperfiltration injury in KTR. Signs of hyperfiltration were not observed in a clinical and biopsy cohort study involving 953 KTR with and without pretransplant diabetes.[42] In this study involving serial protocol biopsies, the rate of mesangial expansion started to differ between KTR with and without diabetes as early as 2 years after transplantation. By 5 years, the cumulative incidence of mesangial expansion was 47.7% among KTR with diabetes and, surprisingly, 27.1% among those without. However, the pathological finding of mesangial expansion was not associated with eGFR at any posttransplant period and was only positively correlated with proteinuria at 24 and 36 months. In an abstract presented at the 2020 American Transplant Congress, mesangial expansion detected at 5 years posttransplant was most frequent in KTR with diabetes and obesity, and was highly correlated with mortality, but not death-censored graft loss.[43]

An important consideration when extrapolating the use of novel cardiorenal strategies to KTR is the outcome studied in the general population. In addition to hard outcomes like major adverse cardiac events (MACE) or the development of ESKD, kidney outcome trials in nontransplant populations also use defined percentage change in eGFR, eGFR slope, and/or albuminuria as part of primary composite outcomes or secondary outcomes. In a series of studies of KTR with and without diabetes, Lam et al demonstrated that lower eGFR and higher proteinuria are independently associated with death-censored graft loss, CV disease, and all-cause mortality.[44,45] Similarly, in a post hoc analysis of the FAVORIT trial involving diabetic and nondiabetic KTR, Weiner and colleagues demonstrated independent associations between

increased baseline albuminuria and graft failure, CV events, and all-cause mortality.[46] In this analysis, diabetes status was an effect modifier such that albuminuria conferred greater risk of graft failure or all-cause mortality among KTR without diabetes versus those with diabetes. With respect to the ability of a specified percentage change in eGFR to predict hard kidney outcomes in KTR, Clayton et al performed a survival analysis demonstrating that a ≥30% decline in eGFR was associated with a 2.2-fold increase in death, 3.5-fold increase in graft failure and 5-fold increase in death-censored graft failure.[47] Sensitivity analyses demonstrated consistent results when the cohort was stratified by diabetes status and cause of graft failure. It remains to be seen whether strategies proven to improve these outcome measures in the general population may be translated to KTR.

OVERVIEW OF CONSENSUS GUIDELINES FOR THE TREATMENT OF PTDM IN KIDNEY TRANSPLANT RECIPIENTS

The most recent consensus guideline on DM in the posttransplant setting was published in 2014 based on a meeting of experts in Vienna in 2013.[48] An important consensus emerging from this conference was the recognition that DM is often present in potential recipients but undetected prior to transplantation. This led to the recommendation to move away from the term 'new onset diabetes after transplantation', in favor of 'PTDM'. This guideline acknowledged the lack of high-quality evidence and inadequate data to recommend 1 glucose-lowering agent over another in KTR with PTDM.

The consensus guideline also recommended identifying patients at increased risk of PTDM prior to transplantation. This recommendation is also supported by the 2020 KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation, which suggests the use of oral glucose tolerance testing in kidney transplant candidates to inform

risk and management.[49] Although lifestyle modifications, glucose-lowering therapies and insulin are all included in the consensus guideline on DM in the posttransplant setting, a therapeutic hierarchy in PTDM is lacking. Insulin was recommended in the acute posttransplant setting due to its safety and efficacy with rapidly changing glucocorticoid dosing regimens and alterations in graft function. Immunosuppressive regimens associated with the best patient and graft outcomes continue to be suggested regardless of the risks related to the development of PTDM. With respect to glycemic control in KTR with DM, the 2009 KDIGO guidelines suggest an HbA1c target of 7.0-7.5% and avoidance of a HbA1c target <6.0% in an ungraded recommendation.[50]

General population guidelines on the management of DM have historically prioritized microvascular and macrovascular protection by targeting blood pressure control, renin angiotensin aldosterone system (RAAS) blockade, and treatment of dyslipidemia.[51] In the following section, we discuss the evidence surrounding the implementation of such strategies in KTR.

CURRENT CARDIORENAL PROTECTIVE STRATEGIES UTILIZED IN KTR

KTR face a three- to five-fold increased risk of CV disease compared to their age-matched counterparts.[52] In the US, CV disease remains the leading cause of death in KTR.[17] As discussed above, KTR with diabetes are disproportionately affected by CV disease. CV disease is often subclinical at the time of transplantation, and angiographic screening in pretransplant candidates remains controversial.[53] In some populations, cardiac mortality in KTR has decreased over time, but women continue to bear an excess relative risk of cardiac death.[54,55] Existing cardiorenal protective strategies in KTR revolve around the modification of CV risk factors. We highlight below 5 strategies in the management of posttransplant CV risk in KTR with and without DM – hypertension, RAAS blockade, dyslipidemia, antiplatelet and immunosuppression modification.

Hypertension

The prevalence of hypertension is estimated to be greater than 70% in KTR and is often suboptimally controlled.[56,57] Posttransplant hypertension is a well-established CV risk factor and is associated with an increased risk of graft failure and mortality.[56] The Collaborative Transplant Study was one of the earlier studies to demonstrate that systolic blood pressures (SBP) as low as 120 mmHg 1-year post transplant were associated with improved long term graft outcomes,[58] with a lower risk of CV mortality when SBP was maintained at <140 mmHg at 3 years posttransplant.[59] However, large clinical trials in KTR are lacking and BP targets in KTR are largely extrapolated from nontransplant populations. The most recent KDIGO guidelines for the care of KTRs suggest a BP target of <130/80 mmHg.[50,60]

Given the absence of specific guideline recommendations, the choice of antihypertensive agents is individualized and on the basis of clinical circumstances: diuretics with volume overload or hyperkalemia, RAAS blockade with proteinuria or posttransplant erythrocytosis, calcium channel blockers (CCB) with borderline allograft function or hypertension attributed to calcineurin inhibitors (CNI). The first Cochrane review on antihypertensive treatment for KTR included 60 studies with 3802 participants, primarily looking at CCBs and angiotensin converting enzyme inhibitor (ACEi) versus placebo or each other.[61] Compared to placebo, CCBs reduced graft loss and improved GFR. Based on 7 studies included in their meta-analysis comparing ACEi vs CCBs, ACEi decreased GFR, proteinuria, hemoglobin and increased hyperkalemia. Data were, however, inconclusive for graft loss. Acknowledging the presence of publication bias in the literature reviewed, authors of this systematic review suggested that CCBs could be considered as a first line agent in KTR, with the role of RAAS blockade in KTR remaining controversial due to lack of clear supportive data.

RAAS blockade

RAAS blockade is ubiquitous in CKD, largely driven by a series of randomized control trials (RCTs) including the Collaborative Group studies, RENAAL study, IDNT and ACEI in Progressive Renal Insufficiency Study.[62-65] These studies demonstrated kidney benefits independent of BP reduction, and the results are often generalized to KTR. Despite the equipoise on RAAS blockade presented by the aforementioned Cochrane review,[61] the 2009 KDIGO guideline recommends the use of ACEi/ARB when urine protein excretion is >1g/day.[50]

However, newer evidence questions these recommendations. In a 2016 RCT by Knoll et al, 213 KTR with proteinuria were randomized to ramipril versus placebo. Although the study may have been underpowered, no benefit was seen in the primary composite outcome of doubling of creatinine, ESKD or death, or the secondary outcome of a change in measure GFR.[66] A follow up systematic review in 2017 with 8 trials and 1502 KTR was similarly negative, with no benefit from RAAS blockade in terms of all-cause mortality or graft survival, with increased hyperkalemia observed.[67] However, this analysis was limited by a relatively small number of events and short follow up.

Dyslipidemia and antiplatelet therapy

Dyslipidemia affects an estimated 60% of KTR,[68] with CNIs, glucocorticoids and mammalian target of rapamycin inhibitors (mTORi) contributing to this disease burden.[69] KDIGO recommends early posttransplant screening for dyslipidemia within 2-3 months of transplantation and annually. The use of statins as the first line therapy is recommended when LDL-C $\geq$100 mg/dL.[68,70] In the ALERT extension study, fluvastatin was well tolerated in KTR and lowered LDL-cholesterol by 36%, and MACE by 21% in the fluvastatin group as compared to control over a mean follow-up of 6.7 years.[71,72] Early introduction of statins

posttransplantation was associated with the greatest benefit with respect to the MACE outcome. A smaller observational study in KTR demonstrated higher eGFR and less interstitial fibrosis at 1 year in statin uses compared to nonusers.[73] Beyond statins, the literature regarding the use of PCSK9 inhibitors in KTR is currently limited to case reports and series, and larger trials in this population are still needed.[74-76]

The use of aspirin (ASA) to reduce CV risk in KTR also remains incompletely understood. In a post hoc analysis of the Folic Acid for Vascular Outcomes Reduction Trial (FAVORIT), propensity-based matching of 981 ASA users with 981 nonusers did not reveal any significant differences in CV events, all-cause mortality, or allograft failure over 4 years.[77] KDIGO recommends the use of ASA in KTR with atherosclerotic CV disease, as well as for primary prevention in those with DM if no contraindications exist,[50] although the latter is not universally supported.[78]

Modification of immunosuppression

Management of immunosuppression in transplantation remains a complex clinical issue and an individualized approach continues to be recommended.[31,50,79]

Glucocorticoids

Minimization or avoidance of glucocorticoids to mitigate CV risks as well as other adverse effects of these drugs in KTR has been previously examined. Two meta-analyses published in 2009 and 2010 explored steroid minimization strategies, each including approximately 30 studies and 5000 participants.[80,81] Both demonstrated that steroid sparing strategies were associated with reduced incidence of hypertension, dyslipidemia, and PTDM, with the former showing a reduction in CV events with steroid avoidance. However, steroid sparing strategies were associated with an increased risk of acute rejection, particularly when cyclosporine was used. Despite this potential

risk, steroid avoidance and withdrawal strategies were not associated with increased mortality or graft loss. In an updated Cochrane review published in 2016, steroid avoidance and withdrawal were again associated with an increased risk of acute rejection with no significant difference in patient mortality or graft loss at 5 years post transplantation.[82] The impact of steroid sparing strategies on longer-term mortality and graft survival remains poorly understood.

Calcineurin Inhibitors

CNIs are associated with the development of PTDM[83] and promote hypertension through several proposed mechanisms.[84] As such, CNI withdrawal/minimization strategies may reduce CV risk in KTR. A Cochrane review in 2017 examined various CNI regimens in 83 studies and 16 156 participants.[85] CNI avoidance and withdrawal were found to increase allograft rejection while possibly reducing the risk of graft loss, with overall low quality of evidence. CNI withdrawal regimens were associated with a lower incidence of hypertension while DM, dyslipidemia and CMV infections were not different between groups. Firm conclusions are limited by the small sample size of included studies and the absence of long-term data. The use of cyclosporine instead of tacrolimus in high vascular risk patients has also been proposed as a CV/PTDM risk management strategy.[19,48] In 2007, Vincenti et al. published the DIRECT study which randomized KTR to tacrolimus or cyclosporine. Both groups received basiliximab induction as well as mycophenolic acid and steroids. The incidence of new onset diabetes after transplantation as well as impaired fasting glucose at 6 months was significantly higher in the tacrolimus group as compared to the cyclosporine group. However, it is important to mention that tacrolimus trough levels in this study were maintained at 10-15 ng/ml during months 1-3, levels that are significantly greater than contemporary targets. There was a trend towards more acute rejection, graft loss or death in the cyclosporine group (12.8% vs 9.8% in the tacrolimus group; p=0.21).[86] The use of

cyclosporine versus tacrolimus was further explored by Wissing in a 12-month study of 87 KTR with PTDM randomized to tacrolimus replacement with cyclosporine versus continuation of tacrolimus. Participants switched to cyclosporine had lower HbA1c levels, were more likely to be off glucose-lowering medications and free of DM.[87]

In another ongoing study exploring the relationships between RAAS blockage, BP control and tacrolimus dosing, results at 24-months demonstrated an interactive effect of combining of low dose tacrolimus (5 ± 1 ng/mL) and RAAS blockade, resulting in less progression of allograft fibrosis and risk of T cell-mediated rejection.[88] It remains to be seen if this translates to improved graft and CV outcomes.

Belatacept

A 2014 Cochrane review compared belatacept with cyclosporine demonstrating similar rates of death, graft loss and rejection, with less PTDM, graft fibrosis, and improved BP and lipid profiles.[89] The 7-year follow up of the BENEFIT trial, also comparing belatacept with cyclosporine, demonstrated superiority with respect to the composite outcome of death or graft loss despite higher rates of acute rejection.[90] A subsequent propensity score matched cohort study compared belatacept with tacrolimus and reported similar rates of death and allograft loss with an increased risk of rejection in the first year with belatacept as previously observed.[91] Adams et al. were able to lower rates of acute rejection with belatacept with a transient course of tacrolimus tapered off by 5 months after transplantation.[92] While the strengths and limitations of the belatacept trials are beyond the scope of this review, it is important to note that the patients included in these trials were at low immunological risk. As such, belatacept may be a useful strategy to improve CV risk in a subset of well-selected KTR.

POTENTIAL TREATMENT STRATEGIES FOR DM IN KTR

Several glucose lowering strategies in the general population have been considered in KTR. We discuss the rationale, safety, and effectiveness of these agents in KTR in the following sections (**Table 1**).

Lifestyle intervention and insulin therapy

Lifestyle interventions have been studied in the KTR. In a single-center study of stable KTR without preexisting diabetes, 130 participants were randomized to a 6-month active lifestyle intervention consisting of personalized dietary advice and encouragement of a graded exercise program, versus a passive control arm.[93] While there were no differences in metabolic parameters including insulin secretion, insulin sensitivity, fasting and postprandial glucose levels over the 6-month period of follow up, the active intervention was associated with significant reductions in fat mass and weight, as well as reductions in PTDM that did not reach statistical significance. It remains to be seen if longer term implementation of such interventions may have positive benefits on preventing PTDM.

Insulin therapy is currently considered the first line treatment of immediate posttransplant hyperglycemia[4,48] given rapidly changing doses of glucocorticoids and fluctuating allograft function. Longer term benefits were demonstrated in a small RCT of 50 KTR by Hecking and colleagues, where insulin therapy for early posttransplant hyperglycemia reduced the odds of developing PTDM by 73%, possibly via reducing the impact of glucose toxicity in the pancreas.[94] It should be pointed out that this strategy of intensive insulin therapy required on average 22 days of hospitalization postsurgery. A follow up clinical trial (NCT03507829) is currently under consideration for publication. In a 2017 Cochrane systematic review, 3 studies including 242 KTR with preexisting type 1 and 2 DM compared more intensive with standard insulin therapy.[95] One

study reported no difference in graft survival at 3 to 5 years follow-up while another reported increased rejection with the intensive insulin regimen after 3 years. All studies reported increased hypoglycemic episodes with the intensive regimen. Longer term insulin use, whether intensive or standard, is also often associated with weight gain.

SGLT2 Inhibitors

SGLT2 inhibitors are highly effective in the treatment of type 2 DM (T2D), promoting glycemic control, weight loss, and reductions in BP and albuminuria.[96,97] SGLT2 inhibitors block glucose reabsorption in renal proximal tubule epithelial cells (PTEC) causing glucosuria and reducing blood glucose levels without risk of hypoglycemia.[97,98] There are significant CV and kidney benefits of SGLT2 inhibitors in nontransplant populations as demonstrated in several CV outcome trials (CVOT). The EMPA-REG OUTCOME trial demonstrated that participants with T2D and established CV disease randomized to empagliflozin had significant reductions in MACE, CV and all-cause mortality, and HF hospitalizations (HHF).[99] The CANVAS Program trial randomized participants with T2D at high CV risk with and without established CV disease and demonstrated a 14% reduction in MACE, a 22% reduction in CV death or HHF, and significant HHF benefits with canagliflozin.[100] The DECLARE TIMI-58 study examined the effects of dapagliflozin on the lowest CV risk cohort of the 3 CVOTs and reported a 17% relative risk reduction in the co-primary composite endpoint of CV death or HHF. All 3 CVOTs reported significant reductions in secondary or exploratory kidney composite endpoints. More recently, VERTIS-CV compared ertugliflozin with placebo showing noninferiority for its primary MACE outcome, as well as a 30% reduction in HHF.[101] For the key composite kidney endpoint, doubling of serum creatinine, the impact of ertugliflozin was neutral. However, a HR of 0.66 was observed (95% CI 0.50-0.88) with a composite kidney endpoint including a sustained 40% eGFR decline.[102]

CREDENCE, the first dedicated kidney outcome trial, randomized >4000 participants with T2D, eGFR 30-90 ml/min/1.73m^2, and macroalbuminuria to canagliflozin vs. placebo.[103] It was stopped early due to a 30% relative risk reduction in the primary outcome of ESKD, serum creatinine doubling, or renal or CV death.[97] Shortly after in 2019, DAPA-HF, conducted in diabetic and nondiabetic participants with HF and reduced ejection fraction, demonstrated that dapagliflozin was associated with a lower rate of worsening HF or CV death.[26] Most recently, DAPA-CKD, studying CKD patients with an eGFR as low as 25 ml/min/1.73m^2 with albuminuria of at least 200 mg/g with or without DM, demonstrated overwhelming benefit with respect to the primary outcome of a sustained decline in the eGFR of at least 50%, ESKD, or death from renal causes with a hazard ratio of 0.56 and number needed to treat to prevent 1 primary outcome event of 19.[27] Impressively, a reduction in all-cause mortality was also noted in the treatment arm. The EMPA-KIDNEY trial (NCT03594110) underway and recruiting participants with eGFRs as low as 20 ml/min/1.73m^2 without albuminuria. Importantly, KTR were consistently excluded from these studies.

These kidney and CV benefits of SGLT2 inhibitors have largely been attributed to several glucose-independent effects. From a kidney perspective, hyperglycemia increases tubular reabsorption of glucose and sodium. This activates tubuloglomerular feedback (TGF) where a decrease in sodium delivery to the macula densa, leads to afferent arteriolar vasodilation and hyperfiltration.[104] SGLT2 inhibitors increases sodium delivery to the macula densa resulting in afferent arteriolar vasoconstriction, and reductions in intraglomerular hypertension, GFR and albuminuria.[105] The SGLT2 inhibitor induced natriuresis may also explain observed reductions in systolic and diastolic blood pressures, and arterial stiffness.[97,106-108] These changes may in turn be responsible for observed decreases in albuminuria and DKD progression.[97,109] Importantly,

natriuresis-related reductions in BP and albuminuria persist with reductions in GFR.[110] From a cardiac perspective, natriuresis-induced decreases in intravascular volume and arterial stiffness is one of many factors that may be cardioprotective by decreasing cardiac preload and afterload, thereby mitigating HF risk.[105,111]

Aside from hemodynamic factors, improved energy balance at the organ level may contribute to heart[112] and kidney[113] protection with SGLT2 inhibitors, discussed in greater detail in the cited reviews. Increases in metabolic demands with hyperglycemia-induced sodium and glucose reabsorption predispose PTECs to hypoxia, thereby promoting fibrosis and kidney injury.[114-116] Increased glucose reabsorption also results in advanced glycation end-product generation, which have been shown to trigger reactive oxygen species generation as well as pro-fibrotic and pro-inflammatory pathways, ultimately leading to progressive DKD.[117,118] Increased proximal albumin reabsorption in DKD also contributes to PTEC toxicity and tubulointerstitial injury.[117-119] By blocking glucose transit across PTECs, experimental studies have demonstrated reductions in pro-fibrotic and pro-inflammatory mediators with SGLT2 inhibition,[120-124] and preliminary studies in humans have shown similar potential benefits on these pathways.[105,125-127] Post hoc mediation analyses of CVOT and kidney outcome trials have suggested that clinically observed CV and kidney benefits of SGLT2 inhibitors may be partially mediated by improvements in hematocrit and hemoglobin concentrations.[128-130] One secondary analysis of CREDENCE reported that canagliflozin reduced the risk of anemia or treatment initiation for anemia.[131] Explanations for SGLT2 inhibitor associated increases in hemoglobin range from simple natriuresis-associated hemoconcentration[132] to alterations in erythropoietin (EPO) and reticulocyte counts[133,134] with potential improvements in hypoxia within different nephron compartments

and/or energy dynamics at cellular and tissue level.[113,135] To date, the literature is inconsistent with respect to the effects of SGLT2 inhibition on EPO.

Based on this data in nontransplant cohorts, SGLT2 inhibition in KTR is potentially attractive considering the high burden of vascular comorbidities, premature death and graft loss. SGLT2 inhibition therapies are safe over a wide range of kidney function in non-KTR and have even been shown to reduce acute kidney injury (AKI) risk.[136] The use of SGLT2 inhibitors in KTR has been described in a number of smaller cases series and observational studies. In 10 KTR and simultaneous pancreas-KTR with preserved eGFR, our group previously demonstrated that canagliflozin was associated with improvements in HbA1c, weight, and BP, in similar magnitudes as nontransplant cohorts (**Table 2**).[137] No episodes of ketoacidosis, AKI, acute rejection, urinary/mycotic infections, or clinically significant changes in CNI levels were observed during treatment. Mahling et al and AlKindi et al similarly published case series of 10 and 8 KTR respectively, treated with SGLT2 inhibitors, which showed similar findings over a short duration of follow-up.[138,139]

In a single-arm study of 14 KTR, Schwaiger and colleagues reported that although glycemic control with empagliflozin was inferior to insulin, the SGLT2 inhibitor group exhibited significant improvements in body weight and bioimpedance (as a measure of volume status) after only 4 weeks.[140] In a retrospective study of 50 KTR by Song et al., the use of a variety of SGLT2 inhibitors was safe, resulting in weight loss and reductions in insulin requirements.[141] A 2019 Australian study retrospectively compared the use of empagliflozin in 22 heart transplant recipients with DM to 79 heart transplant recipients with DM receiving alternate agents.[142] Similar to KTR, the use of empagliflozin over 12 months in this study was associated with HbA1c, weight, and furosemide dose reductions, without significant changes in kidney function or clinically

apparent drug interactions. Halden et al. recently published in 2019 the only RCT in this population, where 49 KTR with PTDM were randomized to empagliflozin 10mg versus placebo.[143] Over a 24-week period, empagliflozin improved glycemic control and body weight, without differences in blood pressure, eGFR, immunosuppressive drug levels, or adverse events. Finally, Beshyah and colleagues conducted a mixed method analysis of case reports and physician surveys to highlight the safety of SGLT2 inhibitors in KTR.[144]

While existing SGLT2 inhibitor studies in KTR focus on glycemic control, the glucose-independent benefits of SGLT2 inhibitors are likely to be of greatest significance in KTR populations with high CKD prevalence.[145] In a biopsy cohort study, Coemans et al demonstrated an apparent independence of glycemic control in developing mesangial matrix expansion and interstitial fibrosis among KTR with pretransplant DM, highlighting the need for pharmacologic kidney protective therapies that act beyond simply targeting improvements in glycemic control.[42] SGLT2 inhibitor related improvements in hemoglobin and hematocrit are also particularly relevant considering high rates of anemia in KTR. Furthermore, kidney transplant candidates with DM frequently receive kidneys from more 'marginal' deceased donors given their high mortality on the transplant waiting list.[146] Although this strategy may be beneficial from a patient survival perspective (vs. chronic dialysis), KTR with DM are more likely to have allografts with reduced kidney function.[147] While HbA1c lowering with SGLT2 inhibitors is attenuated as eGFR declines, the glucose-independent effects persist across the range of eGFR.[110] In KTR, the most clinically relevant effects may be mediated via SGLT2 inhibition-induced natriuresis, with associated reductions in blood pressure and other glucose-independent cardiorenal protective pathways.

GLP-1 Receptor Agonists

Glucagon-like peptide-1 (GLP-1) reduces postprandial glucose levels by stimulating insulin secretion, reducing glucagon release, slowing gastric emptying and reducing hepatic gluconeogenesis.[148] GLP-1 receptor agonists (GLP-1RA) lower HbA1c levels by about 1-1.5%, BP by 2-3 mmHg, body weight by 3 kg, and improve lipid profiles – all contributors to CV and kidney disease.[149] A meta-analysis including liraglutide, semaglutide, lixisenatide and exenatide demonstrated significant reductions in all-cause and CV mortality, and 3-point MACE compared to placebo.[150] Secondary renal analyses of ELIXA (lixisenatide),[151] LEADER (liraglutide),[30,152] SUSTAIN-6 (semaglutide),[29] and EXSCEL (exenatide)[150] showed decreases in urinary albumin excretion and new onset or persistent macroalbuminuria. Similarly, the AWARD-7 trial with dulaglutide in patients with CKD stages 3 and 4 showed important anti-albuminuric effects independent of glycemic lowering, and a modest attenuation of eGFR decline over 1 year.[153] In the REWIND study (dulaglutide), the secondary nephropathy composite endpoint of new macroalbuminuria, 30% fall in eGFR, or renal replacement therapy was reduced by 15%, though this was driven by a significant decline in macroalbuminuria.[154]

While GLP-1RA seem to consistently lower albuminuria, clinical trials have not yet demonstrated significant improvement in harder kidney outcomes, except for modest eGFR preservation in LEADER and AWARD-7, and in post hoc analysis of the SUSTAIN 6 and PIONEER 6 trials.[152,155-159] Decreased urine albumin excretion may be due to direct GLP-1 effects in the human kidney, including the afferent arteriole.[155,160] This is thought to be independent of natriuresis and TGF, though GLP-1RA may also induce natriuresis by acutely inhibiting the sodium hydrogen antiporter NHE3 in the proximal tubule.[155,161,162] Other potential kidney-protective mechanisms include inflammation and oxidative stress reduction, improvement of

insulin sensitivity which may be particularly relevant in PTDM, and mitochondrial dysfunction. Regardless of the principal mechanisms, current evidence supports the concept that clinical benefits are largely based on preventing albuminuria progression rather than harder kidney outcomes.[163] Ongoing trials, such as FLOW (Semaglutide on the Progression of Renal Impairment in Subjects With Type 2 Diabetes and Chronic Kidney Disease; NCT03819153) will help determine if GLP-1RA can improve primary renal outcomes in non-KTR participants with DKD.

GLP-1RA have been safely tolerated in KTR with DM based on smaller case series, though studies in larger groups of patients are lacking.[164-167] From a mechanistic standpoint, Halden et al demonstrated in 24 KTR that PTDM was characterized by reduced hyperglycemia induced insulin secretion and glucagon suppression.[168] Intravenous infusions of GLP-1 were subsequently able to increase insulin secretion and reduce glucagon concentration in these patients.[168] Four case series involving 92 participants treated with GLP-1RA demonstrated improved glycemic control and weight loss, without significant CNI interactions.[164-167] In all cases, eGFR was stable if not improved in the months following GLP-1RA initiation. A small percentage of participants discontinued the medication mainly due to gastrointestinal intolerance. Longer term studies are needed to evaluate CV and kidney benefits among KTR, particularly those with DM.

Combination therapies

The kidney protective benefits of glycemic control, BP control, RAAS blockade, and recently SGLT2 inhibition are established in the general DKD population and could be expected to have additive or synergistic effects in KTR.[22,169] The safety and efficacy of SGLT2 inhibitors in DKD has largely been demonstrated as an add-on therapy to RAAS blockade. The synergistic effects of SGLT2 inhibitors and RAAS blockers are currently being explored in mechanistic studies in individuals with preserved kidney function (NCT02632747). Additionally, SGLT2

inhibitors and GLP-1RA appear to ameliorate proteinuria and cause natriuresis through different mechanisms.[170] Combined use of these 2 classes yields greater glycemic control, weight loss and BP reduction (DURATION-8 and AWARD10).[171,172] Renal and CV mechanisms behind these benefits are currently being studied (NCT03878706). The extent to which benefits of these combination therapies translate to KTR remains to be determined.

NOVEL CARDIORENAL PROTECTIVE STRATEGIES IN KTR

DKD often progresses and CV risk persists despite existing heart and kidney protective strategies, highlighting a need for ongoing research into alternative mechanisms and targets in high risk populations.[173] Here we highlight a number of promising therapies in clinical development, targeting diverse pathways in the pathophysiology of DKD and HF including anti-inflammatory agents, endothelin-1 antagonism, additional RAAS blockade, and neprilysin inhibition.

Anti-inflammatory therapies

Regarding anti-inflammatory therapies, it has been proposed that the innate immune system and other inflammatory pathways are activated by hyperglycemia and RAAS, promoting DKD progression.[174,175] In the CANTOS study, use of the anti-inflammatory agent canakinumab (IL-1β antagonist) was associated with modest CV benefits, even in patients with moderate CKD. While it failed to attenuate CKD progression, it is important to note that patients with significant kidney involvement were excluded from this trial.[176,177]

Endothelin-1 antagonism

Another promising target for kidney protection is endothelin-1 (ET-1) receptor antagonism, which has been studied more extensively in nontransplant patients with more advanced CKD.[178] Avosentan, a nonspecific ET-1 antagonist, markedly reduced proteinuria in DKD but was limited by sodium and fluid retention.[179,180] However, positive results from the

SONAR trial demonstrated that use of the more selective ET-1 antagonist atrasentan in DKD reduced the risk of the primary composite endpoint of doubling of serum creatinine or ESKD without significant adverse effects.[178,181] Combination use with SGLT2 inhibitors or GLP-1RA therapies may be another strategy to avoid sodium and fluid retention with these therapies, although this has not yet been studied in humans. ET-1 antagonists have yet to be studied in KTR and are not yet approved for use as therapies for DKD.

Additional RAAS blockade

Given the importance of RAAS activation to the pathogenesis of cardiorenal disease in diabetes, as well as the lack of benefit with traditional dual RAAS blockers (ACEi, ARBs, renin inhibitors),[170] alternative strategies to safely block the RAAS and prevent progression of cardiac and renal disease are still being investigated. Novel mineralocorticoid receptor antagonists (MRA) have anti-inflammatory/anti-fibrotic effects with the potential to attenuate aldosterone escape in patients taking ACEi/ARBs.[182] While older MRAs such as spironolactone and eplerenone have been demonstrated to reduce proteinuria, adverse events including hyperkalemia could limit their use in the CKD and KTR populations.[170] This had led to growing interest in more selective nonsteroidal MRAs such as finerenone as cardiorenal protective agents. Finerenone reduces albuminuria in the setting of DKD with T2D and has a lower risk of hyperkalemia compared to existing MRAs.[183] The FIDELIO-DKD trial recently demonstrated that in patients with CKD and T2D, finerenone was associated with a lower risk of new onset ESKD, sustained decline in eGFR of ≥ 40% or renal death as compared to placebo.[184] With only top line results available to date, the FIGARO trial (NCT02545049), studying the impact of finerenone vs placebo in patients with T2D and DKD, met its primary endpoint of significantly reducing CV death and nonfatal CV events. The role of additional RAAS blockade with MRAs in KTR with or without DM will need to be

well-studied before clinical use, particularly given existing equipoise on the use of ACEi/ARB in KTR.

Management of Heart Failure and CKD in KTR

KTR have high rates of DM, CKD and HF. Older studies reported 3-year cumulative incidences of postkidney transplant HF ranging from 18 to 27%, with HF diagnoses conferring increased risks of death and graft loss.[185] A more recent analysis demonstrated significant reductions in the rates of HF from 1998 to 2010, though failed to observe improvements in mortality following de novo HF diagnosis.[185] The management of HF has dramatically changed over the last decade, particularly in patients with reduced ejection (HFrEF) with the advent of neprilysin inhibitors, ivabradine and SGLT2i inhibitors. Increasing use of these agents in KTR with HFrEF is expected.

Neprilysin inhibitors in combination with ARBs (ARNi) may be beneficial in CKD, with and without HFrEF. Neprilysin or neutral endopeptidase (NEP) breaks down natriuretic and vasodilating peptide – NEP inhibitors in combination with RAAS blockade promotes natriuresis, BP reductions, RAAS and sympathetic inhibition, and vasodilation.[186] Secondary analysis of the general population in the PARADIGM-HF trial in HFrEF demonstrated a slower rate of eGFR decline with the NEP inhibitor sacubitril plus valsartan compared to enalapril alone – a benefit that was greater in participants with DM.[187] In the 12-month UK-HARP-III trial comparing sacubutril/valsartan with irbesartan in nontransplant CKD patients with eGFR as low as 20 ml/min/1.73m^2, there was no benefit observed with respect to the primary outcome of eGFR change.[188] Use of sacubitril/valsartan in this population was associated with significant reductions in BP and cardiac biomarkers, though it remains unclear if there will ever be a longer-term kidney outcome study in this population. The potential renal vasodilatory effects of ARNi may be

particularly relevant in KTR considering the chronic vasoconstrictive effects of CNIs, though long-term outcomes with sacubitril/valsartan in KTR are lacking. The use of NEP inhibitors in KTR to manage CNI toxicity is not a novel concept as evidenced by several animal and human studies with older NEP inhibitors.[189,190] One such study by Lipkin et al demonstrated increased natriuresis, GFR, renal blood flow, and decreased renal vascular resistance with the NEP inhibitor candoxatrilat.[191] There are other agents with demonstrated benefits in the HF population with and without DM – ivabradine, a sinus node inhibitor, and vericiguat, a novel oral soluble guanylate cyclase inhibitors, are 2 recent examples.[192,193] As demonstrated in a 2020 Cochrane review of pharmacological interventions for HF in CKD, there is a paucity of data to guide which interventions are effective in patients with HF and CKD (this review preceded the EMPEROR-Reduced and DAPA-HF trials).[194] This knowledge gap persists when considering the narrower intersection of KTR with HF and CKD.

TREATMENT OF DM/PTDM IN KTR: SPECIAL CONSIDERATIONS

There are several unique aspects of KTR that are important to consider when using agents with cardiorenal benefits, including the immunosuppressed state of KTR, the impact on denervated kidneys, as well as drug-drug interactions (DDI) particularly with concomitant use of CNIs. Given the susceptibility of KTR to infectious complications due to immunosuppression, there is the potential for concern regarding safety of these agents in this population. For example, mycotic infections are well described with SGLT2 inhibitors,[195] and urinary tract infections are one of the most common infectious complications in KTR.[196] In addition, transplanted kidneys are denervated and therefore the autoregulation of renal blood flow, particularly under conditions of hypotension, may be altered.[197] Importantly, in CVOTs, CREDENCE and DAPA-CKD, SGLT2 inhibition has not been associated with AKI, and may in fact reduce its incidence.[136] Transplant

nephrologists should expect an acute and reversible decline in GFR when starting SGLT2 inhibitors, as observed in the general population and with RAAS blockade. Additional work is required to prove the safety and efficacy of these therapies under conditions of single kidney physiology and with altered autoregulatory conditions – such as with KTR.

DDI between glucose-lowering and immunosuppressive agents are another important consideration, given the narrow therapeutic window of immunosuppression in organ transplantation.[198] Drug elimination of CNIs and mTORi are mainly controlled by the cytochrome P450 (CYP) enzymes CYP3A4 and CYP3A5, and the efflux pump P-glycoprotein (P-gp).[199] Drugs that affect these enzymes may increase or decrease immunosuppression exposure. Metformin and insulin have low potential for DDI with immunosuppressive agents.[199] DPP4 inhibitors also likely have no significant DDI, with the possible exception of sitagliptin with cyclosporine and vildagliptin and tacrolimus.[199] GLP-1RA do not affect CYP or P-gp metabolism. They do however slow gastric emptying, which may impact immunosuppressant absorption and should prompt additional CNI level monitoring after therapy initiation.[199] Regarding SGLT2 inhibitors, canagliflozin weakly inhibits several CYP enzymes and P-gp. It remains to be seen whether this increases exposure to CNIs and mTORi.[199] Few studies have primarily tried to assess DDIs, though small clinical trials have not disclosed any signals of DDI.[143,200,201] CNIs also cause renal vasoconstriction, and result in tubular toxicity and transport alterations.[84,202] The effectiveness of agents with tubular effects including SGLT2 inhibitors and GLP-1RA with concomitant use of CNIs merits further exploration.

CONCLUSIONS

DM in KTR contributes to an increase in allograft failure, CV disease, and mortality. Given the glucose-dependent and independent effects of newer diabetes agents like SGLT2 inhibitors and GLP-1RA, as well as the accumulating evidence demonstrating their cardiorenal protection in the general diabetes population, the use of these agents in KTR is attractive. This is especially relevant considering the lack of proven efficacy with traditional RAAS inhibitors in this population. While the safety of these agents in KTR has been shown mostly in smaller case series and observational studies, larger clinical and mechanistic trials are required to confirm the cardiorenal benefits and safety of these agents in KTR with preexisting and PTDM.

References:

1. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2018 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis.* 2019;73(3 Suppl 1):A7-A8.
2. Hart A, Smith JM, Skeans MA, et al. OPTN/SRTR 2017 annual data report: kidney. *Am J Transplant.* 2019;19 Suppl 2:19-123.
3. Conte C, Secchi A. Post-transplantation diabetes in kidney transplant recipients: an update on management and prevention. *Acta Diabetol.* 2018;55(8):763-779.
4. Werzowa J, Saemann M, Haidinger M, et al. Antidiabetic therapy in post kidney transplantation diabetes mellitus. *Transplant Rev (Orlando).* 2015;29(3):145-153.
5. Montori VM, Basu A, Erwin PJ, et al. Posttransplantation diabetes: a systematic review of the literature. *Diabetes Care.* 2002;25(3):583-592.
6. Sharif A, Cohney S. Post-transplantation diabetes-state of the art. *Lancet Diabetes Endocrinol.* 2016;4(4):337-349.
7. Kasiske BL, Snyder JJ, Gilbertson D, et al. Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant.* 2003;3(2):178-185.
8. Shivaswamy V, Boerner B, Larsen J. Post-transplant diabetes mellitus: causes, treatment, and impact on outcomes. *Endocr Rev.* 2016;37(1):37-61.
9. Huang JW, Famure O, Li Y, et al. Hypomagnesemia and the risk of new-onset diabetes mellitus after kidney transplantation. *J Am Soc Nephrol.* 2016;27(6):1793-1800.
10. Bhat M, Pasini E, Das A, et al. Diabetogenic effects of immunosuppression: an integrative analysis. *Transplantation.* 2020;104(1):211-221.

11. Valderhaug TG, Hjelmesaeth J, Rollag H, et al. Reduced incidence of new-onset posttransplantation diabetes mellitus during the last decade. *Transplantation.* 2007;84(9):1125-1130.

12. Londero TM, Giaretta LS, Farenzena LP, et al. Microvascular complications of posttransplant diabetes mellitus in kidney transplant recipients: a longitudinal study. *J Clin Endocrinol Metab.* 2019;104(2):557-567.

13. Lentine KL, Schnitzler MA, Abbott KC, et al. De novo congestive heart failure after kidney transplantation: a common condition with poor prognostic implications. *Am J Kidney Dis.* 2005;46(4):720-733.

14. Sharif A, Baboolal K. Complications associated with new-onset diabetes after kidney transplantation. *Nat Rev Nephrol.* 2011;8(1):34-42.

15. Taber DJ, Meadows HB, Pilch NA, et al. Pre-existing diabetes significantly increases the risk of graft failure and mortality following renal transplantation. *Clin Transplant.* 2013;27(2):274-282.

16. Ponticelli C, Moroni G, Glassock RJ. Recurrence of secondary glomerular disease after renal transplantation. *Clin J Am Soc Nephrol.* 2011;6(5):1214-1221.

17. Ojo AO, Hanson JA, Wolfe RA, et al. Long-term survival in renal transplant recipients with graft function. *Kidney Int.* 2000;57(1):307-313.

18. Briggs JD. Causes of death after renal transplantation. *Nephrol Dial Transplant.* 2001;16(8):1545-1549.

19. Ghisdal L, Van Laecke S, Abramowicz MJ, et al. New-onset diabetes after renal transplantation: risk assessment and management. *Diabetes Care.* 2012;35(1):181-188.

20. Stephen J, Anderson-Haag TL, Gustafson S, et al. Metformin use in kidney transplant recipients in the United States: an observational study. *Am J Nephrol.* 2014;40(6):546-553.

21. Perkovic V, de Zeeuw D, Mahaffey KW, et al. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. *Lancet Diabetes Endocrinol.* 2018;6(9):691-704.

22. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med.* 2019;380:2295-2306.

23. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2019;380(4):347-357.

24. Zelniker TA, Wiviott SD, Raz I, 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(10166):31-39.

25. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373(22):2117-2128.

26. McMurray JJV, Solomon SD, Inzucchi SE, et al; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2019;381:1995-2008.

27. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med.* 2020;383(15):1436-1446.

28. Packer M, Anker SD, Butler J, et al; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med.* 2020;383(15):1413-1424.

29. Marso SP, Bain SC, Consoli A, et al; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2016;375(19):1834-1844.

30. Marso SP, Daniels GH, Brown-Frandsen K, et al; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2016;375(4):311-322.

31. Kuo HT, Sampaio MS, Vincenti F, et al. Associations of pretransplant diabetes mellitus, new-onset diabetes after transplant, and acute rejection with transplant outcomes: an analysis of the Organ Procurement and Transplant Network/United Network for Organ Sharing (OPTN/UNOS) database. *Am J Kidney Dis.* 2010;56(6):1127-1139.

32. Lim WH, Wong G, Pilmore HL, et al. Long-term outcomes of kidney transplantation in people with type 2 diabetes: a population cohort study. *Lancet Diabetes Endocrinol.* 2017;5(1):26-33.

33. Hjelmesaeth J, Hartmann A, Leivestad T, et al. The impact of early-diagnosed new-onset post-transplantation diabetes mellitus on survival and major cardiac events. *Kidney Int.* 2006;69(3):588-595.

34. Israni AK, Snyder JJ, Skeans MA, et al; PORT Investigators. Predicting coronary heart disease after kidney transplantation: Patient Outcomes in Renal Transplantation (PORT) study. *Am J Transplant.* 2010;10(2):338-353.

35. Cole EH, Johnston O, Rose CL, et al. Impact of acute rejection and new-onset diabetes on long-term transplant graft and patient survival. *Clin J Am Soc Nephrol.* 2008;3(3):814-821.

36. Dienemann T, Fujii N, Li Y, et al. Long-term patient survival and kidney allograft survival in post-transplant diabetes mellitus: a single-center retrospective study. *Transpl Int.* 2016;29(9):1017-1028.

37. Merion RM, Goodrich NP, Johnson RJ, et al. Kidney transplant graft outcomes in 379 257 recipients on 3 continents. *Am J Transplant.* 2018;18(8):1914-1923.

38. Pilmore H, Dent H, Chang S, et al. Reduction in cardiovascular death after kidney transplantation. *Transplantation.* 2010;89(7):851-857.

39. Ying T, Shi B, Kelly PJ, et al. Death after kidney transplantation: an analysis by era and time post-transplant. *J Am Soc Nephrol.* 2020;31(12):2887-2899.

40. Sharma SG, Bomback AS, Radhakrishnan J, et al. The modern spectrum of renal biopsy findings in patients with diabetes. *Clin J Am Soc Nephrol.* 2013;8(10):1718-1724.

41. Porrini E, Bayes B, Diaz JM, et al. Hyperinsulinemia and hyperfiltration in renal transplantation. *Transplantation.* 2009;87(2):274-279.

42. Coemans M, Van Loon E, Lerut E, et al. Occurrence of diabetic nephropathy after renal transplantation despite intensive glycemic control: an observational cohort study. *Diabetes Care.* 2019;42(4):625-634.

43. Kukla A, Merzkani M, Park W, et al. Recurrent diabetic nephropathy post kidney transplant is associated with high risk of mortality [abstract]. *Am J Transplant.* 2020;20 (suppl 3).

44. Lam NN, Klarenbach S, Quinn RR, et al. Renal function, albuminuria, and the risk of cardiovascular events after kidney transplantation. *Transplant Direct.* 2018;4(10):e389.

45. Lam NN, Tonelli M, Lentine KL, et al. Albuminuria and posttransplant chronic kidney disease stage predict transplant outcomes. *Kidney Int.* 2017;92(2):470-478.

46. Weiner DE, Park M, Tighiouart H, et al. Albuminuria and allograft failure, cardiovascular disease events, and all-cause death in stable kidney transplant recipients: a cohort analysis of the FAVORIT trial. *Am J Kidney Dis.* 2019;73(1):51-61.

47. Clayton PA, Lim WH, Wong G, et al. Relationship between eGFR decline and hard outcomes after kidney transplants. *J Am Soc Nephrol.* 2016;27(11):3440-3446.

48. Sharif A, Hecking M, de Vries APJ, et al. Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. *Am J Transplant.* 2014;14(9):1992-2000.

49. Chadban SJ, Ahn C, Axelrod DA, et al. KDIGO clinical practice guideline on the evaluation and management of candidates for kidney transplantation. *Transplantation.* 2020;104(4S1 Suppl 1):S11-S103.

50. Kasiske BL, Zeier MG, Chapman JR, et al; Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. *Kidney Int.* 2010;77(4):299-311.

51. Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes.* 2018;42:S1-S325.

52. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis.* 1998;32(5 Suppl 3):S112-119.

53. Ramanathan V, Goral S, Tanriover B, et al. Screening asymptomatic diabetic patients for coronary artery disease prior to renal transplantation. *Transplantation.* 2005;79(10):1453-1458.

54. Wyld MLR, De La Mata NL, Masson P, et al. Cardiac mortality in kidney transplant patients: a population-based cohort study 1988-2013 in Australia and New Zealand. *Transplantation.* 2021;105:413-422.

55. Methven S, Steenkamp R, Fraser S. UK Renal Registry 19th annual report: chapter 5 survival and causes of death in UK adult patients on renal replacement therapy in 2015: national and centre-specific analyses. *Nephron.* 2017;137 Suppl 1:117-150.

56. Kasiske BL, Anjum S, Shah R, et al. Hypertension after kidney transplantation. *Am J Kidney Dis.* 2004;43(6):1071-1081.

57. Carpenter MA, Weir MR, Adey DB, et al. Inadequacy of cardiovascular risk factor management in chronic kidney transplantation - evidence from the FAVORIT study. *Clin Transplant.* 2012;26(4):E438-446.

58. Opelz G. Cadaver kidney graft outcome in relation to ischemia time and HLA match. Collaborative Transplant Study. *Transplant Proc.* 1998;30(8):4294-4296.

59. Opelz G, Döhler B; Collaborative Transplant Study. Improved long-term outcomes after renal transplantation associated with blood pressure control. *Am J Transplant.* 2005;5(11):2725-2731.

60. EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: long-term management of the transplant recipient. IV.5.2. Cardiovascular risks. Arterial hypertension. *Nephrol Dial Transplant.* 2002;17:25-26.

61. Cross NB, Webster AC, Masson P, et al. Antihypertensives for kidney transplant recipients: systematic review and meta-analysis of randomized controlled trials. *Transplantation.* 2009;88(1):7-18.

62. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med.* 2001;345(12):861-869.

63. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med.* 1993;329(20):1456-1462.

64. Lewis EJ, Hunsicker LG, Clarke WR, et al; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med.* 2001;345(12):851-860.

65. Maschio G, Alberti D, Janin G, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *N Engl J Med.* 1996;334(15):939-945.

66. Knoll GA, Fergusson D, Chassé M, et al. Ramipril versus placebo in kidney transplant patients with proteinuria: a multicentre, double-blind, randomised controlled trial. *Lancet Diabetes Endocrinol.* 2016;4(4):318-326.

67. Hiremath S, Fergusson DA, Fergusson N, et al. Renin-angiotensin system blockade and long-term clinical outcomes in kidney transplant recipients: a meta-analysis of randomized controlled trials. *Am J Kidney Dis.* 2017;69(1):78-86.

68. Kasiske B, Cosio FG, Beto J, et al; National Kidney Foundation. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: a report from the Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. *Am J Transplant.* 2004;4 Suppl 7:13-53.

69. Boots JMM, Christiaans MHL, van Hooff JP. Effect of immunosuppressive agents on long-term survival of renal transplant recipients: focus on the cardiovascular risk. *Drugs.* 2004;64(18):2047-2073.

70. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant.* 2009;9 Suppl 3:S1-155.

71. Holdaas H, Fellström B, Jardine AG, et al; Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. *Lancet.* 2003;361(9374):2024-2031.

72. Holdaas H, Fellström B, Cole E, et al; Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators. Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin: the ALERT extension study. *Am J Transplant.* 2005;5(12):2929-2936.

73. Masterson R, Hewitson T, Leikis M, et al. Impact of statin treatment on 1-year functional and histologic renal allograft outcome. *Transplantation.* 2005;80(3):332-338.

74. Sabatine MS, Giugliano RP, Keech AC, et al; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med.* 2017;376(18):1713-1722.

75. Warden BA, Kaufman T, Minnier J, et al. Use of PCSK9 inhibitors in solid organ transplantation recipients. *JACC Case Rep.* 2020;2(3):396-399.

76. Ordóñez-Fernández L, Rodríguez-Ferreras A, Carriles C, et al. Pneumonia in a patient with kidney transplant treated with alirocumab and everolimus. *Farm Hosp.* 2019;43(2):74-76.

77. Dad T, Tighiouart H, Joseph A, et al. Aspirin use and incident cardiovascular disease, kidney failure, and death in stable kidney transplant recipients: a post hoc analysis of the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) trial. *Am J Kidney Dis.* 2016;68(2):277-286.

78. Knoll GA, Blydt-Hansen TD, Campbell P, et al. Canadian Society of Transplantation and Canadian Society of Nephrology commentary on the 2009 KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Kidney Dis.* 2010;56(2):219-246.

79. Weiner DE, Carpenter MA, Levey AS, et al. Kidney function and risk of cardiovascular disease and mortality in kidney transplant recipients: the FAVORIT trial. *Am J Transplant.* 2012;12(9):2437-2445.

80. Knight SR, Morris PJ. Steroid avoidance or withdrawal after renal transplantation increases the risk of acute rejection but decreases cardiovascular risk. A meta-analysis. *Transplantation.* 2010;89(1):1-14.

81. Pascual J, Zamora J, Galeano C, et al. Steroid avoidance or withdrawal for kidney transplant recipients. *Cochrane Database Syst Rev.* 2009;(1):CD005632.

82. Haller MC, Royuela A, Nagler EV, et al. Steroid avoidance or withdrawal for kidney transplant recipients. *Cochrane Database Syst Rev.* 2016;(8):CD005632.

83. Heit JJ, Apelqvist AA, Gu X, et al. Calcineurin/NFAT signalling regulates pancreatic beta-cell growth and function. *Nature.* 2006;443(7109):345-349.

84. Hoorn EJ, Walsh SB, McCormick JA, et al. Pathogenesis of calcineurin inhibitor-induced hypertension. *J Nephrol.* 2012;25(3):269-275.

85. Karpe KM, Talaulikar GS, Walters GD. Calcineurin inhibitor withdrawal or tapering for kidney transplant recipients. *Cochrane Database Syst Rev.* 2017;7:CD006750.

86. Vincenti F, Friman S, Scheuermann E, et al. Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. *Am J Transplant.* 2007;7(6):1506-1514.

87. Wissing KM, Abramowicz D, Weekers L, et al. Prospective randomized study of conversion from tacrolimus to cyclosporine A to improve glucose metabolism in patients with posttransplant diabetes mellitus after renal transplantation. *Am J Transplant.* 2018;18(7):1726-1734.

88. Cockfield SM, Wilson S, Campbell PM, et al. Comparison of the effects of standard vs low-dose prolonged-release tacrolimus with or without ACEi/ARB on the histology and function of renal allografts. *Am J Transplant.* 2019;19(6):1730-1744.

89. Masson P, Henderson L, Chapman JR, et al. Belatacept for kidney transplant recipients. *Cochrane Database Syst Rev.* 2014(11):CD010699.

90. Vincenti F, Rostaing L, Grinyo J, et al. Belatacept and long-term outcomes in kidney transplantation. *N Engl J Med.* 2016;374(4):333-343.

91. Cohen JB, Eddinger KC, Forde KA, et al. Belatacept compared with tacrolimus for kidney transplantation: a propensity score matched cohort study. *Transplantation.* 2017;101(10):2582-2589.

92. Adams AB, Goldstein J, Garrett C, et al. Belatacept combined with transient calcineurin inhibitor therapy prevents rejection and promotes improved long-term renal allograft function. *Am J Transplant.* 2017;17(11):2922-2936.

93. Kuningas K, Driscoll J, Mair R, et al. Comparing glycaemic benefits of active versus passive lifestyle intervention in kidney allograft recipients: a randomized controlled trial. *Transplantation.* 2020;104(7):1491-1499.

94. Hecking M, Haidinger M, Doller D, et al. Early basal insulin therapy decreases new-onset diabetes after renal transplantation. *J Am Soc Nephrol.* 2012;23(4):739-749.

95. Lo C, Jun M, Badve SV, et al. Glucose-lowering agents for treating pre-existing and new-onset diabetes in kidney transplant recipients. *Cochrane Database Syst Rev.* 2017;2:CD009966.

96. Zhang L, Feng Y, List J, et al. Dapagliflozin treatment in patients with different stages of type 2 diabetes mellitus: effects on glycaemic control and body weight. *Diabetes Obes Metab.* 2010;12(6):510-516.

97. Heerspink HJ, Perkins BA, Fitchett DH, et al. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation.* 2016;134(10):752-772.

98. Ferrannini E, Solini A. SGLT2 inhibition in diabetes mellitus: rationale and clinical prospects. *Nat Rev Endocrinol.* 2012;8(8):495-502.

99. Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373(22):2117-2128.

100. Neal B, Perkovic V, Mahaffey KW, et al; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med.* 2017;377(7):644-657.

101. Cannon CP, Pratley R, Dagogo-Jack S, et al; VERTIS CV Investigators. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med.* 2020;383:1425-1435.

102. Cherney DZI, Charbonnel B, Cosentino F, et al; VERTIS CV Investigators. Effects of ertugliflozin on kidney composite outcomes, renal function and albuminuria in patients with type 2 diabetes mellitus: an analysis from the randomised VERTIS CV trial. *Diabetologia.* 2021;64:1256-1267.

103. Jardine MJ, Mahaffey KW, Neal B, et al; CREDENCE Study Investigators. The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study rationale, design, and baseline characteristics. *Am J Nephrol.* 2017;46(6):462-472.

104. Fioretto P, Zambon A, Rossato M, et al. SGLT2 inhibitors and the diabetic kidney. *Diabetes Care.* 2016;39 Suppl 2:S165-171.

105. Rajasekeran H, Lytvyn Y, Cherney DZI. Sodium-glucose cotransporter 2 inhibition and cardiovascular risk reduction in patients with type 2 diabetes: the emerging role of natriuresis. *Kidney Int.* 2016;89(3):524-526.

106. Cherney DZI, Scholey JW, Jiang S, et al. The effect of direct renin inhibition alone and in combination with ACE inhibition on endothelial function, arterial stiffness, and renal function in type 1 diabetes. *Diabetes Care.* 2012;35(11):2324-2330.

107. Cherney DZI, Perkins BA, Soleymanlou N, et al. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. *Cardiovasc.* 2014;13:28.

108. Lytvyn Y, Bjornstad P, Udell JA, et al. Sodium glucose cotransporter-2 inhibition in heart failure: potential mechanisms, clinical applications, and summary of clinical trials. *Circulation.* 2017;136(17):1643-1658.

109. Baker WL, Smyth LR, Riche DM, et al. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: a systematic review and meta-analysis. *J Am Soc Hypertens.* 2014;8(4):262-275.e9.

110. Thomas MC, Cherney DZI. The actions of SGLT2 inhibitors on metabolism, renal function and blood pressure. *Diabetologia.* 2018;61(10):2098-2107.

111. Verma S, Garg A, Yan AT, et al. Effect of empagliflozin on left ventricular mass and diastolic function in individuals with diabetes: an important clue to the EMPA-REG OUTCOME trial? *Diabetes Care.* 2016;39(12):e212-e213.

112. Ferrannini E, Mark M, Mayoux E. CV protection in the EMPA-REG OUTCOME trial: a "thrifty substrate" hypothesis. *Diabetes Care.* 2016;39(7):1108-1114.

113. Hesp AC, Schaub JA, Prasad PV, et al. The role of renal hypoxia in the pathogenesis of diabetic kidney disease: a promising target for newer renoprotective agents including SGLT2 inhibitors? *Kidney Int.* 2020;98(3):579-589.

114. Zhao L, Gao H, Lian F, et al. 1H-NMR-based metabonomic analysis of metabolic profiling in diabetic nephropathy rats induced by streptozotocin. *Am J Physiol Renal Physiol.* 2011;300(4):F947-956.

115. Gilbert RE. Proximal tubulopathy: prime mover and key therapeutic target in diabetic kidney disease. *Diabetes.* 2017;66(4):791-800.

116. Fine LG, Orphanides C, Norman JT. Progressive renal disease: the chronic hypoxia hypothesis. *Kidney Int Suppl.* 1998;65:S74-78.

117. Zeni L, Norden AGW, Cancarini G, et al. A more tubulocentric view of diabetic kidney disease. *J Nephrol.* 2017;30(6):701-717.

118. Tang SCW, Lai KN. The pathogenic role of the renal proximal tubular cell in diabetic nephropathy. *Nephrol Dial Transplant.* 2012;27(8):3049-3056.

119. Remuzzi G, Ruggenenti P, Benigni A. Understanding the nature of renal disease progression. *Kidney Int.* 1997;51(1):2-15.

120. Yao D, Wang S, Wang M, et al. Renoprotection of dapagliflozin in human renal proximal tubular cells via the inhibition of the high mobility group box 1-receptor for advanced glycation end products-nuclear factor-κB signaling pathway. *Mol Med Rep.* 2018;18(4):3625-3630.

121. Bonnet F, Scheen AJ. Effects of SGLT2 inhibitors on systemic and tissue low-grade inflammation: the potential contribution to diabetes complications and cardiovascular disease. *Diabetes Metab.* 2018;44(6):457-464.

122. Mancini SJ, Boyd D, Katwan OJ, et al. Canagliflozin inhibits interleukin-1beta-stimulated cytokine and chemokine secretion in vascular endothelial cells by AMP-

activated protein kinase-dependent and -independent mechanisms. *Sci Rep.* 2018;8(1):5276.

123. Xu C, Wang W, Zhong J, et al. Canagliflozin exerts anti-inflammatory effects by inhibiting intracellular glucose metabolism and promoting autophagy in immune cells. *Biochem Pharmacol.* 2018;152:45-59.

124. Yaribeygi H, Butler AE, Atkin SL, et al. Sodium-glucose cotransporter 2 inhibitors and inflammation in chronic kidney disease: possible molecular pathways. *J Cell Physiol.* 2018;234(1):223-230.

125. Dekkers CCJ, Petrykiv S, Laverman GD, et al. Effects of the SGLT-2 inhibitor dapagliflozin on glomerular and tubular injury markers. *Diabetes Obes Metab.* 2018;20(8):1988-1993.

126. Díaz-Rodríguez E, Agra RM, Fernández AL, et al. Effects of dapagliflozin on human epicardial adipose tissue: modulation of insulin resistance, inflammatory chemokine production, and differentiation ability. *Cardiovasc Res.*2018;114(2):336-346.

127. Garvey WT, Van Gaal L, Leiter LA, et al. Effects of canagliflozin versus glimepiride on adipokines and inflammatory biomarkers in type 2 diabetes. *Metabolism.* 2018;85:32-37.

128. Inzucchi SE, Zinman B, Fitchett D, et al. How does empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA-REG OUTCOME trial. *Diabetes Care.* 2018;41(2):356-363.

129. Li J, Neal B, Perkovic V, et al. Mediators of the effects of canagliflozin on kidney protection in patients with type 2 diabetes. *Kidney Int.* 2020;98(3):769-777.

130. Li J, Woodward M, Perkovic V, et al. Mediators of the effects of canagliflozin on heart failure in patients with type 2 diabetes. *JACC Heart Fail.* 2020;8(1):57-66.

131. Oshima M, Neuen BL, Jardine MJ, et al. Effects of canagliflozin on anaemia in patients with type 2 diabetes and chronic kidney disease: a post-hoc analysis from the CREDENCE trial. *Lancet Diabetes Endocrinol.* 2020;8(11):903-914.

132. Lawler PR, Liu H, Frankfurter C, et al. Changes in cardiovascular biomarkers associated with the sodium-glucose cotransporter 2 (SGLT2) inhibitor ertugliflozin in patients with chronic kidney disease and type 2 diabetes. *Diabetes Care.* 2021;44(3):e45-e47.

133. Sano M, Takei M, Shiraishi Y, et al. Increased hematocrit during sodium-glucose cotransporter 2 inhibitor therapy indicates recovery of tubulointerstitial function in diabetic kidneys. *J Clin Med Res.* 2016;8(12):844-847.

134. Lambers Heerspink HJ, De Zeeuw D, Wie L, et al. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. *Diabetes Obes Metab.* 2013;15(9):853-862.

135. Packer M. Cardioprotective effects of sirtuin-1 and its downstream effectors: potential role in mediating the heart failure benefits of SGLT2 (Sodium-Glucose Cotransporter 2) inhibitors. *Circ Heart Fail.* 2020;13(9):e007197.

136. Sridhar VS, Tuttle KR, Cherney DZI. We can finally stop worrying about SGLT2 inhibitors and acute kidney injury. *Am J Kidney Dis.* 2020;76(4):454-456.

137. Rajasekeran H, Kim SJ, Cardella CJ, et al. Use of canagliflozin in kidney transplant recipients for the treatment of type 2 diabetes: a case series. *Diabetes Care.* 2017;40(7):e75-e76.

138. Mahling M, Schork A, Nadalin S, et al. Sodium-glucose cotransporter 2 (SGLT2) inhibition in kidney transplant recipients with diabetes mellitus. *Kidney Blood Press Res.* 2019;44(5):984-992.

139. AlKindi F, Al-Omary HL, Hussain Q, et al. Outcomes of SGLT2 inhibitors use in diabetic renal transplant patients. *Transplant Proc.* 2020;52(1):175-178.

140. Schwaiger E, Burghart L, Signorini L, et al. Empagliflozin in posttransplantation diabetes mellitus: a prospective, interventional pilot study on glucose metabolism, fluid volume, and patient safety. *Am J Transplant.* 2019;19(3):907-919.

141. Song CC, Brown A, Winstead R, et al. Early initiation of sodium-glucose linked transporter inhibitors (SGLT-2i) and associated metabolic and electrolyte outcomes in diabetic kidney transplant recipients. *Endocrinol Diabetes Metab.* 2021;4(2):e00185.

142. Cehic MG, Muir CA, Greenfield JR, et al. Efficacy and safety of empagliflozin in the management of diabetes mellitus in heart transplant recipients. *Transplant Direct.* 2019;5(5):e450.

143. Halden TAS, Kvitne KE, Midtvedt K, et al. Efficacy and safety of empagliflozin in renal transplant recipients with posttransplant diabetes mellitus. *Diabetes Care.* 2019;42(6):1067-1074.

144. Beshyah SA, Beshyah AS, Beshyah WS, et al. Use of SGLT2 inhibitors in diabetic renal transplant recipients: a mixed method exploratory exercise. *Int J Diabetes Metab.* 2018;24:16-21.

145. Karthikeyan V, Karpinski J, Nair RC, et al. The burden of chronic kidney disease in renal transplant recipients. *Am J Transplant.* 2004;4(2):262-269.

146. Canadian Institute for Health Information. *Canadian Organ Replacement Register (CORR).* Available at https://www.cihi.ca/en/canadian-organ-replacement-register-corr. Accessed October 1, 2019.

147. Young A, Dixon SN, Knoll GA, et al. The Canadian experience using the expanded criteria donor classification for allocating deceased donor kidneys for transplantation. *Can J Kidney Health Dis.* 2016;3:15.

148. Drucker DJ. The biology of incretin hormones. *Cell Metab.* 2006;3(3):153-165.

149. Nauck M. Incretin therapies: highlighting common features and differences in the modes of action of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. *Diabetes Obes Metab.* 2016;18(3):203-216.

150. Bethel MA, Patel RA, Merrill P, et al; EXSCEL Study Group. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. *Lancet Diabetes Endocrinol.* 2018;6(2):105-113.

151. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med.* 2015;373(23):2247-2257.

152. Mann JFE, Ørsted DD, Brown-Frandsen K, et al; LEADER Steering Committee and Investigators. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med.* 2017;377(9):839-848.

153. Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus 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(8):605-617.

154. Gerstein HC, Colhoun HM, Dagenais GR, et al; 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.

155. Tonneijck L, Muskiet MHA, Smits MM, et al. Glomerular hyperfiltration in diabetes: mechanisms, clinical significance, and treatment. *J Am Soc Nephrol.* 2017;28(4):1023-1039.

156. Tonneijck L, Smits MM, Muskiet MHA, 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(11):2042-2050.

157. Muskiet MHA, Tonneijck L, Huang Y, et al. Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: an exploratory analysis of the ELIXA randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol.* 2018;6(11):859-869.

158. Tuttle KR, Lakshmanan MC, Rayner B, et al. Body weight and eGFR during dulaglutide treatment in type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7). *Diabetes Obes Metab.* 2019;21(6):1493-1497.

159. Tuttle KR, Cherney DZ, Hadjadj S, et al. Effects of semaglutide on CKD outcomes: a post hoc pooled analysis from the SUSTAIN 6 and PIONEER 6 trials [abstract]. *Articles, Abstracts, and Reports*. 2020;3956.

160. Pyke C, Heller RS, Kirk RK, et al. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. *Endocrinology.* 2014;155(4):1280-1290.

161. Muskiet MHA, Tonneijck L, Smits MM, et al. Acute renal haemodynamic effects of glucagon-like peptide-1 receptor agonist exenatide in healthy overweight men. *Diabetes Obes Metab.* 2016;18(2):178-185.

162. Tonneijck L, Smits MM, Muskiet MHA, et al. Acute renal effects of the GLP-1 receptor agonist exenatide in overweight type 2 diabetes patients: a randomised, double-blind, placebo-controlled trial. *Diabetologia.* 2016;59(7):1412-1421.

163. Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. *Circulation.* 2019;139(17):2022-2031.

164. Kukla A, Hill J, Merzkani M, et al. Use of GLP-1 receptor agonists in kidney transplant recipients with type 2 diabetes [abstract]. *Am J Transplant.* 2019;19.

165. Pinelli NR, Patel A, Salinitri FD. Coadministration of liraglutide with tacrolimus in kidney transplant recipients: a case series. *Diabetes Care.* 2013;36(10):e171-172.

166. 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(8):2502-2505.

167. Singh P, Pesavento TE, Washburn K, et al. Largest single-centre experience of dulaglutide for management of diabetes mellitus in solid organ transplant recipients. *Diabetes Obes Metab.* 2019;21(4):1061-1065.

168. Halden TAS, Egeland EJ, Åsberg A, et al. GLP-1 restores altered insulin and glucagon secretion in posttransplantation diabetes. *Diabetes Care.* 2016;39(4):617-624.

169. Chan GCW, Tang SCW. Diabetic nephropathy: landmark clinical trials and tribulations. *Nephrol Dial Transplant.* 2016;31(3):359-368.

170. Cherney DZI, Lam TKT. A gut feeling for metformin. *Cell Metab.* 2018;28(6):808-810.

171. Frías JP, Guja C, Hardy E, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol.* 2016;4(12):1004-1016.

172. Ludvik B, Frías JP, Tinahones FJ, et al. Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol.* 2018;6(5):370-381.

173. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. *Clin J Am Soc Nephrol.* 2017;12(12):2032-2045.

174. Navarro-González JF, Mora-Fernández C, Muros de Fuentes M, et al. Inflammatory molecules and pathways in the pathogenesis of diabetic nephropathy. *Nat Rev Nephrol.* 2011;7(6):327-340.

175. Pichler R, Afkarian M, Dieter BP, et al. Immunity and inflammation in diabetic kidney disease: translating mechanisms to biomarkers and treatment targets. *Am J Physiol Renal Physiol.* 2017;312(4):F716-F731.

176. Ridker PM, Everett BM, Thuren T, et al; CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med.* 2017;377(12):1119-1131.

177. Ridker PM, MacFadyen JG, Glynn RJ, et al. Inhibition of interleukin-1β by canakinumab and cardiovascular outcomes in patients with chronic kidney disease. *J Am Coll Cardiol.* 2018;71(21):2405-2414.

178. Heerspink HJL, Parving HH, Andress DL, et al; SONAR Committees and Investigators. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. *Lancet.* 2019;393:1937-1947.

179. Mann JF, Green D, Jamerson K, et al; ASCEND Study Group. Avosentan for overt diabetic nephropathy. *J Am Soc Nephrol.* 2010;21(3):527-535.

180. Wenzel RR, Littke T, Kuranoff S, et al; SPP301 (Avosentan) Endothelin Antagonist Evaluation in Diabetic Nephropathy Study Investigators. Avosentan reduces albumin excretion in diabetics with macroalbuminuria. *J Am Soc Nephrol.* 2009;20(3):655-664.

181. Kohan DE, Pritchett Y, Molitch M, et al. Addition of atrasentan to renin-angiotensin system blockade reduces albuminuria in diabetic nephropathy. *J Am Soc Nephrol.* 2011;22(4):763-772.

182. Ruggenenti P, Cravedi P, Remuzzi G. The RAAS in the pathogenesis and treatment of diabetic nephropathy. *Nat Rev Nephrol.* 2010;6(6):319-330.

183. Lytvyn Y, Godoy LC, Scholtes RA, et al. Mineralocorticoid antagonism and diabetic kidney disease. *Curr Diab Rep.* 2019;19(1):4.

184. Bakris GL, Agarwal R, Anker SD, et al; FIDELIO-DKD Investigators. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med.* 2020;383(23):2219-2229.

185. Lenihan CR, Liu S, Deswal A, et al. De novo heart failure after kidney transplantation: trends in incidence and outcomes. *Am J Kidney Dis.* 2018;72(2):223-233.

186. Haynes R, Zhu D, Judge PK, et al. Chronic kidney disease, heart failure and neprilysin inhibition. *Nephrol Dial Transplant.* 2020;35(4):558-564.

187. Packer M, Claggett B, Lefkowitz MP, et al. Effect of neprilysin inhibition on renal function in patients with type 2 diabetes and chronic heart failure who are receiving target doses of inhibitors of the renin-angiotensin system: a secondary analysis of the PARADIGM-HF trial. *Lancet Diabetes Endocrinol.* 2018;6(7):547-554.

188. Haynes R, Judge PK, Staplin N, et al. Effects of sacubitril/valsartan versus irbesartan in patients with chronic kidney disease. *Circulation.* 2018;138(15):1505-1514.

189. Capasso G, Unwin R, Ciani F, et al. Inhibition of neutral endopeptidase potentiates the effects of atrial natriuretic peptide on acute cyclosporin-induced nephrotoxicity. *Nephron.* 2000;86(3):298-305.

190. Takeda Y, Inaba S, Furukawa K, et al. Effects of chronic neutral endopeptidase inhibition in rats with cyclosporine-induced hypertension. *J Hypertens.* 2000;18(7):927-933.

191. Lipkin GW, Thuraisingham R, Dawnay AB, et al. Acute reversal of cyclosporine nephrotoxicity by neutro endopeptidase inhibition in stable renal transplant recipients. *Transplantation.* 1997;64(7):1007-1017.

192. Armstrong PW, Pieske B, Anstrom KJ, et al; VICTORIA Study Group. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2020;382(20):1883-1893.

193. Swedberg K, Komajda M, Böhm M, et al; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet.* 2010;376(9744):875-885.

194. Lunney M, Ruospo M, Natale P, et al. Pharmacological interventions for heart failure in people with chronic kidney disease. *Cochrane Database Syst Rev.* 2020;2:CD012466.

195. Tang H, Li D, Zhang J, et al. Sodium-glucose co-transporter-2 inhibitors and risk of adverse renal outcomes among patients with type 2 diabetes: a network and cumulative meta-analysis of randomized controlled trials. *Diabetes Obes Metab.* 2017;19(8):1106-1115.

196. Parasuraman R, Julian K; AST Infectious Diseases Community of Practice. Urinary tract infections in solid organ transplantation. *Am J Transplant.* 2013;13 Suppl 4:327-336.

197. Morita K, Seki T, Nonomura K, et al. Changes in renal blood flow in response to sympathomimetics in the rat transplanted and denervated kidney. *Int J Urol.* 1999;6(1):24-32.

198. Cippà PE, Schiesser M, Ekberg H, et al. Risk stratification for rejection and infection after kidney transplantation. *Clin J Am Soc Nephrol.* 2015;10(12):2213-2220.

199. Vanhove T, Remijsen Q, Kuypers D, et al. Drug-drug interactions between immunosuppressants and antidiabetic drugs in the treatment of post-transplant diabetes mellitus. *Transplant Rev (Orlando).* 2017;31(2):69-77.

200. Haidinger M, Werzowa J, Hecking M, et al. Efficacy and safety of vildagliptin in new-onset diabetes after kidney transplantation--a randomized, double-blind, placebo-controlled trial. *Am J Transplant.* 2014;14(1):115-123.

201. Strøm Halden TA, Åsberg A, Vik K, et al. Short-term efficacy and safety of sitagliptin treatment in long-term stable renal recipients with new-onset diabetes after transplantation. *Nephrol Dial Transplant.* 2014;29(4):926-933.

202. Naesens M, Kuypers DRJ, Sarwal M. Calcineurin inhibitor nephrotoxicity. *Clin J Am Soc Nephrol.* 2009;4(2):481-508.

FIGURE TITLE AND LEGEND

Figure 1. Pharmacologic agents, their mechanisms of action, and potential clinical impact in kidney transplant recipients. CCB, calcium channel blocker; CNI, calcineurin inhibitor; DBP, diastolic blood pressure; DPP4i, dipeptidyl peptidase-4 inhibitor; ET-1R, endothelin-1 receptor; GFR, glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; mTORi, mammalian target of rapamycin inhibitor; MRA, mineralocorticoid receptor antagonist; PCSK9, proprotein convertase subtilisin/kexin type 9; RAASi, renin angiotensin aldosterone system inhibitor; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Table 1. Summary of the benefits and risks observed with potential glucose-lowering strategies in studies with KTRs.

	Potential benefits	Benefits studied in KTR	Risks
Insulin therapy	↓ risk of developing PTDM Used across a wide eGFR range	↓ risk of developing PTDM by 73% in KTR with hyperglycemia NPH insulin well-suited to diurnal effect of prednisone	↑ risk of hypoglycemia Neutral or ↓ graft survival with intensive insulin therapy ↑weight
Metformin	↓ insulin resistance ↓ risk of hypoglycemia Weight neutral	Favorable safety profile Low risk of drug-drug interactions	GFR cut off for KTR use is unknown GI side effects
SGLT2i	↓ HbA1c ↓ risk of hypoglycemia ↓ weight ↓ blood pressure ↓ major adverse cardiac events ↓ albuminuria ↓ decline in eGFR	↓ HbA1c ↓ weight ↓ blood pressure No significant side effects observed (ketoacidosis, AKI, acute rejection, urinary/mycotic infections, or clinically significant changes in CNI levels)	GFR cut off for KTR use is unknown Small sample size and few short-term studies available Risk of UTIs Heart and kidney benefits have yet to be demonstrated in this population
GLP-1R agonists	↓ HbA1c ↓ weight ↓ blood pressure Improved lipid profiles ↓ albuminuria ↓ decline in eGFR	Safely tolerated ↑ insulin secretion ↓ glucagon concentration ↓ HbA1c ↓ weight No CNI interactions Stable or improved eGFR	Only data from small, short-term case studies available GI intolerance. Effect of delayed gastric emptying on drug disposition unknown. Heart and kidney benefits have yet to be demonstrated in this population
DPP-4 inhibitors	↓ HbA1c ↓ albuminuria ↓ glomerulosclerosis Weight neutral	Safely tolerated ↓ HbA1c Used across a wide eGFR range	Only data from small short-term studies available No evidence of renal protection

AKI, acute kidney injury; CNI, calcineurin inhibitor; DPP-4, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GLP-1R, glucagon-like peptide-1 receptor; HbA1c, hemoglobin A1c; KTR, kidney transplant recipient; NPH, neutral protamine Hagedorn; PTDM, posttransplantation diabetes mellitus; SGLT2i, sodium-glucose cotransporter 2 inhibitor; UTI, urinary tract infections.

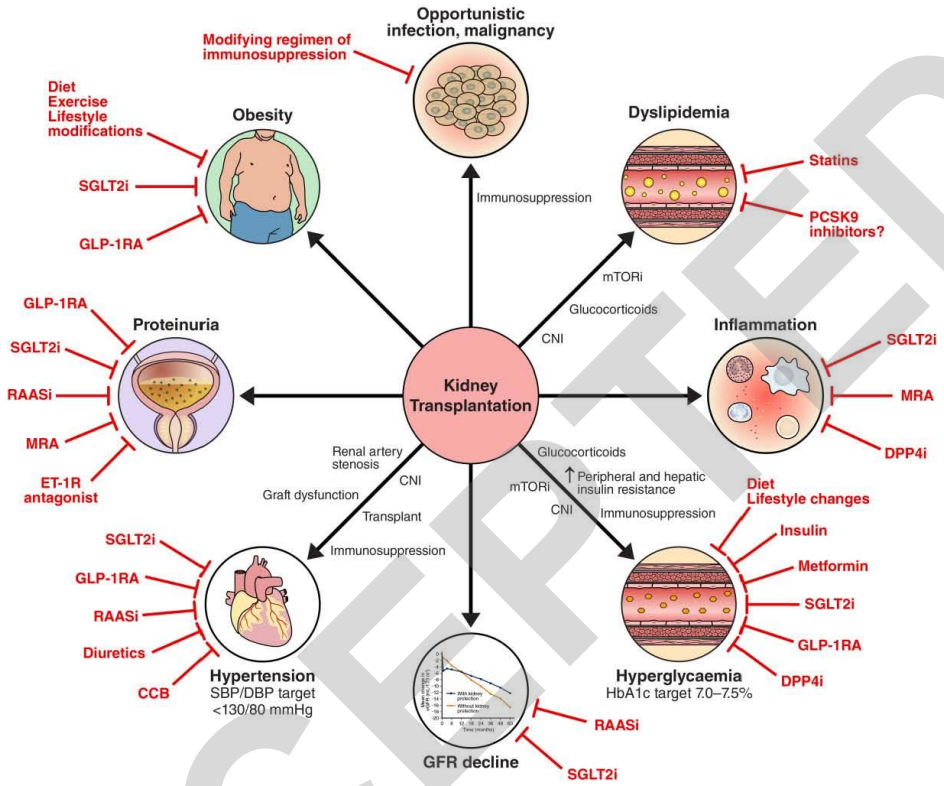
Table 2. Summary of studies of SGLT2i's in kidney transplant recipients.

Observational studies				
Author, year	**Participants**	**Design**	**Treatment**	**Results**
Rajasekeran et al,[137] 2017	N = 10 KTR & SPKTR with PTDM or T2D	Observational cohort study, 80.5 person-months follow-up	Canagliflozin	Weight, kg: -2.14 (SD 2.8) Systolic blood pressure, mmHg: -6.5 (SD 10.8) Diastolic blood pressure, mmHg: -4.8 (SD 12) Serum creatinine, mmol/L: 9.7 (SD 14.6); eGFR, mL/min/1.73m^2 : -4.3 (SD 12.2) No urinary/mycotic infections, AKI or acute rejection
Mahling et al,[138] 2019	N = 10 KTR with PTDM or T2D	Observational study, 6.3 person-years	Empagliflozin	Weight, kg: -1.9 (-1.9 to 0.1) Systolic blood pressure, mmHg: -2.5 (-36.3 to 0.8) Diastolic blood pressure, mmHg: -0.5 (-9.5 to 7.5) 2 episodes of UTI, 1 episode of AKI
Alkindi et al,[139] 2020	N = 8 KTR with PTDM or T2D	Retrospective chart review	Empagliflozin (6 patients), dapagliflozin (2 patients)	BMI, kg/m^2, 32.7±7.2 to 27.4±4.2 after 12 months (P <0.05) Systolic blood pressure, mmHg: 135±9.6 to 126.4±11.5 after 12 months (P >0.05) Diastolic blood pressure, mmHg: 80.6±10 to 74.5±7.3 after 12 months (P >0.05) eGFR, no significant change 1 episode of UTI, no AKI, ketoacidosis, acute rejection
Schwaiger et al,[140] 2019	N = 14 KTR with PTDM, 6 months posttransplant, eGFR ≥ 30ml/min/1.73 m^2, stable on insulin therapy	Open-label, single-arm, noninferiority study Single-center study	Treatment with empagliflozin 10 mg after discontinuation of insulin therapy, 4 weeks	Change in baseline to 4 week OGTT - fasting and 2- hour glucose levels increased to 144 ± 45 mg/dL (P = 0.005) and 273 ± 116 mg/dL (P = 0.06), respectively Avg body weight: -1.6kg; Bioimpedance volume status: fluid overload decreased from 2.7 ± 2.1 (baseline) to 1.8 ± 1.8L (P = 0.006) 5 episodes of urinary tract

				infection
Song et al,[141] 2021	N = 50 KTR with T2D or PTDM, no UTI in 6 months prior to SGLT2i initiation, eGFR ≥ 30ml/min/1.73 m^2	Retrospective, observational study	Varying SGLT2i's based on patients' insurance coverage	Weight loss: −2.95 kg [(SD 3.54, *P* = <0.0001 (CI: 3.53, 1.50)]; Increase in magnesium: 0.13 [(SD 1.73, *P* = 0.0004 (CI: 0.06, 0.20)]; eGFR, no significant change 7 (14%) cases of treated urinary tract infections; No episodes of DKA, amputation, AKI.
RCT				
Author, year	**Participants**	**Design**	**Treatment**	**Results**
Halden et al,[143] 2019	N = 49 KTR with PTDM, 1 year posttransplant, eGFR ≥30m/min/1.73 m^2	Double-blind RCT Single-center study	1:1 empagliflozin 10mg vs placebo, 24 weeks	**Secondary outcomes** Change in median HbA1c (%): -0.2 (-0.6 to -0.1) with empagliflozin vs +0.1 (-0.1 to 0.4); *P* = 0.025 Body weight: -2.5 kg (-4.0 to -0.05) with empagliflozin vs +1.0 kg (0.0 to 2.0); *P* = 0.014 24hr blood pressure – no difference in blood pressure between groups Safety outcomes – no significant between group differences

AKI, acute kidney injury; BMI, body mass index; CI, confidence interval; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; KTR, kidney transplant recipient; OGTT, Oral Glucose Tolerance Test; PTDM, posttransplant diabetes mellitus; RCT, randomized controlled trial; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SPKTR, simultaneous pancreas-kidney transplant recipient; T2D, type 2 diabetes; UTI, urinary tract infection.

Figure 1: Pharmacologic agents, their mechanisms of action and potential clinical impact in kidney transplant recipients



SGLT2i – sodium-glucose cotransporter 2 inhibitor; GLP-1RA – glucagon-like peptide-1 receptor agonist; RAASi – renin angiotensin aldosterone system inhibitor; MRA – mineralocorticoid receptor antagonist; ET-1R – endothelin-1 receptor; CCB – calcium channel blocker; DPP4i – dipeptidyl peptidase-4 inhibitors; CNI – calcineurin inhibitor; mTORi – mammalian target of Rapamycin inhibitors.