A year in diabetic nephropathy

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Abstract

Whilst 2020 was a year of unique healthcare challenges, in people with type 2 diabetes and diabetic kidney disease (DKD), it was a year of seminal progress. Randomised clinical trials have shown a significant benefit of sodium-glucose transporter-2 inhibitors in patients with DKD, and guidelines now suggest these drugs should be considered in all patients with type 2 diabetes and DKD irrespective of glucose control. Glucagon-like peptide-1 receptor agonists have shown some benefit in reducing progression of albuminuria in DKD, and should also be considered early in the therapeutic pathway. There are new guidelines on the management of post-transplant diabetes, and some new ideas in the management of diabetes in patients on haemodialysis. This article aims to review the year in diabetic nephropathy.

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Introduction

It is estimated that 40% of people living with type 2 diabetes (T2D) have diabetic kidney disease (DKD).[1] DKD is defined as persistently reduced estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 with micro- or macro-albuminuria.[2] T2D is the commonest cause of chronic kidney disease (CKD) worldwide requiring renal replacement therapy (RRT).[3] CKD and albuminuria are independent predictors of cardiovascular morbidity and mortality.[4]

In this article we review developments in the last year in patients with T2D and DKD, with a focus on new agents, new guidance on management of post-transplant diabetes mellitus (PTDM), and possible interventions in people with T2D on haemodialysis (HD).

New agents in diabetic kidney disease (DKD)

Patients with DKD are exemplars of multi-morbidity, often living with a number of long-term conditions and frailty. Treatment of DKD involves management of hypertension with angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), improvement in glucose control individualised to the patient, management of cardiovascular risk factors, regular monitoring of renal function and screening for other complications.[5] Multidisciplinary management with nephrologists is desirable when CKD is progressive. A number of interventions, such as combined ACEI/ARB,[6] direct renin inhibitors,[7] bardoxolone[8] and endothelin-A receptor antagonists[9] have been tested in DKD, with no evidence of benefit.

Cardiovascular outcomes trials (CVOTs) of newer agents in T2D have led to a wealth of cardiovascular and renal outcome data which have informed clinical practice.

Sodium-glucose transporter-2 inhibitors (SGLT2i)

Sodium-glucose transporter-2 inhibitors (SGLT2i) act on the proximal tubule to inhibit glucose reabsorption, promote glycosuria and result in improvements in glucose and body weight. As renal function declines, less glucose is filtered hence attenuating the anti-hyperglycaemic efficacy of these agents in CKD.[10] Several studies, however, suggest significant benefit in DKD independent of glucose control. Table 1 outlines the studies of SGLT2i in DKD.

In contrast to ACEI/ARBs, renoprotective effects of SGLT2i are thought to be mediated by tubuloglomerular feedback, natriuresis and glucose-induced osmotic diuresis which reduce intraglomerular pressure.[11]

Empagliflozin

In the EMPA-REG OUTCOME study, empagliflozin was shown to be effective and safe in patients with mild renal impairment (mean eGFR 74.1 mL/min/1.73 m²) and established cardiovascular disease (CVD).[12] Empagliflozin reduced all-cause mortality by 32% (hazard ratio (HR) 0.68 [95% confidence interval (CI) 0.57 to 0.82]; p<0.001), hospitalisation for heart failure (hHF) by 35% (HR 0.65 [0.50 to 0.85]; p=0.002) and cardiovascular-related death by 38% (HR 0.62 [0.49 to 0.77]; p<0.001). In a subgroup analysis, the EMPA-REG RENAL study, a 38% reduction in macroalbuminuria onset, 44% reduction in doubling serum creatinine and 55% reduction in patients requiring RRT was seen across all CKD stages.[13]

The EMPEROR-Reduced trial examined participants with heart failure and mean eGFR 62 mL/min/1.73 m^2, 50% of whom had T2D.[14] Empagliflozin led to a significantly lower rate of eGFR decline compared with placebo (–0.55 vs –2.28 mL/min/1.73 m^2; p<0.001). The risk of dialysis/transplantation or sustained reduction

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Table 1 Cardiovascular and renal outcome studies using sodium-glucose transporter-2 inhibitors (SGLT-2i)

Trial Intervention (N) Median follow-up	Study population characteristics General	 Renal	Cardiovascular outcomes	Renal outcomes
Dapagliflozin				
DECLARE TIMI 58[18] Dapagliflozin 10 mg vs placebo N=17,160 4.2 years	T2D (100%) Established CVD (40.6%) CV risk factors (59.4%) ACE-I/ARB (86.7%)	**eGFR (mL/min/1.73 m²)** Mean 85 ≥90 (47.6%) 60–90 (45.1%) <60 (7.4%) **Albuminuria (mg/g)** <30 (69.1%) ≥30-≤30 (23.9%) >300 (6.9%)	**17% reduction CV death or hHF** (HR 0.83 [0.73 to 0.95]; p=0.005) **No effect on MACE** (HR 0.93 [0.84 to 1.03]; p=0.17) No significant difference in CV death, death from any cause	**47% RRR in the renal composite*** (HR 0.53 [0.43 to 0.66]; p<0.0001) **59% RRR in risk of ESKD or renal death** (HR 0.41 [0.20 to 0.82]; p=0.012) **Reduced eGFR decline at 3.4 years**
DAPA-CKD[17] Dapagliflozin 10 mg vs placebo N= 4,304 2.4 years	T2D (67.5%) Established CVD (37%) Nearly all patients on an ACE-I/ARB	**eGFR (mL/min/1.73 m²)** mean eGFR 43.1 ≥60 (10%) 45–<60 (31%) 30–<45 (44.1%) <30 (14.5%) **Albuminuria (mg/g)** Range 200–5000 >1000 (48.3%) Mean/median 949	**29% reduction in the composite of death from CV causes or hHF** (HR 0.71 [0.55 to 0.92]; p=0.009) **31% reduction in death from any cause** (HR 0.69 [0.53 to 0.88]; p=0.004)	**44% reduction in the renal composite†** (HR 0.56 [0.45 to 0.68]; p<0.001)
DAPA-HF[16] N= 4644 18.2 months	T2D (45%) NYHA 2,3,4, EF ≤40% Majority of patients on ACE-I/ARB	**eGFR (mL/min/1.73 m²)** eGFR >30 Mean 66 <60 (40.6%)	**25% reduction in CV death or hHF** (HR 0.75 [0.65 to 0.85]; p<0.001) **17% reduction in all-cause mortality** (HR 0.83 [0.71 to 0.97])	**39% non-significant reduction in worsening renal function†** (HR 0.71 [0.44 to 16]; p=0.17) **Smaller eGFR decline per year** (dapagliflozin –1.09 (–1.41, –0.78) vs placebo –2.87(–3.19, –2.55)(p<0.001)
Empagliflozin				
EMPA-REG OUTCOME[11] Empagliflozin 10 mg/ 15 mg vs placebo 3.1 years N=7,020	T2D (100%) Established CVD (99%) ACE-I/ARB (80.7%)	**eGFR (mL/min/1.73 m²)** eGFR >30 Mean 74·1 45–59 (17.8%) 30–44 (7.7%) **Albuminuria (mg/g)** 30–300 (28.7%) >300 (11%)	**14% reduction in 3p-MACE§** (HR 0.86 [0.74 to 0.99]) **38% RRR in CV death** (HR 0.62 [0.49 to 0.77]; p<0.001) **35% reduction in hHF** (HR 0.65 [0.50 to 85]; p=0.002) **32% reduction in death from any cause** (HR 0.68 [0.57 to 0.82]; p<0.001) No effect on MI/stroke	**46% reduction in composite renal outcome††** (HR 0.54 [0.40 to 0.75]; p<0.001) **39% reduction in incident or worsening of nephropathy‡** (HR 0.61 [0.53 to 0.70]; p<0.001)
EMPEROR REDUCED[13] Empagliflozin 10 mg vs placebo N=3,730 16 months	T2D (50%) EF ≤40% EF <30% (73%) >30% (27%) hHF in last 12 months or NT-proBNP of at least 1000 pg/mL (79%) Majority on ACEi/ARB	**eGFR (mL/min/1.73 m²)** Mean 62 eGFR <60 (48%)	**25% reduction in hHf or CV death** (HR 0.75 [0.65 to 0.86]; p<0.001)	**50% reduction in renal composite renal §§** (HR 0.50 [0.32 to 0.77]; significance level not specified)

Continued...

Table 1 Cardiovascular and renal outcome studies using sodium-glucose transporter-2 inhibitors (SGLT-2i) continued

Trial Intervention (N) Median follow-up	Study population characteristics General	 Renal	Cardiovascular outcomes	Renal outcomes
Canagliflozin				
CANVAS Program[14] (CANVAS and CANVAS-R trials) Canagliflozin 100 mg/ 300 mg vs placebo N=10,142 2.4 years	T2D (100%) Established CVD (65.6%) CV risk factors (34.4%)	**eGFR (mL/min/1.73 m²)** eGFR >30 Mean eGFR 76.5 **Albuminuria (mg/g)** Median 12.3 30–300 (22.6%) >300 (7.6%)	**14% reduction in 3p-MACE§** (HR 0.86 [0.75 to 0.97]; p=0.02) No significant difference in CV death, death from any cause	**40% reduction in the composite renal outcome¶** (HR 0.60 [0.47 to 0.77];p<0.01) **27% reduction in albuminuria progression** (HR 0.73 [0.67 to 0.79]; p<0.001)
CREDENCE[15] Canagliflozin 100 mg vs placebo N=4,401 2.62 years	T2D (100%) ACE-i/ARB (100%)	**eGFR (mL/min/1.73 m²)** eGFR >30 Mean 56.2 **Albuminuria (mg/g)** 300–5000	**31% reduction in CV composite**** (HR 0.69 [0.57 to 0.83]; p<0.001) **20% reduction in CV death, MI, stroke** (HR 0.80 [0.67 to 0.95]; p=0.01)	**34% reduction in renal-specific composite††** (HR 0.66 [0.53 to 0.81];p<0.001) **32% reduction in ESRD‡‡** (HR 0.68 [0.54 to 0.86];p=0.002) **40% reduction in doubling of serum creatinine** (HR 0.60 [0.48 to 0.76];p<0.001)
Sotagliflozin				
SCORED trial[68] Sotagliflozin vs placebo N=10,500 95 days	T2D (100%) CKD and one additional cardiovascular risk factor RAAS inhibitor (88%)	**eGFR (mL/min/1.73 m²)** Median 44.5 <30 (7%) 30–45 (44%) ≥45 (48%) **Albuminuria (mg/g)** Median 74 <30 (35%) 30–<300 (33%) ≥300 (32%)	**26% reduction in CV deaths, hHF, urgent HF visits** (HR 0.74 [0.63 to 0.88]; p=0.0004)	**29% reduction in renal composite¶¶** (HR 0.71 [0.46 to 1.08]; significance level not specified)
Ertugliflozin				
VERTIS-CV[69] Ertugliflozin 5 mg/15 mg vs placebo N=8,246 3.5 years	T2D (100%) Established ASCVD Known coronary artery disease: 76%, prior MI: 48%, known CVD: 23%	**eGFR (mL/min/1.73 m²)** eGFR >30 Mean 76 60–89 (53%) 30–59 (22%) **Albuminuria (mg/g)** <30 (60%) >30 (40%)	**3% reduction in 3p-MACE** (HR 0.97 [0.85 to 1.11];	**19% reduction in renal composite††** (HR 0.81 [0.63 to 1.04]; p=0.08)

* Renal composite: eGFR decline of ≥40% to <60 mL/min/1.73 m², ESKD (dialysis for >90 days, kidney transplantation or confirmed sustained eGFR <15 mL/min/1.73 m² or death from renal causes.
† Worsening renal function: eGFR decline of ≥50%, ESKD or death from renal causes.
‡ Worsening/incident nephropathy: progression to severely increased ACR, doubling of serum creatinine and an eGFR <45 mL/min/1.73 m², initiation of RRT or death from renal disease.
§ 3p-MACE: non-fatal MI, non-fatal stroke, death from CV causes.
¶ Renal composite: sustained 40% reduction in eGFR, need for RRT or death from renal causes.
** Cardiovascular composite: CV death or hospitalisation for heart failure.
†† Renal-specific composite: ESRD, doubling of creatinine, death from renal causes.
‡‡ ESRD: chronic dialysis for >30 days, kidney transplantation, eGFR <15 mL/min/1.73 m² sustained for >30 days.
§§ Renal composite: RRT, transplant, sustained eGFR reduction of 40% or more, eGFR <15 mL/min/1.73 m².
¶¶ Renal composite: ≥50% decrease in eGFR, RRT, renal transplantation, sustained eGFR of <15 mL/min/1.73 m² for ≥30 days.

ACE, angiotension converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CANVAS, CANagliflozin cardioVascular Assessment Study; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trials; DECLARE-TIMI-58, The Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; DAPA-CKD, dapagliflozin in chronic kidney disease; DAPA-H, dapagliflozin in heart failure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; EMPA-REG OUTCOME, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; EMPEROR-REDUCED, EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction; ESKD, end stage kidney disease; HbA_{1c}, glycated haemoglobin; HR, hazard ratio; 3p-MACE, three-point major adverse cardiovascular events; MI, myocardial infarction; RRR, relative risk reduction; RRT, renal replacement therapy; SCORED, Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease; T2D, type 2 diabetes; UACR, urine albumin creatinine ratio; VERTIS-CV, Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial.

in eGFR was halved in the empagliflozin group (HR 0.50 [0.32 to 0.77]; p<0.001).

A specific study of empagliflozin in patients with CKD, many of whom will have T2D, (EMPA-KIDNEY) is due to report in 2022.

Canagliflozin

Cardiovascular outcomes of canagliflozin were studied in the CANVAS program, involving 10,142 participants with T2D receiving standard care with inadequate glycaemic control, established CVD or high cardiovascular risk.[15] Mean eGFR was 76.5 mL/min/1.73 m^2 and median albumin/creatinine ratio (ACR) was 12.3 mg/g. Canagliflozin led to a lower three-point major adverse cardiovascular outcomes (3p-MACE) (HR 0.86 [0.75 to 0.97]; p<0.001), with the largest benefit seen in stroke reduction in subgroups with more advanced CKD (HR 0.56 for eGFR 45–60 mL/min/1.73 m^2 and 0.32 for 30–45 mL/min/1.73 m^2 group).

Specific renal outcomes with canagliflozin in people with T2D were examined in the CREDENCE study.[16] A total of 4,401 patients had albuminuric CKD (mean eGFR 56.2 mL/min/1.73 m^2) and included patients with eGFR ≥30 mL/min/1.73 m^2. Median ACR was 927 mg/g. Canagliflozin was associated with a 34% reduction (HR 0.66 [0.53 to 0.81]; p<0.001) in the renal specific composite (doubling of baseline creatinine, end stage renal disease (ESRD) or death from renal causes). Canagliflozin reduced 3p-MACE by 20% (HR 0.80 [0.67 to 0.95]; p<0.01) and hHF by 39% (HR 0.61 [0.47 to 90.8]; p<0.001). The numbers needed to treat (NNT) to prevent one case of doubling of serum creatinine, ESRD or death from renal or cardiovascular cause was 21.

Efficacy was seen across all stages of CKD, with highest efficacy in eGFR 45–60 mL/min/1.73 m^2 and urinary ACR >1000 mg/g. Based on this evidence, canagliflozin is now considered an effective option for renal and cardiovascular protection in DKD and can be initiated in people with T2D and macroalbuminuria and eGFR >30 mL/min/1.73 m^2, as an add-on to ACEI, irrespective of glucose control.

Dapagliflozin

Three large trials have studied the effects of dapagliflozin, two of which (DAPA-HF[17] and DAPA-CKD[18]) included people with and without diabetes.[17–19] Overall, dapagliflozin demonstrated a benefit in reducing cardiovascular death and hHF, irrespective of the baseline cardiovascular risk or renal function, but did not reduce 3p-MACE. Dapagliflozin reduced the number of deaths from any cause in people with impaired renal function (DAPA-CKD) (HR 0.69 [0.53 to 0.88]; p=0.004), irrespective of the baseline eGFR. In patients with eGFR 25–75 mL/min/1.73 m^2 and albuminuria, dapagliflozin demonstrated a 44% reduction in the composite renal outcome (HR 0.56 [0.45 to 0.68]; p<0.001).[18] The NNT to prevent doubling of serum creatinine, ESRD or death from cardiovascular or renal causes was 19.

In DECLARE TIMI 58,[19] in people with T2D with either established CVD or multiple risk factors and relatively normal renal function (mean eGFR 85.2 mL/min per 1.73 m²), dapagliflozin reduced eGFR decline >40% by 46% (HR 0.54 [0.43 to 0.67]; p<0.0001) and 59% reduced incidence of ESRD or renal death (HR 0.41 [0.20 to 0.82]; p=0.012).

Meta-analysis

Meta-analysis confirms favourable effects of SGLT2i on the renal composite of doubling of serum creatinine (eGFR 40% decline), RRT initiation or renal-related death (RR 0.63 [0.56 to 0.71]), even in the presence of CVD or multiple risk factors (RR 0.67 [0.59 to 0.76]).[20] The pooled NNT for renal outcomes was 67. SGLT2i also reduce albuminuria progression (RR 0.80 [0.76 to 0.84]). The renal and cardiovascular effects of SGLT2i are present across all stages of CKD, irrespective of baseline albuminuria.[21,22] Importantly, however, the effects appear to be strongest amongst those patients with albuminuria, compared with those who are normoalbuminuric. The effect is additive to ACEI or ARB use.

These benefits have been confirmed also in an observational cohort study (CVD-REAL 3),[23] examining 65,231 people with T2D over 14.9 months, 35,561 of whom were newly started on an SGLT2i. SGLT2i led to a reduced eGFR decline compared with other glucose-lowering drugs (between-group difference in rate of decline 1.53 mL/min/1.73 m² per year [1.34 to 1.72]; p<0.0001). The composite end point of eGFR reduction by 50% or ESRD was also significantly lower with SGLT2i (HR 0.49 [0.35 to 0.67]; p<0.0001). Lower RRT incidence is also associated with use of SGLT2i compared with patients taking dipeptidylpeptidase-4 inhibitors (HR 0.32 [0.22 to 0.47]; p<0.0001).[24]

Current UK licensing suggests that empagliflozin and dapagliflozin can be initiated at eGFR ≥60 mL/min/1.73 m^2.[25,26] Dapagliflozin should be discontinued at eGFR <60 mL/min/1.73 m^2, whilst empaglifozin should be stopped at eGFR <45 mL/min/1.73 m^2. It is likely, however, that on the basis of new evidence, dapagliflozin will gain a licence for use at eGFR >30 mL/min/1.73 m^2. Canagliflozin is approved for initiation in people with T2D with eGFR ≥30 mL/min/1.73 m^2 and can be continued in eGFR <30 mL/min/1.73 m^2 in the presence of albuminuria ≥300 mg/day unless dialysis is initiated.[27] ADA-EASD consensus guidelines recommend that SGLT2i can be used in any patient with T2D with HF or CKD.[28]

Adverse effects

The commonest adverse event is genital mycotic infections, which commonly occur early in treatment and responds well to over-the-counter medication.[29] Urinary tract infections are less frequent.

SLGT2i may cause euglycaemic ketoacidosis, and careful patient education around sick day rules is needed, including avoidance prior to surgery and avoidance of ketogenic diets.[30] A reduction in bone mineral density and increased risk of fractures has been suggested, although meta-analysis has not confirmed this.[31] CANVAS showed a slight increase in amputations associated with canagliflozin, which was not replicated in the CREDENCE study or with any other SGLT2i. Previous concerns regarding acute kidney injury (AKI) have been alleviated by more recent trials, and no increase in AKI has been seen in observational cohorts.[32]

Glucagon-like peptide-1 receptor agonists (GLP-1RA)

GLP-1RAs can be divided into incretin mimetics (exendin-4 analogues – exenatide/lixisenatide) or human GLP-1RA (albiglutide, liraglutide, dulaglutide, semaglutide). Elimination of exendin-4 analogues relies on glomerular filtration, and hence they accumulate

in renal insufficiency. They have not demonstrated improved outcomes in CVOTs.[33,34] In contrast, human GLP-1RA are safe in CKD.[35] Studies of GLP-1RAs in DKD are shown in Table 2.

Liraglutide,[35,36] dulaglutide,[37,38] and subcutaneous[39] or oral[40] semaglutide have demonstrated effective glycaemic control in T2D and CKD. Liraglutide has shown these effects in patients on dialysis,[41] and was superior to placebo in people with T2D and moderate renal impairment.[35] In patients with moderate–severe CKD, weekly dulaglutide was non-inferior to insulin glargine.[42] Oral semaglutide was superior to placebo both in weight and HbA_{1c} reduction in people with T2D and CKD, with no additional risk of adverse events.[43]

GLP-1RAs have shown promising results in CVOTs. Meta-analysis of the seven large GLP-1 trials of 56,004 patients showed a 12% reduction in 3p-MACE.[44] Composite renal outcome was reduced by 17% for all GLP1-RAs, mainly due to a reduction in new macroalbuminuria.

These properties of GLP-1RAs have been linked to their direct actions on blood pressure, glucose and weight, but also to improving endothelial dysfunction and inflammation.[45] They frequently cause an initial eGFR reduction upon administration, with subsequent plateauing. Human GLP-1RAs are approved for use at eGFR ≥15 mL/min/1.73 m^2.

Liraglutide

Liraglutide has shown some renoprotective properties.[36] People with T2D with established CVD or high CVD risk and mean eGFR 80 mL/min/1.73 m^2 showed a 22% risk reduction (HR 0.78 [0.67 to 0.92]; p=0.003) in a pre-specified renal outcome (new onset macroalbuminuria, doubling serum creatinine, eGFR <45 mL/min/1.73 m^2, need for RRT, death from renal disease), predominantly attributed to a 26% reduction in new onset persistent macroalbuminuria (HR 0.74 [0.60 to 0.91]; p=0.004).

Semaglutide

SUSTAIN-6 involved 3,297 people with T2D and CVD, heart failure or CKD stage 3–5.[39] Semaglutide decreased the incidence of non-fatal myocardial infarction by 26% and stroke by 39%, but had no effect on hHF or cardiovascular death. Semaglutide led to a 36% reduction in the renal composite of new or worsening nephropathy (persistent macroalbuminuria, persistent doubling of serum creatinine or eGFR <45 mL/min/1.73 m^2) (HR 0.64 [0.46 to 0.88]; p=0.005), mainly due to reduction in new macroalbuminuria (HR 0.54 [0.34 to 0.77]; p=0.001). Post hoc analysis of SUSTAIN studies suggested favourable effects on decreasing onset of microalbuminuria.[46]

Renal effects of once-weekly subcutaneous semaglutide are being studied in the FLOW trial which includes people with T2D and CKD (eGFR 50–75 mL/min/1.73 m^2 and ACR 300–5000 mg/g or eGFR 25–50 mL/min/1.73 m^2 and ACR 100–5000 mg/g). The primary end point is persistent eGFR decline (≥50% from baseline), ESRD, renal or cardiovascular death, and will report in 2024.[47]

Dulaglutide

In the REWIND study, dulaglutide was associated with a 15% reduction in the composite renal outcome in patients with either established CVD or risk factors and a mean eGFR of 76.9 mL/min/1.73 m^2, driven by a 23% reduction in macroalbuminuria onset (HR 0.77 [0.68 to 0.87]; p=0.0001).[37]

Dulaglutide has also shown superiority over insulin glargine on attenuating eGFR decline in T2D with moderate–severe CKD (eGFR reduction by 3.3 mL/min/1.73 m^2/year with glargine; eGFR reduction by 0.7 mL/min/1.73 m^2/year with dulaglutide).[42] Risk of progression to ESRD or >40% eGFR decline was also reduced with dulaglutide compared with glargine (5.2% vs 10.8%; p=0.038).

Overall, the GLP-1RA data suggest a favourable effect in DKD, predominantly due to a reduction in the rate of appearance or progression of macroalbuminuria.

Aldosterone receptor antagonist

A recent study of the aldosterone receptor antagonist finerenone in 5,734 people with T2D and CKD showed some positive benefits.[48] Patients included had eGFR 25–60 mL/min/1.73 m^2 and urine ACR 30–300 mg/g, and maximum tolerated ARB or ACEI therapy. The primary composite outcome of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline or death from renal causes was reduced by 18% in the finerenone group (HR 0.82 [0.73 to 0.93]; p=0.001). Hyperkalaemia necessitating cessation of finerenone occurred in 2.3% of patients treated.

New guidance on post-transplant diabetes (PTDM)

Solid organ transplantation (SOT) is a life changing therapy for hundreds of thousands of people worldwide. Advances in immunosuppression have led to dramatic improvements in graft and patient survival, but morbidity and mortality from CVD is high, with PTDM being an important contributor. PTDM is a distinct clinical entity that affects between 10% and 40% of SOT recipients,[49] and confers a higher risk of graft failure and mortality.[50] Recent guidance on the diagnosis, management and prevention of PTDM have been developed by the Association of British Clinical Diabetologists (ABCD) and Renal Association (RA) diabetic nephropathy clinical specialty group.[51] These guidelines do not include the management of patients undergoing pancreas transplantation.

Pathogenesis

Weight gain (due to glucocorticoids and fewer dietary restrictions) is common in patients post SOT.[52] Risk factors for the development of PTDM are similar to T2D, but specific transplant-related risks also contribute, including immunosuppression and infection (eg, hepatitis C).

Calcineurin is an important factor in β-cell function and growth, and calcineurin inhibitors have adverse effects on β-cell function leading to reduction in insulin secretion.[53] Whilst tacrolimus is a highly effective immunosuppressant, it has a more potent adverse effect on β-cell function, leading more frequently to significant hyperglycaemia compared with ciclosporin.[54]

Diagnosis

Early hyperglycaemia is common in SOT recipients due to stress

Table 2 Cardiovascular and renal outcome studies using glucagon-like peptide-1 receptor agonists (GLP-1RAs)

Study	LEADER[36]	AWARD-7[43]	REWIND[38]	SUSTAIN-6[40]	PIONEER-5[41]
Drugs studied	Liraglutide vs placebo	Dulaglutide 0.75–1.5 mg vs insulin glargine	Dulaglutide 1.5 mg vs placebo	Subcutaneous semaglutide vs placebo	Oral semaglutide vs placebo
Characteristics	N=9,340 64% male Mean age: 64	N=577 52% male Mean age: 65	N=9,901	N=3,297 61% male Mean age: 65	N=3,183 Age >50
	72.4% established CVD Mean HbA_{1c} 8.7% (72 mol/mol) Mean BP 167/77 mmHg Mean eGFR 80 20.7% eGFR 30–59 2.4% eGFR <30 26.3% UACR >30 mg/g 10.5% UACR >300 mg/g	Mean HbA_{1c} 7.5–10.5% Mean BP 137/7 5mmHg Mean eGFR 38 26% eGFR 45–60 35% eGFR 30–45 31% eGFR <30 29% UACR >30 mg/g 46% UACR >300 mg/g	CVD or risk factors mean eGFR 76.9 7.9% UACR >30 mg/g	83% established CVD, CKD, or both 17% CV risk factors Mean HbA_{1c} 8.7% Mean BP 136/77 mmHg CKD stage 3–5 25.2% eGFR 30–59 2.9% eGFR ≤30 12.7% UACR >300 mg/g	Established CVD or CKD and >50 CV risk factors and >60 26.9% eGFR <60
ACE/ARB	82%	90–94%		83.5%	———
Median duration	3.84 years	52 weeks	5.4 years	2.1 years	15.9 months
Outcome	**22% lower composite renal outcome** (new onset macroalbuminuria, doubling serum creatinine, eGFR <45, need for RRT or renal death) (HR 0.78 [0.67 to 0.92]; p=0.003) **26% reduction in new macroalbuminuria** (HR 0.74 [0.60 to 0.91]; p=0.004) No statistically significant reduction to the composite of the doubling of the serum creatinine level, use of RRT or death from renal disease 13% lower new microalbuminuria (HR 0.87 [0.83 to 0.93]; p<0.001)	**eGFR decline (mL/min)** –3.3 insulin glargine –0.7 dulaglutide 0.75 mg* –0.7 dulaglutide 1.5 mg* **eGFR decline (mL/min) in UACR >300 mg/g group** –5.5 insulin glargine –0.7 dulaglutide 0.75 mg* –0.5 dulaglutide 1.5mg* **UACR reduction** –13% insulin glargine –12.3% dulaglutide 0.75 mg –29% dulaglutide 1.5 mg* *p<0.05 (vs insulin glargine)	**15% lower composite renal outcome** (new macroalbuminuria, eGFR reduction of 30% or more from baseline, need for RRT) (HR 0.85 [0.77 to 0.93]; p=0.0004) **23% reduction in new macroalbuminuria** (HR 0.7 [0.68 to 0.87]; p=0.0001) No statistically significant reduction to the composite of sustained eGFR reduction of 30% and RRT	**36% lower new or worsening nephropathy** (new macroalbuminuria (UACR >300 mg/g), doubling serum creatinine, eGFR <45 mL/min/1.73 m^2, need for RRT or renal death) (HR 0.64 [0.46 to 0.88]; p=0.005) **46% reduction in new macroalbuminuria with semaglutide** (HR 0.54 [0.34 to 0.77]; p=0.001) **UACR reduction** 0.75 [0.66 to 0.85] (semaglutide 0.5 mg) 0.66 [0.58 to 0.75] (semaglutide 1.0 mg) --- Lower 3p-MACE (HR 0.74 [0.58 to 0.95]) Lower rate of non-fatal MI (HR 0.74 [0.51 to 1.08]) Lower rate of non-fatal stroke (HR 0.61 [0.38 to 0.99]) No significant difference in CV deaths, hHF	Non-inferior to placebo for 3p-MACE No composite renal outcome pre-specified No significant difference in eGFR reduction and renal death

ACE, angiotension converting enzyme inhibitor; ARB, angiotensin receptor blocker; AWARD-7, dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate to severe CKD; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trials; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HR, hazard ratio; hHF, hospitalisation for heart failure; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; 3p-MACE, three point major adverse cardiovascular events; MI, myocardial infarction; PIONEER-6, Peptide Innovation for Early Diabetes Treatment; REWIND, dulaglutide and cardiovascular outcomes in type 2 diabetes; RRT, renal replacement therapy; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; UACR, urine albumin creatinine ratio.

hyperglycaemia, infection, pain, immunosuppression and parenteral/enteral feeding.[55] In the immediate post-transplant period where doses of immunosuppression are high, screening for post-transplant hyperglycaemia should involve frequent capillary blood glucose (CBG) testing, predominantly later in the day (post lunch or evening meal). International consensus suggests a clear method of diagnosis of PTDM based on the oral glucose tolerance test or glycated haemoglobin (HbA_{1c}).[56] Interpretation of HbA_{1c} can, however, be problematic postoperatively and in patients with renal disease. It is therefore recommended that HbA_{1c} only be used at least three months post-transplant, and prior to this, glucose tests should be undertaken.

Management

Early post-transplant hyperglycaemia requires active monitoring and management (Figure 1). Persistent hyperglycaemia (≥2 CBGs >11 mmol/L) should prompt treatment. CBGs <14 mmol/L may respond to oral hypoglycaemic agents. Higher levels should be treated with intravenous or subcutaneous insulin, with once daily NPH insulin as a suggested starting regimen.

As immunosuppression doses reduce, hyperglycaemia may improve or resolve. Insulin doses must be reduced accordingly, and the patient must be taught to self-test glucose levels and adjust insulin doses. Input from the diabetes specialist team is important.

In the absence of randomised controlled trials, the management of PTDM should follow that of T2D. There is currently no evidence that tight glycaemic control will improve graft or patient outcomes in PTDM, so glycaemic targets should be individualised according to age, co-morbidity, ability to self-manage and patient preference.[28] Safe options for oral hypoglycaemics include metformin (if renal function allows), dipeptidylpeptidase-4 inhibitors (of which linagliptin can be used in any level of renal function), glitazones and meglitinides/sulfonylureas (although hypoglycaemic risk and weight gain must be considered).[57] GLP-1RAs may be useful if weight gain is a concern.[58] The potential for increased risk of genitourinary infection has led to concern over the use of SGLT-2i in the post-transplant setting, but a small trial of 44 patients with PTDM randomised to empagliflozin or placebo showed a modest glucose benefit, but with significant weight loss, and no increase in risk of infections.[59]

Change in immunosuppression regimen may aid the management of hyperglycaemia. If feasible, consideration may be given for conversion of tacrolimus to ciclosporin or mycophenolate mofetil plus azathioprine in patients with difficult to control hyperglycaemia.[60]

All patients with established PTDM must be put on to a primary care diabetes register and undergo structured diabetes care, including referral to structured diabetes education and regular screening for complications (eyes, feet and kidneys). In addition, they require control of cardiovascular risk factors such as smoking cessation, statin therapy and anti-hypertensive therapy aiming for blood pressure <130/80 mmHg.

Patients with PTDM may be most effectively managed in a multidisciplinary setting with diabetes and transplant specialists co-managing the patient.

Key messages

- SGLT-2i agents provide renal and cardiovascular protection in people with Type 2 diabetes and DKD
- PTDM is an important clinical condition and requires active detection and management
- Diabetes management in patient on HD may be challenging, and consideration should be given to the use of diagnostic CGM or Flash GM in such patients

Managing people with diabetes on haemodialysis (HD)

Diabetes is common in people on HD, and may occur prior to or during dialysis therapy. Managing glycaemia in people with diabetes on HD is uniquely challenging. Glycaemic variability is exacerbated in people with diabetes on HD, as HD clears glucose and glucoregulatory hormones (insulin and glucagon); dialysis-related improvement in uraemia, acidosis and hyperphosphataemia can lead to periodic changes in insulin secretion, and symptoms of hypoglycaemia can often be confused with hypotension.[61,62] Assessment of glycaemia may be difficult due to problems in interpreting HbA_{1c} in renal anaemia.[63] Therefore, glycaemic management may be reliant on self-monitoring of blood glucose, an additional burden on patients undergoing already burdensome therapy.

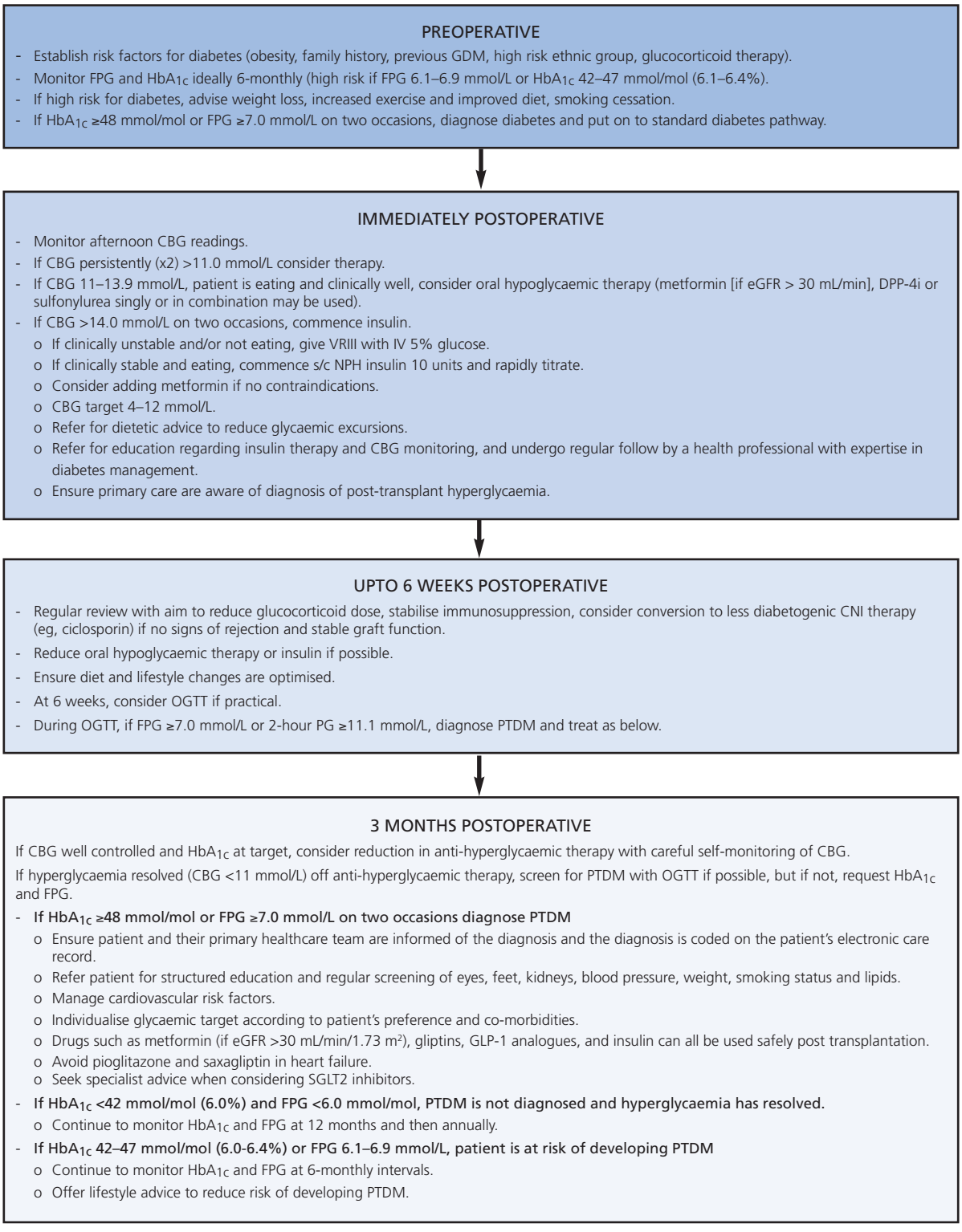
Guidance on the management of diabetes in patients on HD has been published by the Joint British Diabetes Societies in 2016,[64] and is due to be updated in 2021. There is growing evidence that asymptomatic hypoglycaemia is common in people undergoing HD, and that this may contribute to adverse outcomes.[65] With a significant improvement in glucose monitoring technology available for managing people with diabetes, it may be appropriate to consider intermittent 'diagnostic' use of flash or continuous glucose monitoring in high-risk patients on HD, especially those on insulin or sulfonylurea. Indeed, NHS guidance on the use of FreeStyle Libre includes people with any form of diabetes on haemodialysis and on insulin treatment.[66]

Conclusions

A paradigm shift in the management of early DKD using SGLT2i irrespective of glycaemic control is now established and needs to be implemented safely. Most international guidelines now recommend these agents as at least second-line treatment following metformin in people with T2D and, in addition, GLP-RAs are high in the therapeutic pathway. European Society of Cardiology guidelines suggest use of SGLT2i in renal disease even in metformin-naïve patients.[67]

Recent guidance on PTDM suggests that the condition is an important risk marker for early and late graft failure and mortality. Immediate post-transplant hyperglycaemia requires active monitoring and management. Once PTDM is established, treatment targets and pathways should be as for T2D.

Figure 1. Pathway for diagnosis and management of post-transplant diabetes mellitus



FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; CBG, capillary blood glucose; DPP-4i, dipeptidylpeptidase-4 inhibitor; VRIII, variable rate intravenous infusion of insulin; NPH, Neutral protamine Hagedorn; CNI, calcineurin inhibitor; 2-hour PG, 2-hour plasma glucose; eGFR, estimated glomerular filtration rate; PTDM, post-transplant diabetes mellitus; SGLT2, sodium glucose transporter-2.

People with diabetes on HD have a significant risk of adverse effects from anti-hyperglycaemic therapy, and newer technologies may enable their care to be made safer.

The year 2020 will be remembered for its unique healthcare challenges related to the COVID-19 pandemic. In DKD, however, it has been an important year, with a number of seminal publications enabling people living with this condition, and their physicians, to hope for better outcomes in the future.

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