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Perspective

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Pharmacological management of type 2 diabetes: clinical considerations and future perspectives

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Abstract

The management of type 2 diabetes continues to evolve with the historical glucocentric nature of care, paving the way toward more holistic and comorbidity-based management largely due to the advent of newer medications and trial data. Clinicians need to be aware that an understanding of not only the current treatment landscape but also the future developments in care and therapy is required in order to understand the best options for the management of their patients. This article will discuss current perspectives in the pharmacological management of type 2 diabetes, largely focusing on recent trial developments and associated future trials and molecules that may impact type 2 diabetes care in the near future.

Keywords: Type 2 diabetes, pharmacotherapy, cardiovascular disease, multimorbidity

INTRODUCTION

The last ten years have witnessed a shift in the care and management of people with type 2 diabetes, largely

driven by the advent of novel medication classes such as sodium-glucose co-transporter inhibitors (SGLT2s) and Glucagon-Like Peptides receptor agonists (GLP-1s); recent data and guidelines have even questioned the glucocentric nature of diabetes management. While the current treatment options provide many considerations for the person with type 2 diabetes, it does pose questions as to where do the existing therapies sit. Additionally, as data continue to arrive, the increasing burden of multimorbidity in those with type 2 diabetes and new molecules being developed, one must consider the impact and future landscape of type 2 diabetes care.

This article will highlight the recent advances in the pharmacological management of type 2 diabetes, current perspectives, future considerations of comorbidities, and therapeutic options. It will largely focus on non-insulin therapies except in certain settings.

CURRENT LANDSCAPE

Up until relatively recently, type 2 diabetes management centered around Hba1c lowering and cardiovascular risk factor management. Recent cardiovascular outcome trials, as mandated by the Food and Drug Administration, resulted in evidence of superiority in some medications within the SGLT2 and GLP-1 RA classes for cardiovascular outcomes[1]. Additionally, benefits in heart failure hospitalization reduction and renal outcomes (in the setting of SGLT2s) have resulted in a shift in guidelines from being glucose-centered (glucocentric) to highlighting cardiovascular disease and CV risk assessment at the onset of any management considerations. One of the first diabetes-specific guidelines to focus on this was the joint American Diabetes Association and the European Association for the Study of Diabetes (ADA-EASD) guidelines which incorporated cardiovascular risk assessment as part of the initial management (following metformin, dietary and lifestyle advice)[2]. However, even these guidelines appear to have now progressed, with the most recent draft guidelines (2022) highlighting CV risk assessment independent of glucose lowering[3].

The low Numbers Needed To Treat (NNT) of SGLT2 inhibitors and the multitude of beneficial effects were so apparent that the National Institute for Clinical Excellence (NICE), long known to champion the balance between cost-effectiveness and clinical effectiveness, has now also included SGLT2s as a first-line therapy irrespective of Hba1c level in those with established ASCVD or heart failure or high cardiovascular risk[4,5]. While these guidelines highlight the use of SGLT2s, they fall short of recommending dual initiation directly but suggest separate consideration. As the development of SGLT2s and incretins continues, the role of traditional medications remains under debate. While data from UKPDS and multiple metanalyses show that metformin remains a key agent in the treatment of type 2 diabetes, its role in the modern management of cardiovascular disease specifically is starting to diminish compared to the stronger evidence base for SGLT2s and GLP-1s in this area[6]. However, its role in a pure glucocentric sense remains in most, if not all, guidelines.

With the move towards these newer therapies, one might question the role of the other 'traditional' medications in the modern and future management of Type 2 Diabetes Mellitus. This will be discussed in more detail in the article with reference to more recent trials of medications as seen in[Table 1].

ROLE OF SULPHONYLUREAS, THIAZOLIDINEDIONES, AND DIPEPTIDYL PEPTIDASE-4 INHIBITORS

Sulphonylureas are moving further out of favour in many places due to the rise of medications with extraglycaemic benefits and lesser side effect profiles, specifically lower hypoglycaemia risk and weight neutrality or reduction. The risk of hypoglycaemia in diabetes is well known and the impact on

Table 1. An overview of key trials as discussed in the article focussing on medication type, primary outcome and key findings

Trial	Medication	Overview	Primary outcome	Main Result
VERIFY	DPP4i (vildagliptin) + metformin	Assessment of early combination therapy with vildagliptin/metformin *vs.* monotherapy	Treatment failure (defined as HbA1c measurement of at least 53 mmol/mol (7.0%) at two consecutive scheduled visits, 13 weeks apart from randomisation	Reduction in relative risk for time to initial treatment failure in the early combination treatment group vs monotherapy group over the 5-year study duration (hazard ratio 0.51 [95%CI: 0.45-0.58]; *P* < 0.0001)
TRIMASTER	DPP4i (sitagliptin), pioglitazone, SGLT2i (canagliflozin)	Three-way crossover trial assessing patient preference and glycaemic lowering as third-line therapy	HbA1c after 4 months of therapy (allowing a range of 12-18 weeks for analysis)	HbA1c on pioglitazone 59.5 sitagliptin 59.9, canagliflozin 60.5 mmol/mol, *P* = 0.19). 115 patients (25%) preferred pioglitazone, 158 patients (35%) sitagliptin, and 175 patients (38%) canagliflozin. The drug preferred by individual patients was associated with a lower HbA1c (mean: 4.6; 95%CI: 3.9, 5.3) mmol/mol versus nonpreferred)
GRADE	SU (glimepiride), DPP4i (sitagliptin), GLP-1 RA (liraglutide), insulin (glargine)	Comparing 4 commonly used medications in combination with metformin on glucose lowering and patient-centered outcomes	Time to primary failure - Hba1c >= 7% (53 mmol/mol)	Rates of treatment failure with glargine (26.5 per 100 participant-years) and liraglutide (26.1) lower than those with glimepiride (30.4) and sitagliptin (38.1). (*P* < 0.001)
DAPA- CKD	SGLT2i dapagliflozin	Assessment of dapagliflozin vs placebo in those with CKD (eGFR 25-75 ml/min/1.73m^2 and uACR 200-5,000 mg/g) with or without T2DM	A composite of sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes	197 participants (9.2%) in the dapagliflozin group and 312 participants (14.5%) in the placebo group (hazard ratio, 0.61; 95% confidence interval, 0.51 to 0.72; *P* < 0.001)
CREDENCE	SGLT2icanagliflozin	Assessment of canagliflozin 100 mg in patients with T2DM, albuminuria (200-5,000 mg/g), and CKD (eGFR 30 to < 90 mL/min/1.73 m^2)	A composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of < 15 mL per minute per 1.73 m^2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes	Primary outcome 30% lower in the canagliflozin group than in the placebo group, with event rates of 43.2 and 61.2 per 1,000 patient-years (hazard ratio, 0.70; 95% confidence interval, 0.59 to 0.82; *P* = 0.00001)
EMPA KIDNEY	SGLT2i Empagliflozin	Assessment of empagliflozin 10mg in patients with CKD (eGFR 20-45 ml/min/1.73 m^2 or eGFR 45-90 mL/min/1.73 m^2 and uACR at least 200 mg/g) with or without T2DM	Composite of progression of kidney disease (defined as end-stage kidney disease, a sustained decrease in eGFR to < 10 mL per minute per 1.73 m^2, a sustained decrease in eGFR of ≥ 40% from baseline, or death from renal causes) or death from cardiovascular causes	432 of 3,304 patients (13.1%) in the empagliflozin group and in 558 of 3,305 patients (16.9%) in the placebo group (hazard ratio, 0.72; 95% confidence interval, 0.64 to 0.82; *P* < 0.001)
CAROLINA	DPP4i linagliptin vs sulphonylurea	Assessment of linagliptin *vs.* glimepiride on major adverse cardiovascular events in patients with T2DM and elevated CV risk	Time to first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke with the aim to establish non-inferiority of linagliptin vs glimepiride	56 of 3,023 participants (11.8%) in the linagliptin group and 362 of 3,010 (12.0%) in the glimepiride group (HR, 0.98 [95.47%CI, 0.84-1.14]; *P* < 0.001 for non-inferiority) met the primary outcome, meeting the non-inferiority criterion but not superiority (*P* = 0.76)
PROACTIVE	pioglitazone	Assessment of pioglitazone on macrovascular morbidity and mortality in high-risk patients with T2DM	Composite of all-cause mortality, nonfatal myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle	514 of 2,605 patients in the pioglitazone group and 572 of 2,633 patients in the placebo group had at least one event in the primary composite endpoint (HR 0.90, 95%CI: 0.80-1.02, *P* = 0.095)
IRIS	pioglitazone	Assessment of pioglitazone in patients with a recent TIA or stroke and insulin resistance (based on HOMA-IR index)	Fatal or nonfatal stroke or myocardial infarction	Primary outcome met in 175 of 1939 patients (9.0%) in the pioglitazone group and 228 of 1,937 (11.8%) in the placebo group (hazard ratio in the pioglitazone

				group, 0.76; 95% confidence interval, 0.62 to 0.93; *P* = 0.007)
DAPA-HF	SGLT2i dapagliflozin	Assessment of dapagliflozin 10mg in patients with heart failure and reduced ejection fraction (</= 40%) with or without T2DM	Composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death	Primary outcome met in 386 of 2,373 patients (16.3%) in the dapagliflozin group and 502 of 2,371 patients (21.2%) in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.65 to 0.85; *P* < 0.001). A first worsening heart failure event occurred in 237 patients (10.0%) in the dapagliflozin group and in 326 patients (13.7%) in the placebo group (hazard ratio, 0.70; 95%CI: 0.59 to 0.83).
EMPEROR-Reduced	SGLT2i Empagliflozin	Assessment of empagliflozin 10mg in patients with heart failure and reduced ejection fraction (LVEF </= 40%) with or without T2DM	composite of cardiovascular death or hospitalization for worsening heart failure	361 of 1863 patients (19.4%) in the empagliflozin group and in 462 of 1,867 patients (24.7%) in the placebo group (hazard ratio for cardiovascular death or hospitalization for heart failure, 0.75; 95% confidence interval [CI], 0.65 to 0.86; *P* < 0.001)
DELIVER	SGLT2i Dapagliflozin	Assessment of dapagliflozin 10mg in patients with heart failure and LVEF > 40%	Composite of worsening heart failure (which was defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure) or cardiovascular death	512 of 3,131 patients (16.4%) in the dapagliflozin group and in 610 of 3,132 patients (19.5%) in the placebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.92; *P* < 0.001). Worsening heart failure occurred in 368 patients (11.8%) in the dapagliflozin group and in 455 patients (14.5%) in the placebo group (hazard ratio, 0.79; 95%CI: 0.69 to 0.91)
EMPEROR-Preserved	SGLT2i Empagliflozin	Assessment of empagliflozin 10 mg in patients with heart failure and LVEF > 40%	Composite of cardiovascular death or hospitalization for heart failure	Primary outcome met in 415 of 2,997 patients (13.8%) in the empagliflozin group and in 511 of 2,991 patients (17.1%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.69 to 0.90; *P* < 0.001). Total number of hospitalizations for heart failure lower in the empagliflozin group than the placebo group (407 with empagliflozin and 541 with placebo; hazard ratio, 0.73; 95% CI, 0.61 to 0.88; *P* < 0.001)
EMPULSE	SGLT2i Empagliflozin	Assessment of empagliflozin 10mg in patients hospitalized with acute heart failure	Clinical benefit, defined as a hierarchical composite of death from any cause, number of heart failure events and time to first heart failure event, or a 5 point or greater difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score at 90 days, as assessed using a win ratio	More patients treated with empagliflozin had a clinical benefit compared with placebo (stratified win ratio, 1.36; 95% confidence interval, 1.09-1.68; *P* = 0.0054)
DARE-19	SGLT2i Dapagliflozin	Assessment of dapagliflozin 10 mg in patients hospitalised with COVID-19 and with at least one cardiometabolic risk factor (i.e., hypertension, type 2 diabetes, atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease)	Dual primary outcomes: prevention (time to new or worsened organ dysfunction or death) and the hierarchical composite outcome of recovery (change in clinical status by day 30)	Outcome of prevention showed organ dysfunction or death occurred in 70 patients (11.2%) in the dapagliflozin group, and 86 (13.8%) in the placebo group (hazard ratio [HR] 0.80, 95%CI: 0.58-1.10; *P* = 0.17). For the primary outcome of recovery, 547 patients (87.5%) in the dapagliflozin group and 532 (85.1%) in the placebo group showed clinical status improvement, not statistically

				significant (win ratio 1.09, 95%CI: 0.97-1.22; *P* = 0.14)
EMPA-ELDERLY	SGLT2i Empagliflozin	Assessment of the effects of empagliflozin in the elderly Japanese population (>/= 65 years old) on body composition and glycaemic control and evaluation of effects on skeletal muscle mass, muscle strength and physical performance	Change in HbA1c level from baseline at week 52. Secondary endpoints include changes from baseline to 52 weeks in body composition, including muscle mass and body fat, measured by bioelectrical impedance analysis, as well as skeletal muscle index, grip strength, and time in the five-time chair stand test	Awaited
CONFIDENCE	MRA Finerenone vs SGT2i Empagliflozin	Assessment of dual therapy with finerenone and empagliflozin if superior to either agent alone in those with T2D, stage 2-3 CKD and a urine albumin:creatinine ratio (UACR) ≥ 300-< 5,000 mg/g	To demonstrate that 6 months of dual therapy is superior for reducing albuminuria versus either agent alone	Awaited
FLOW	GLP1-RA Semaglutide	Assessment of the effects of once-weekly semaglutide on renal outcomes in those with (eGFR) ≥ 50 - ≤ 75 mL/min/1.73 m_2 and urine albumin-to-creatinine ratio (UACR) > 300-< 5,000 mg/g or eGFR ≥ 25- < 50 mL/min/1.73 m^2 and UACR > 100- < 5,000 mg/g and T2DM	Time to first: kidney failure (persistent eGFR < 15 mL/min/1.73 m^2 or initiation of chronic kidney replacement therapy); persistent ≥ 50% reduction in eGFR; or death from kidney or CV causes	Awaited
D-LIFT	GLP1-RA Dulaglutide	Assessment of the effect of dulaglutide on liver fat content (LFC) in those with NAFLD and T2DM	Difference of the change in LFC from 0 (baseline) to 24 weeks between groups	Dulaglutide treatment resulted in an absolute change in LFC of -3.5% (95%CI: -6.6, -0.4; *P* = 0.025) and a relative change of -26.4% (-44.2, -8.6; *P* = 0.004), equating to a 2.6-fold greater reduction
SURPASS 1	GIP/GLP1 RA Tirzepatide	Assessing the efficacy, safety, and tolerability of tirzepatide vs placebo in patients with T2DM	Mean change in glycated haemoglobin (HbA1c) from baseline at 40 weeks	Mean HbA1c decreased from baseline by 1.87% (20 mmol/mol) with tirzepatide 5 mg, 1.89% (21 mmol/mol) with tirzepatide 10 mg, and 2.07% (23 mmol/mol) with tirzepatide 15 mg versus +0.04% with placebo (+ 0.4 mmol/mol), Estimated treatment differences versus placebo of -1.91% (-21 mmol/mol) with tirzepatide 5 mg, -1.93% (-21 mmol/mol) with tirzepatide 10 mg, and -2.11% (-23 mmol/mol) with tirzepatide 15 mg (all *P* < 0.0001)
SURPASS 2	GIP/GLP1 RA Tirzepatide	Assessing the safety and efficacy of tirzepatide compared to semaglutide in those with T2DM	Change in the glycated hemoglobin level from baseline to 40 weeks	Estimated mean changes from baseline in the glycated hemoglobin level were -2.01 percentage points, -2.24 percentage points, and -2.30 percentage points with 5 mg, 10 mg, and 15 mg of tirzepatide, respectively, and -1.86 percentage points with semaglutide; Estimated differences between the 5- mg, 10 -mg, and 15 -mg tirzepatide groups and the semaglutide group were -0.15 percentage points (95% confidence interval [CI], -0.28 to -0.03; *P* = 0.02), -0.39 percentage points (95%CI: -0.51 to -0.26; *P* < 0.001), and -0.45 percentage points (95% CI, -0.57 to -0.32; *P* < 0.001), respectively. Reductions in body weight were greater with tirzepatide vs semaglutide (least-squares mean

				estimated treatment difference, -1.9 kg, -3.6 kg, and -5.5 kg, respectively; $P < 0.001$ for all comparisons)
SURPASS 3	GIP/GLP1 RA Tirzepatide	Assessing the efficacy and safety of tirzepatide versus titrated insulin degludec in people with T2DM inadequately controlled by metformin with or without SGLT2 inhibitors	Non-inferiority of tirzepatide 10 mg or 15 mg, or both, versus insulin degludec in mean change from baseline in HbA1c at week 52	Reductions in HbA1c at week 52 were 1.93% (SE 0.05) for tirzepatide 5 mg, 2.20% (0.05) for tirzepatide 10 mg, and 2.37% (0.05) for tirzepatide 15 mg, and 1.34% (0.05) for insulin degludec. The non-inferiority margin of 0.3% was met. The estimated treatment difference (ETD) versus insulin degludec ranged from -0.59% to -1.04% for tirzepatide ($P < 0.0001$ for all tirzepatide doses)
SURPASS 4	GIP/GLP1 RA Tirzepatide	Assessing efficacy and safety (especially CV safety) of tirzepatide versus insulin glargine in adults with T2DM and high CV risk inadequately controlled on oral glucose-lowering medications	Non-inferiority (0.3% non-inferiority boundary) of tirzepatide 10 mg or 15 mg, or both, versus glargine in HbA1c change from baseline to 52 weeks	Mean HbA1c changes with tirzepatide were -2.43% (SD 0.05) with 10 mg and -2.58% (0.05) with 15 mg, versus -1.44% (0.03) with glargine. The estimated treatment difference versus glargine was -0.99% (multiplicity adjusted 97.5%CI: -1.13 to -0.86) for tirzepatide 10 mg and -1.14% (-1.28 to -1.00) for 15 mg
SURPASS CVOT	GIP/GLP1 RA Tirzepatide	Assessing the efficacy and safety of tirzepatide to dulaglutide in participants with type 2 diabetes and increased cardiovascular risk	Time to the first occurrence of death from cardiovascular (CV) causes, myocardial infarction (MI), or stroke (MACE-3)	Awaited
ESSENCE	GLP1-RA Semaglutide	Assessing the safety and efficacy of semaglutide in biopsy-proven NASH and liver fibrosis	Resolution of NASH with no worsening of fibrosis	The percentage of patients in whom NASH resolution was achieved with no worsening of fibrosis was 40% in the 0.1 -mg group, 36% in the 0.2 -mg group, 59% in the 0.4 -mg group, and 17% in the placebo group ($P < 0.001$ for semaglutide 0.4 mg *vs.* placebo). An improvement in fibrosis stage occurred in 43% of the patients in the 0.4 -mg group and in 33% of the patients in the placebo group ($P = 0.48$)
SYNERGY-NASH	GIP/GLP1 RA Tirzepatide	Assessing the safety and effectivity of tirzepatide as a treatment for Nonalcoholic Steatohepatitis (NASH)	Percentage of participants with an absence of NASH with no worsening of fibrosis on liver histology	Awaited

cardiovascular outcomes never fully abated, although the data from the CAROLINA trial which compared linagliptin with glimepiride and showed no differences in CV outcomes may reassure many with regards to sulphonylureas[7]. The role of sulphonylureas in the current landscape perhaps focuses on the management of hyperglycaemia, where insulin is not deemed necessary or where quick glucose lowering is required, including in some instances of steroid-induced hyperglycaemia[8,9]. From a global perspective, the low cost and efficacy in terms of glucose lowering still suggest a role in economies where cost is a key consideration and the role of sulphonylureas in maturity-onset diabetes of the young (MODY) remains[10].

Thiazolidinediones, specifically pioglitazone, may not be utilized as often as they once were, in part due to alternative options with lesser side effect profiles, but there are still some considerations for their use in type 2 diabetes. Their effect on those with insulin resistance remains of note, with recent trials such as the TriMaster study identifying that in patients with BMI over 30 kg/m^2, pioglitazone offered greater Hba1c

reductions than sitagliptin and was similarly tolerated by participants[11,12]. Other trials such as PRoACTIVE suggest there may be some benefit in CV disease - in this trial, pioglitazone compared to placebo resulted in a reduced composite endpoint of all-cause mortality, nonfatal myocardial infarction and stroke in patients with type 2 diabetes at high risk of macrovascular events[13]. Additionally, the Insulin Resistance Intervention after Stroke (IRIS) trial, which assessed patients with insulin resistance (based on HOMA-IR index), found those on pioglitazone had a lower risk of stroke or myocardial infarction[14]. However, given the stronger data for SGLT2s and GLP-1s in these areas, specifically with cardiac outcomes but less so with cerebrovascular (given the lack of clear benefit with SGLT-2 inhibitors on stroke outcomes and the secondary analyses of GLP-1 outcome trials), pioglitazone remains overlooked to some extent in recent guidelines.

One area where they remain an attractive option and perhaps have stronger data is in those with fatty liver disease. Data suggest that pioglitazone improves liver function tests, steatosis, inflammation and ballooning grade in those with pre-diabetes or diabetes and NAFLD[15]. Reversal of lipotoxicity with pioglitazone leading to significant histological improvement has the potential to modify the natural history of the disease and data also suggest potential benefit in non-diabetic patients - though that is beyond the scope of this article[16].With the recent increased awareness about the prevalence and impact of NAFLD in those with type 2 diabetes and suggestions for screening, it may be that in the near future the use of pioglitazone may increase. Though, with upcoming trials with incretin molecules in NAFLD (discussed below), there may be competition for pioglitazone in this area.

DPP4 inhibitors, the first oral medication after metformin that did not cause weight gain or increase hypoglycaemia risk, were accepted fairly well into clinical practice; however, they were also limited by their limitation beyond glucocentric efficacy and acquisitional cost. However, with patents due to expire for some DPP4 inhibitor molecules and together with data from the VERIFY trial highlighting benefits of dual initiation with metformin (higher percentage of participants achieving target Hba1c compared to monotherapy), the use of DPP4 inihibitors may start to rise. This may result in increased use of combination metformin/DPP4 as the first line for glucose lowering in order to rapidly achieve glycaemic targets, especially in countries where SGLT2s or the higher cost of GLP-1s limit their utilization. Currently, their role has been highlighted in those where hypoglyacemia is a concern, such as in the ADA-EASD consensus or, more specifically, in frail older adults where their reasonable efficacy balanced with the favourable side effect and tolerability profile make them an ideal consideration[18]. Although promising benefits, it must be noted that the US Food and Drug Administration has issued a warning about an increased risk of serious heart failure events for both saxagliptin and alogliptin; therefore, in the older individual, assessing such risks together with the choice of medication used should be considered[19].

SGLT2 INHIBITORS

SGLT2 inhibitors have changed the way type 2 diabetes has been managed, not just from a glycaemic perspective, but since the cardiovascular outcome trials showed benefits not just from composite cardiovascular outcomes but also secondary outcome findings of reductions in hospitalization for heart failure and prevention of deterioration in Egfr[20-22]. Recent trials such as DAPA-HF and EMPEROR-Reduced have moved SGLT2s from solely glucose-lowering medications to heart failure medications (specifically reduced ejection fraction) with reductions in hospitalization for heart failure, improved quality of life and CV mortality[23,24]. Similar trials such as CREDENCE and DAPA-CKD have highlighted the benefits in chronic kidney disease (in those with and without type 2 diabetes) with prevention of eGFR deterioration and composite renal outcomes[25,26]. There is clear evidence for the class in heart failure and/or CKD; however, there remain a few considerations for SGLT2 inhibitors that may further develop.

Heart failure with preserved ejection fraction

The use of SGLT2 inhibitors, although now established in reduced ejection fraction, still has not been fully confirmed in those with preserved ejection fraction. The first SGLT2 inhibitor trial to provide some evidence of potential benefit in HFpEF was the SOLOIST-WHF and SCORED trials involving sotagliflozin, a dual SGLT2/SGLT1 inhibitor - though both were terminated early and their primary endpoints were altered in the trial. The SOLOIST -WHF trial showed that regardless of ejection fraction < 50% or > 50%, sotagliflozin was associated with reductions in a composite of CV death, hospitalization for worsening heart failure, and urgent visits for heart failure (HR 0.67, $P < 0.001$)[27]. Additionally, pooled analysis from both trials looking at patients with preserved ejection fraction (LVEF > 50%) found that sotagliflozin was associated with benefit in terms of the primary outcome (HR 0.63, $P = 0.009$)[27] .

More recently, the Emperor Preserved trial compared empagliflozin 10mg to placebo in patients with preserved ejection fraction with and without type 2 diabetes. The primary outcome of cardiovascular mortality or hospitalization for heart failure was achieved with a hazard ratio of 0.73 ($P < 0.001$) though this was driven by the hospitalization for heart failure[28]. Additionally, Empagliflozin was associated with improvements in quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, and this occurred regardless of baseline scores[29]. The lack of hard endpoints in terms of mortality benefit must be balanced against the benefits seen in reduced hospitalization and QOL, and this has been reflected in approval from the FDA and SmPC for chronic heart failure (irrespective of ejection fraction)[30-31]. It is worth noting that the benefits of empagliflozin were seen in those with ejection fraction < 60%, which has led to a debate on what constitutes HFpEF and whether EF < 50% is just a continuum and given the benefits seen at higher EF with Empagliflozin, perhaps these classifications should be revised or re-considered when deciding therapy benefit[32].

This may be further explored with the Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure (DELIVER) trial. This trial assessed the primary outcome of cardiovascular mortality or worsening heart failure with dapagliflozin 10mg in patients with heart failure and mildly reduced or preserved ejection fraction (LVEF > 40%) and was stopped early due to the achievement of its primary endpoint. The trial met its primary endpoint with an HR of 0.82 (CI 0.73-0.92, $P < 0.001$), largely driven by worsening heart failure (HR 0.79, CI 0.69-0.91)[33]. It is likely that soon SGLT2 inhibitors will be considered in some form across the spectrum of reduced and preserved ejection fraction; however, there may be a review of classification and evidence-based benefit depending on ejection fraction given the variation in trial findings.

Inpatient initiation of SGLT2s

Although SGLT2 inhibitors have been largely outpatient-initiated medications, the overwhelming evidence of benefit and early benefit within weeks with regard to heart failure outcomes has started to draw the conversation to earlier initiation in the acute setting. A post hoc analysis of empagliflozin from the EMPA-REG trial showed primary outcome benefit by day 59 and hHF benefit by day 17[34]. Similarly, data from DAPA-HF and EMPEROR-REDUCED showed benefits in primary outcome by day 28 and day 12, respectively, highlighting the potential benefits of early initiation[35,36]. The previously mentioned SOLOIST-WHF trial first looked at this consideration and showed benefits of sotagliflozin in patients with recent worsening heart failure, with just under half of patients (48.8%) given the first dose prior to discharge and the remainder within a median of two days post discharge[27].

The EMPULSE study provided some further focus on patients with acute or newly decompensated heart failure, who, regardless of ejection fraction, started either empagliflozin 10mg or placebo for 90 days. The primary outcome was clinical benefit defined by a composite of all-cause mortality, number of heart failure

events, time to first heart failure event, and additionally a five-point change in KCCQ score at 90 days. The trial achieved its primary outcome (win ratio 1.36 CI 1.09-1.68, $P = 0.0054$) with good tolerability and safety profile and no ketoacidosis events in either group, thereby suggesting that inpatient initiation is a valid and safe consideration[37]. Additionally, quality of life as well as physical limitations and symptoms were also improved with empagliflozin as early as day 15 and benefits persisted for the 90 days of the trial[38].

The initiation of SGLT2 inhibitors in an inpatient setting may already occur in current practice; however, driven by the aforementioned trials, the conversations around inpatient cessation of SGLT2s during intercurrent illness will also be debated with recent consensus suggesting the consideration that the DKA risk must be balanced with the harms of not restarting these medications[39,40]. This is also supported by findings from the DARE-19 trial, which assessed the organ protective effects of dapagliflozin 10mg in patients hospitalized with COVID-19. Though not achieving its primary outcome, it did show a numerical tendency and, more importantly, no increased safety signals in the dapagliflozin group, suggesting that potentially these medications are safe to be continued in some inpatients[41]. Although from an evidence base perspective, the risk of DKA in patients with diabetes has been shown, the risk of inpatient cessation in terms of harms has yet to be revealed and with patient safety a key consideration, it is hard to see risk mitigation in current non-trial based care - although future pragmatic controlled trials might provide real-world answers to this consideration.

SGLT2s and other considerations

Older adults and frailty

The use of SGLT2 inhibitors is fairly ubiquitous in many guidelines and clinical practices across the world, with their cardiovascular outcome data and clinical efficacy one of the key reasons. Their benefits have been seen across the age spectrum, but their use in frailty and in older individuals balancing the risks versus benefits remains undecided with the potential for harm in such individuals with their side effect profile of genitourinary infections and DKA risk as well as weight loss and blood pressure reduction[42]. A recent presentation looking at 1-year follow-up of individuals over 70 years old on SGLT-2 inhibitors for type 2 diabetes found good tolerance and safety, although with some caveats around frailty status, which, as mentioned, is a key area for future trials to gather evidence[43].

The EMPA-ELDERLY trial is a 52-week trial assessing empagliflozin 10 mg over 52 weeks in an elderly (> 65yrs) Japanese population. It will be the first SGLT2 inhibitor randomized controlled trial to assess effects specifically in this older population with secondary outcomes of physical performance, skeletal muscle mass and muscle strength, which may provide evidence in this rapidly evolving area[44]. Additionally, the potential benefit for heart failure must also be considered in the setting of older adults and frailty, with recent consensus perhaps suggesting this benefit may offset the potential risks[18]. Recently the implications of frailty in heart failure have been considered in cardiology fields, and there would be interesting considerations for the use of SGLT2 inhibitors and their impact on frailty in those with heart failure though this area is yet to be explored.

Pre-diabetes, gestational diabetes and cardiovascular risk

Recent data is starting to highlight the evolving continuum of the impact of dysglycaemia on cardiovascular disease, with observational studies in pre-diabetes suggesting that they are at higher risk of poorer outcomes with heart failure[45]. A recent meta-analysis of studies with gestational diabetes also noted an increased risk of postpartum cardiovascular events regardless of the development of type 2 diabetes, thereby suggesting risk factor management and closer follow-up for cardiovascular disease[46].

The DAPA-HF, DAPA-CKD, and EMPEROR-REDUCED trials all showed benefits of the respective SGLT2 classes across the spectrum of Hba1c and also with regard to reduction in new-onset type 2 diabetes, thereby suggesting possible added benefits of this class in these populations. Whether this would be a consideration seems unlikely, but a cardiovascular outcome trial in those with pre-diabetes on these medications would be an interesting consideration to test this hypothesis.

Uric acid and gout

The reduction in uric acid levels by SGLT2 inhibitors has long been noted and even considered one of the possible mechanisms of their cardiovascular benefit[47]. Recent post hoc analysis from the EMPA-REG OUTCOME trial has shown that empagliflozin reduced uric acid levels and a composite of gout and gout medications in the study population[48]. This uric acid reduction effect has also been shown with dapagliflozin in the DAPA-HF trial and with canagliflozin[49,50]

In keeping with their multitude of effects, added benefits of SGLT2is in those with type 2 diabetes, hyperuricaemia, and/or gout could be another treatment consideration.

Recommendation of SGLT2 Inhibitors in NAFLD

Non-alcoholic fatty liver disease (NAFLD) or Metabolic associated fatty liver disease (MAFLD) is becoming an increasing concern for patients with type 2 diabetes, not just from a progression to cirrhosis but also due to the association of cardiovascular disease[51]. There is increasing push toward screening and managing patients with type 2 diabetes for NAFLD; however, the pharmacological treatment options beyond pioglitazone are yet to be determined. There have been a number of studies looking at SGLT2 inhibitors in this population, with benefits seen in liver transaminases, liver fat on imaging, and body weight though there are minimal studies looking at those without type 2 diabetes and limited histological studies[52].

Real-world registries such as the ABCD National Audits have also shown reductions in ALT with SGLT2s suggesting potential benefit in NAFLD, though again, there are arguments for its correlation with histological benefits. Though limited data on histological benefits, a trial involving ipragliflozin did show resolution of NASH in 66.7% of patients treated with Ipragliflozin[53]. Similarly, a small 6-patient study looking at liver biopsies in patients treated with canagliflozin suggested favourable histological impact[54].

Perhaps the most convincing trial to date looked at metabolic and histological parameters of another SGLT2 inhibitor, tofogliflozin, compared to glimepiride and identified improvements in hepatocellular ballooning, lobular inflammation and steatosis with tofogliflozin as well as biochemical findings[55].

Future studies are considering the use of SGLT2s in NAFLD, though to truly appreciate benefit, there would need to be specifically designed hepatic outcome trials 'HOTs' to determine the benefit of medication in this comorbidity. Until then, recommendations of SGLT-2 inhibitors in NAFLD will centre around improvements in surrogate markers.

SGLT2 Inhibitors and CKD

Just as with heart failure, SGLT2 inhibitors have now been recommended as one of the key pillars in the management of CKD in those with and without type 2 diabetes, as seen in the recent ADA-EASD and KDIGO guidelines[56]. Specifically, in those with established CKD, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo[26]. More recently, the EMPA-KIDNEY trial was halted early due to the achievement of the

primary endpoint[57]. This trial will look at a broader spectrum of CKD (mild to severe stages and underlying causes) in those with and without type 2 diabetes, including those with normal urine albuminuria, and will therefore expand the understanding of the effects of SGLT2 inhibitors.

There are a few unanswered questions with regards to SGLT2 inhibitors in CKD management which perhaps will be addressed with EMPA-KIDNEY results; however, one area of consideration for SGLT2 inhibitors is, as with heart failure, whether inpatient initiation is considered in this group. Additionally, with the presence of finerenone now being recommended by the FDA and EMA for the treatment of CKD in those with T2DM, the potential benefits of SGLT2 inhibitor therapy in addition to non-steroidal mineralocorticoid antagonists (ns-MRAs) remains to be evaluated. The FIDELIO and FIGARO-DKD trials both had a small proportion of patients on dual therapy with SGLT2i and ns-MRAs (6.7% across both trials), with the pooled analysis FIDELITY showing that finerenone effects were independent of the presence of SGLT2i use[58-60]. Additionally, another interesting finding was that those on dual therapy had a lower incidence of hyperkalaemia. In fact, this finding of reduced hyperkalaemia with SGLT2 inhibitors has been noted from analyses with SGLT2s reducing the risk of serious hyperkalaemia in those with high CV risk or CKD and type 2 diabetes[61]. This may provide reassurance for combination therapy with ACEi/ARBs/nsMRAs and SGLT2is though more specific trials would be required to fully reassure.

A phase II trial CONFIDENCE assessing the effect of finerenone in combination with empagliflozin on urine ACR compared with each agent on their own may help address this knowledge gap and guide more support for the positioning of either agent in CKD and the role of combination therapy[62].

INCRETINS

GLP-1 RAs

GLP-1 receptor agonists have been shown to be very effective glucose-lowering and weight-lowering medications in those with type 2 diabetes. In addition, their cardiovascular benefits, especially for the human analogue based GLP-1s such as dulaglutide and semaglutide, further support their clinical benefits, especially in stroke reduction - a benefit which the SGLT2 class has not particularly shown[63,64]. The other benefit of GLP-1 RAs in the management of type 2 diabetes is their efficacy at lower eGFR thresholds, with the three mainly used therapies (liraglutide, dulaglutide, and semaglutide) all licensed for eGFR over 15 mL/min. The areas where they perhaps have not shown clear benefit and require further evidence have been on renal and heart failure outcomes - especially in the setting of preserved ejection fraction and their effect on obesity/weight loss. Post-hoc analysis of the REWIND cardiovascular outcome trial with dulaglutide revealed a reduction in a composite renal outcome of new macroalbuminuria, and a decline in eGFR by 30% or more from baseline or chronic renal replacement therapy. This benefit was predominantly with a reduction in new-onset macroalbuminuria (HR 0.77); however, this alone is not sufficient to recommend their use specifically for renal protection and the gold standard primary renal outcome trials with GLP-1 RAs are still awaited[65]. This may well be answered in the FLOW trial, a randomized, double-blinded, placebo-controlled trial assessing the effect of semaglutide on renal outcomes in participants at high risk of CKD progression. Baseline characteristics of participants include those with type 2 diabetes, eGFR 25-75 mL/min/1.73 m^2, and urine ACR > 100 to < 5,000 mg/g with the primary endpoint being time to first occurrence of renal or cardiovascular death, >/= 50% persistent eGFR reduction from baseline and kidney failure (eGFR< 15 mL/min/1.73 m^2 or chronic dialysis or kidney transplantation). This trial is the first dedicated renal outcome trial for the GLP-1 class and may help define the role of GLP-1s in those with renal disease and type 2 diabetes beyond glycaemia[66].

Higher dose GLP-1s in T2DM

With the establishment of the GLP-1 class as good glycaemic and weight-lowering medications, the use of higher doses has also been looked at to see if there was a further benefit in their effects with a balance to the side effect profile - a key limiting factor in medication tolerability.

The Sustain Forte trial looked at semaglutide 2 mg compared to 1 mg once weekly in those with T2DM on metformin and/or sulphonylurea. Semaglutide 2 mg had a -0.23% Hba1c and -0.93 kg estimated treatment difference (as per treatment policy estimand) with a similar adverse event profile (34% *vs.* 31% reported gastrointestinal disturbances)[67]. Similarly, Dulaglutide 3 mg and 4.5 mg, which is already licensed in the UK for T2DM, showed a -0.24% Hba1c and -1.6 kg weight reduction with 4.5 mg compared to 1.5 mg dose[68]. Both these higher strength doses show benefits in terms of Hba1c and weight loss compared to the conventional dosing with a relatively similar side effect profile, though one could argue the Hba1c reduction was relatively minimal compared to the weight loss. However, the role of these higher-dose medications may be limited in the near future due to the potential favouring of newer dual incretin molecules and other higher-dose GLP-1 therapies in obesity, which are more efficacious in weight reduction.

Semaglutide 2.4 mg is currently licensed in UK and USA for the treatment of obesity based on the findings from the STEP trials. Though these trials were specifically in participants with obesity, the STEP 2 trial looked at those with type 2 DM and obesity or overweight with semaglutide 2.4 mg compared to 1mg and placebo. Semaglutide 2.4 mg resulted in a -1.2% Hba1c reduction and a -6.2% weight reduction compared to placebo, with 69% of participants achieving weight loss of at least 5% compared to 29% in the placebo arm. Side effect profile was notably higher in those on semaglutide 2.4mg compared to placebo group, with mild to moderate gastrointestinal side effects noted in 63.5% to 34.3%, but less notable in those on semaglutide 1 mg (57.5%), suggesting reasonable tolerability[69]. This poses an interesting consideration for patients with T2DM who are on semaglutide, with potentially three treatment options of 1 mg, 2 mg or 2.4 mg once weekly with escalation, perhaps more based on the requirement for weight loss over Hba1c lowering for dose escalation.

Dual Agonists

Imminently due on the treatment landscape is Tirzepatide, a dual GLP-1/GIP agonist, which is FDA-approved and available in the USA with a license and NICE guidance in the UK due in the near future. Building on the efficacy of the GLP-1 molecules, the addition of a second incretin - GIP (Glucose-dependent insulinotropic polypeptide) further enhances glycaemic and weight lowering, thereby providing a potentially powerful agent in the management of type 2 diabetes and obesity.

The evidence for this molecule comes from the SURPASS phase III trials which assessed the effects of Tirzepatide against various comparators.

The SURPASS 1 trial was a placebo-controlled trial assessing 5 mg, 10 mg and 15 mg Tirzepatide with an estimated treatment difference of -21-23 mmol/mol reduction in Hba1c across the doses compared to placebo (+ 0.4 mmol/mol) and a 7-9.5 kg reduction in weight loss. Tolerability was similar across the doses and not far different from previous GLP-1-only studies, with 12%-18% on Tirzepatide developing nausea or diarrhoea, 2%-6% vomiting, and 14% discontinuing the medication. Impressively, a high proportion of participants on Tirzepatide achieved Hba1c targets of < 53 mmol/mol (87%-92%) and < 48 mmol/mol (81%-86%), showing the efficacy of the glucose-lowering agent Tirzepatide[70].

Directly providing a comparison to GLP-1 therapy, the SURPASS 2 trial compared Tirzepatide (5 mg, 10 mg, 15 mg) to Semaglutide 1mg dose and showed greater reductions (estimated treatment differences) in Hba1c (-0.15, -0.39 and -0.45 percentage points respectively) and weight (-1.9 kg, -3.6 kg and -4.5 kg respectively). Although this may show the benefits of Tirzepatide over the current GLP-1 therapy, there is still debate about whether it is the GLP-1 or the GIP that provides this added benefit, with mechanistic studies and clarity still awaited[71].

The SURPASS 3 trial similarly showed reductions in Hba1c and weight with Tirzepatide compared to insulin degludec though perhaps the more interesting aspects of this trial were the added trial elements of continuous glucose monitoring and measurement of liver fat. A sub-study of the trial (SURPASS-3 CGM) looked at 243 participants of the SURPASS-3 trial and assessed CGM metrics in this group at 3 points across the trial (baseline, 24 weeks and 52 weeks). Pooled analysis of the Tirzepatide 10 mg and 15mg doses revealed a greater proportion achieving time in range (71-140 mg/dL or 3.9 -10 mmol/L), with a 25% estimated treatment difference. Given the increasing use of technology in diabetes care, this data provides further interesting information and reassurance beyond the limitations of Hba1c targets, such as time in hypoglycaemia or hyperglycaemia[72,73]. The SURPASS 3 trial had another substudy, the SURPASS-3 MRI, which assessed MRI changes in liver fat content in a subset of participants in the trial with a fatty liver index of at least 60 (by MRI-proton density fat fraction MRI-PDFF). Again utilising pooled data from the Tirzepatide 10 and 15mg groups, liver fat content was reduced compared to placebo (-8.09% *vs.* -3.38% in the degludec group) with reductions seen in the volume of visceral and abdominal subcutaneous adipose tissue (VAT and ASAT)[74]. This adds interest in the effects of Tirzepatide on liver fat, potentially suggesting a future therapeutic option in NAFLD - something that is being assessed in the ongoing SYNERGY-NASH trial, which will also assess histological changes in addition to MRI-PDFF[75].

Tirzepatide is the most advanced of the dual incretin agonists currently in development though another, Codatutide, has undergone phase 2 trials and is in development, thereby adding further molecules to this class of agents[76].

One obvious important area is the lack of hard cardiovascular outcomes for this molecule. The SURPASS 4 trial assessed the effects, specifically cardiovascular safety, of Tirzepatide compared to insulin glargine in a population at high cardiovascular risk, assessing for a MACE-4 composite of cardiovascular mortality, myocardial infarction, stroke and hospitalization for unstable angina[77]. Tirzepatide was not associated with an increased cardiovascular risk in this study and an additional pre-specified metanalysis confirmed this[78]. However, though reassuring, such data still requires results from the dedicated cardiovascular outcome trial SURPASS-CVOT, assessing the cardiovascular effects of Tirzepatide against dulaglutide, a first for CVOTs - comparison against a medication already proven to have cardiovascular benefit, with completion due in 2024[79].

While the data from the SURPASS trials make clinical interest in the utilisation of this medication in those with type 2 diabetes, there are a few clinical considerations and real-world data will be beneficial once widely available. The key is the positioning in the management of type 2 diabetes: could it be reasonable to start this medication as first choice incretin in order to initiate the treatment most likely to achieve required targets, or would it be considered only after 'failure' of current single incretin GLP-1 therapy. Additionally, the dose steps involved -2.5 mg increments at 6 weekly intervals could mean that it takes 6 months to reach the maximum 20 mg dose (if required), thereby posing adherence and treatment persistence considerations. Nevertheless, the addition of this new class of dual incretins provides an exciting opportunity to enhance the management of those with type 2 diabetes and/or obesity.

GLP-1s and other considerations

Stroke and cognition

The cardiovascular beneficial effects of human analogue GLP-1s have been established with perhaps more focus on the cardiac benefits compared to the cerebrovascular findings. In fact, with such strong data for stroke prevention from the dulaglutide and semaglutide cardiovascular outcome trials, it is perhaps surprising that there has not been more focus on this area in guidelines or in practice. An exploratory analysis of the REWIND trial revealed a reduction in ischaemic but not haemorrhagic stroke in those with type 2 diabetes but no impact on stroke severity[80]. Similarly, a post hoc analysis of the semaglutide cardiovascular outcome trials (SUSTAIN-6 and PIONEER 6) also revealed that semaglutide reduced the risk of stroke irrespective of prior stroke at baseline[81]. Prioritisation of such GLP-1 molecules in those with type 2 diabetes at high risk of stroke (including prior TIA) and increased awareness amongst neurologists and stroke physicians remains one of the future considerations for these medications and future guidelines. Additionally, given the beneficial effects on stroke and the impact of stroke on cognitive function, it may also be considered that these molecules may also have an impact on cognitive impairment. Additionally, the atherosclerotic impact, insulin resistance effects, and glycaemic benefits of this class may be further mechanisms whereby their beneficial effects on cognition may be seen. This has been somewhat considered in small trials, but stands to be further assessed in a larger population with the upcoming trial of oral semaglutide in Alzheimer's disease to provide more insight into this area[82].

The role of incretins in obesity is another rapidly developing area and beyond the scope of this article; however, it is important to note that amylin analogues such as cagrilintide have been combined with GLP-1 semaglutide with trials in progress and cardiovascular outcome trials of these molecules in those with obesity such as SELECT for semaglutide ongoing and already reports of benefits of dual incretin Tirzepatide in obesity[83-85], . Together with the recent update to ADA-EASD guidance highlighting weight loss in type 2 diabetes management, the future of therapeutic options and focus on diabetes and obesity care with these molecules seems numerous.

GLP-1s and NAFLD

As with SGLT2s, the effect of GLP-1s in those with NAFLD continues to be of interest. The recent D-LIFT randomized controlled trial assessed MRI parameters of liver fat content in patients on dulaglutide and found that dulaglutide significantly reduced liver fat content and gamma GT in subjects with NAFLD with non-significant reductions in ALT, AST, and liver stiffness[86]. A recent phase 2 trial assessed semaglutide 0.1 mg, 0.2 mg and 0.4 mg against placebo in patients with biopsy-proven NASH and liver fibrosis. Semaglutide resulted in a higher percentage of participants with NASH resolution than placebo (40%, 36%, and 59% with the semaglutide doses compared to 17% with placebo)[87]. A larger, more specific study is in progress to further assess semaglutide in those with NASH to further explore and support evidence in this area, but completion is not expected until 2028[88]. Although an increasingly developing area of assessment for the GLP-1 molecule, it is likely that with the newer incretin molecules, specifically double and triple agonists, the role of GLP-1s, specifically in NAFLD or obesity, may soon be superceded by these molecules.

Recently the development of once-weekly insulins has been seen as an interesting addition to the treatment landscape - with ease of use and reduced number of injections being the main reason for positivity. Confidence still remains unclear around the safety aspects with regard to hypoglycaemia, especially in the older adult population. The combination of once-weekly GLP-1 with the once-weekly insulin provides hope for further simplification of management options in those with type 2 diabetes, especially with the hypoglycaemia and weight gain effects of insulin being reduced by the GLP-1 component. Trials are underway, with the most advanced being the semaglutide/insulin icodec combination in the COMBINE 3 trial, which is due to report in 2023[89].

FUTURE PERSPECTIVES FOR CARE

As we move forward in our management of type 2 diabetes, we see more understanding and development of the intensification and appropriateness of therapeutic interventions. Some of these developments are being driven by different age spectrums of those with type 2 diabetes. As we continue to encounter an aging population, the impact of multimorbidity on type 2 diabetes management continues to be considered[90]. Additionally, with the increasing awareness of the impact of younger onset T2DM in populations, the importance of intensification of regimes and treating to targets and dealing with associated comorbidities adds further impetus. While guidelines and management at the moment focus on dual comorbidities such as heart failure, ASCVD, or CKD in the setting of type 2 diabetes, in reality, it is not uncommon to find all three comorbidities in individuals with type 2 diabetes, and if you additionally consider overweight or obesity, we may be starting to deal with triple or quadruple comorbidities and therefore decisions and guidelines need to be developed accordingly[91]. Diabetes, due to its associations and links with other chronic conditions such as cardiorenal metabolic disease, obesity, and frailty, provides an opportune area to develop not just multimorbidity care but specific patient-based care strategies[92].

The term precision medicine or personalised medicine is an approach to disease management considering individual characteristics such as genetic background, environment, and lifestyle to create a person-specific management plan[93]. Recent trials such as TRIMASTER and GRADE have taken this practice in a trial setting to highlight that beyond glycaemic and extraglycaemic benefits, patient choice and perspectives need to be considered to identify those therapeutic options more likely to be accepted and therefore support treatment concordance[11,94]. Interestingly, the GRADE study showed that Hba1c reduction was notable regardless of treatment choice (metformin, sulphonylurea, GLP-1 RA, or DPP-4 inhibitor), but glargine and liraglutide were more effective in achieving and maintaining target Hba1c[94]. Additionally, recent genetic factors have also been found to identify individuals more likely to develop nephropathy, potentially heralding a further way of stratifying patient risk and identifying optimal therapies to target their individual risks[95]. While this is being increasingly relevant and considered, the appropriate method and factors to consider still require clarity and support in mainstream guidelines and care.

CONCLUSION

The treatment landscape continues to develop at a rapid pace, and with each new molecule being developed, there is a layer of complexity and finesse in the choice of agent used and the individualization of therapeutic options. Additionally, our understanding of the impact of diabetes on a variety of conditions and comorbidities has led to an even broader consideration for management and diabetes care in various settings from the current landscape of cardiovascular and renal disease toward obesity and fatty liver disease with future considerations potentially to include youth onset T2DM, cancer, bone health, and periodontal disease. Guidelines will need to be fluid and continue to adapt to this ever-changing landscape, as will clinicians and healthcare systems and methods of delivering care, including telehealth and digital interventions.

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Authors' contributions

Created the concept for the article and content, as well as the overall review: Puttanna A
Contributed to the main manuscript and the reviewers' comments: Kalloo J, Priscilla S

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REFERENCES

1. North EJ, Newman JD. Review of cardiovascular outcomes trials of sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists. *Curr Opin Cardiol* 2019;34:687-92. DOI PubMed PMC
2. Buse JB, Wexler DJ, Tsapas A, et al. Erratum. 2019 Update to: management of hyperglycemia in type 2 diabetes, 2018. a consensus report by the American diabetes association (ADA) and the European association for the study of diabetes (EASD). *Diabetes Care* 2020;43:1670. DOI PubMed PMC
3. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycaemia in type 2 diabetes, 2022. a consensus report by the American Diabetes Association (ADA) and the European association for the study of diabetes (EASD). *Diabetologia* 2022;65:1925-66. DOI PubMed PMC
4. Palmer SC, Tendal B, Mustafa RA, et al. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *BMJ* 2021;372:m4573. DOI PubMed PMC
5. NICE guideline NG28, Type 2 diabetes in adults: management Available from: https://www.nice.org.uk/guidance/ng28 [Last accessed on 6 May 2023].
6. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*; 1998 ;352:854-65. DOI
7. Rosenstock J, Marx N, Kahn SE, et al. Cardiovascular outcome trials in type 2 diabetes and the sulphonylurea controversy: rationale for the active-comparator CAROLINA trial. *Diab Vasc Dis Res* 2013;10:289-301. DOI
8. Wallace MD, Metzger NL. Optimizing the treatment of steroid-induced hyperglycemia. *Ann Pharmacother* 2018;52:86-90. DOI PubMed
9. Roberts A, James J, Dhatariya K; Joint British Diabetes Societies (JBDS) for Inpatient Care. Management of hyperglycaemia and steroid (glucocorticoid) therapy: a guideline from the joint British diabetes societies (JBDS) for inpatient care group. *Diabet Med* 2018;35:1011-7. DOI PubMed
10. Hattersley AT, Greeley SAW, Polak M, et al. ISPAD clinical practice consensus guidelines 2018: the diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes* 2018;19 Suppl 27:47-63. DOI
11. Angwin C, Jenkinson C, Jones A, et al; MASTERMIND consortium. TriMaster: randomised double-blind crossover study of a DPP4 inhibitor, SGLT2 inhibitor and thiazolidinedione as second-line or third-line therapy in patients with type 2 diabetes who have suboptimal glycaemic control on metformin treatment with or without a sulfonylurea-a MASTERMIND study protocol. *BMJ Open* 2020;10:e042784. DOI PubMed PMC
12. Available from: https://www.easd.org/virtualmeeting/home.html#!resources/b-results-of-the-trimaster-trial-b [Last accessed on 24 May 2023].
13. Dormandy JA, Charbonnel B, Eckland DJ, et al; PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005;366:1279-89. DOI
14. Young LH, Viscoli CM, Schwartz GG, et al; IRIS Investigators. Heart failure after ischemic stroke or transient ischemic attack in insulin-resistant patients without diabetes mellitus treated with pioglitazone. *Circulation* 2018;138:1210-20. DOI PubMed PMC
15. Lian J, Fu J. Pioglitazone for NAFLD patients with prediabetes or type 2 diabetes mellitus: a meta-analysis. *Front Endocrinol* 2021;12:615409. DOI PubMed PMC
16. Stefan N, Cusi K. A global view of the interplay between non-alcoholic fatty liver disease and diabetes. *Lancet Diabetes Endocrinol* 2022;10:284-96. DOI
17. Matthews DR, Paldánius PM, Proot P, Chiang Y, Stumvoll M, Del Prato S; VERIFY study group. Glycaemic durability of an early

combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. *Lancet* 2019;394:1519-29. DOI PubMed

18. Strain WD, Down S, Brown P, Puttanna A, Sinclair A. Diabetes and frailty: an expert consensus statement on the management of older adults with type 2 diabetes. *Diabetes Ther* 2021;12:1227-47. DOI PubMed PMC
19. Available from: https://www.fda.gov/drugs/fda-drug-safety-podcasts/fda-announced-safety-review-has-found-type-2-diabetes-medicines-containing-saxagliptin-and#:~:text=On%20April%205%2C%202016%2C%20FDA,have%20heart%20or%20kidney%20disease [Last accessed on 23 May 2023].
20. 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;373:2117-28. DOI
21. 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;377:644-57. DOI PubMed
22. Wiviott SD, Raz I, Bonaca MP, et al; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;380:347-57. DOI PubMed
23. 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. DOI PubMed
24. 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;383:1413-24. DOI PubMed
25. Perkovic V, Jardine MJ, Neal B, et al; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;380:2295-306. DOI PubMed
26. 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;383:1436-46. DOI PubMed
27. Bauersachs J. SCORED and SOLOIST: the next scores for SGLT2 inhibitors. *Cardiovasc Res* 2021;117:e49-51. DOI PubMed
28. Anker SD, Butler J, Filippatos G, et al; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021;385:1451-61. DOI PubMed
29. Butler J, Filippatos G, Jamal Siddiqi T, et al. Empagliflozin, health status, and quality of life in patients with heart failure and preserved ejection fraction: the EMPEROR-preserved trial. *Circulation* 2022;145:184-93. DOI PubMed PMC
30. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-treatment-wider-range-patients-heart-failure [Last accessed on 24 May 2023].
31. Available from: https://www.medicines.org.uk/emc/product/5441/smpc#gref [Last accessed on 24 May 2023].
32. Hasegawa K, Lewis BS. Are SGLT2 inhibitors effective against 'all' heart failure with preserved ejection fraction? *Eur Heart J Cardiovasc Pharmacother* 2022;8:E10. DOI PubMed
33. Solomon SD, McMurray JJV, Claggett B, et al; DELIVER Trial Committees and Investigators. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2022;387:1089-98. DOI PubMed
34. Verma S, Leiter LA, Zinman B, et al. Time to cardiovascular benefits of empagliflozin: a post hoc observation from the EMPA-REG OUTCOME trial. *ESC Heart Fail* 2021;8:2603-7. DOI PubMed PMC
35. Berg DD, Jhund PS, Docherty KF, et al. Time to clinical benefit of dapagliflozin and significance of prior heart failure hospitalization in patients with heart failure with reduced ejection fraction. *JAMA Cardiol* 2021;6:499-507. DOI PubMed PMC
36. Packer M, Anker SD, Butler J, et al. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: the EMPEROR-reduced trial. *Circulation* 2021;143:326-36. DOI PubMed PMC
37. Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med* 2022;28:568-74. DOI PubMed PMC
38. Kosiborod MN, Angermann CE, Collins SP, et al. Effects of empagliflozin on symptoms, physical limitations, and quality of life in patients hospitalized for acute heart failure: results from the EMPULSE trial. *Circulation* 2022;146:279-88. DOI PubMed PMC
39. Koufakis T, Mustafa OG, Ajjan RA, et al. The use of sodium-glucose co-transporter 2 inhibitors in the inpatient setting: is the risk worth taking? *J Clin Pharm Ther* 2020;45:883-91. DOI PubMed
40. Khunti K, Aroda VR, Bhatt DL, et al. Re-examining the widespread policy of stopping sodium-glucose cotransporter-2 inhibitors during acute illness: a perspective based on the updated evidence. *Diabetes Obes Metab* 2022;24:2071-80. DOI PubMed
41. Kosiborod MN, Esterline R, Furtado RHM, et al. Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol* 2021;9:586-94. DOI PubMed PMC
42. Fralick M, Colacci M, Thiruchelvam D, Gomes T, Redelmeier DA. Sodium-glucose co-transporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors and the risk of heart failure: a nationwide cohort study of older adults with diabetes mellitus. *Diabetes Obes Metab* 2021;23:950-60. DOI PubMed
43. Available from: https://www.easd.org/media-centre/home.html%20#!resources/b-safety-and-efficacy-of-sglt2-inhibitors-in-over-70-years-old-type-2-diabetic-patients-1-year-of-follow-up-b-bac06cfd-6ee4-4476-a43d-096cb7d74cd4 [Last accessed on 24 May 2023].
44. Yabe D, Shiki K, Suzaki K, et al. Rationale and design of the EMPA-ELDERLY trial: a randomised, double-blind, placebo-controlled, 52-week clinical trial of the efficacy and safety of the sodium-glucose cotransporter-2 inhibitor empagliflozin in elderly Japanese patients with type 2 diabetes. *BMJ Open* 2021;11:e045844. DOI PubMed PMC

45. Mai L, Wen W, Qiu M, et al. Association between prediabetes and adverse outcomes in heart failure. *Diabetes Obes Metab* 2021;23:2476-83. DOI
46. Kramer CK, Campbell S, Retnakaran R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. *Diabetologia* 2019;62:905-14. DOI PubMed
47. Bailey CJ. Uric acid and the cardio-renal effects of SGLT2 inhibitors. *Diabetes Obes Metab* 2019;21:1291-8. DOI PubMed
48. Ferreira JP, Inzucchi SE, Mattheus M, et al. Empagliflozin and uric acid metabolism in diabetes: a post hoc analysis of the EMPA-REG OUTCOME trial. *Diabetes Obes Metab* 2022;24:135-41. DOI PubMed PMC
49. McDowell K, Welsh P, Docherty KF, et al. Dapagliflozin reduces uric acid concentration, an independent predictor of adverse outcomes in DAPA-HF. *Eur J Heart Fail* 2022;24:1066-76. DOI PubMed PMC
50. Davies MJ, Trujillo A, Vijapurkar U, Damaraju CV, Meininger G. Effect of canagliflozin on serum uric acid in patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 2015;17:426-9. DOI PubMed PMC
51. Duell PB, Welty FK, Miller M, et al; American Heart Association Council on Arteriosclerosis; Thrombosis and Vascular Biology; Council on Hypertension; Council on the Kidney in Cardiovascular Disease; Council on Lifestyle and Cardiometabolic Health; and Council on Peripheral Vascular Disease. Nonalcoholic fatty liver disease and cardiovascular risk: a scientific statement from the American heart association. *Arterioscler Thromb Vasc Biol* 2022;42:e168-85. DOI
52. Androutsakos T, Nasiri-Ansari N, Bakasis AD et al. SGLT-2 Inhibitors in NAFLD: expanding their role beyond diabetes and cardioprotection. *Int J Mol Sci* 2022;13:3107. DOI PubMed PMC
53. Takahashi H, Kessoku T, Kawanaka M, et al. Ipragliflozin improves the hepatic outcomes of patients with diabetes with NAFLD. *Hepatol Commun* 2022;6:120-32. DOI PubMed PMC
54. Akuta N, Kawamura Y, Fujiyama S, et al. Favorable impact of long-term SGLT2 inhibitor for NAFLD complicated by diabetes mellitus: a 5-year follow-up study. *Hepatol Commun* 2022;6:2286-97. DOI PubMed PMC
55. Takeshita Y, Honda M, Harada K, et al. Comparison of tofogliflozin and glimepiride effects on nonalcoholic fatty liver disease in participants with type 2 diabetes: a randomized, 48-week, open-label, active-controlled trial. *Diabetes Care* 2022;45:2064-75. DOI PubMed PMC
56. Available from: https://kdigo.org/wp-content/uploads/2022/03/KDIGO-2022-Diabetes-Management-GL_Public-Review-draft_1Mar2022.pdf [Last accessed on 24 May 2023].
57. Available from: https://www.boehringer-ingelheim.com/human-health/metabolic-diseases/early-stop-chronic-kidney-disease-trial-efficacy [Last accessed on 24 May 2023].
58. 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;383:2219-29. DOI PubMed
59. Pitt B, Filippatos G, Agarwal R, et al; FIGARO-DKD Investigators. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med* 2021;385:2252-63. DOI PubMed
60. Agarwal R, Filippatos G, Pitt B, et al; FIDELIO-DKD and FIGARO-DKD investigators. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. *Eur Heart J* 2022;43:474-84. DOI PubMed PMC
61. Neuen BL, Oshima M, Agarwal R, et al. Sodium-glucose cotransporter 2 inhibitors and risk of hyperkalemia in people with type 2 diabetes: a meta-analysis of individual participant data from randomized, controlled trials. *Circulation* 2022;145:1460-70. DOI
62. Available from: https://clinicaltrials.gov/ct2/show/NCT05254002 [Last accessed on 24 May 2023].
63. 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;375:1834-44. DOI PubMed
64. Gerstein HC, Colhoun HM, Dagenais GR, et al; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019;394:121-30. DOI PubMed
65. 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;394:131-8. DOI PubMed
66. Rossing P, Baeres FMM, Bakris G, et al. The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease. *Nephrol Dial Transplant* ;2023:gfad009. DOI
67. Frías JP, Auerbach P, Bajaj HS, et al. Efficacy and safety of once-weekly semaglutide 2·0 mg versus 1·0 mg in patients with type 2 diabetes (SUSTAIN FORTE): a double-blind, randomised, phase 3B trial. *Lancet Diabetes Endocrinol* 2021;9:563-74. DOI
68. Frias JP, Bonora E, Nevarez Ruiz L, et al. Efficacy and safety of dulaglutide 3.0 mg and 4.5 mg versus dulaglutide 1.5 mg in metformin-treated patients with type 2 diabetes in a randomized controlled trial (AWARD-11). *Diabetes Care* 2021;44:765-73. DOI PubMed PMC
69. Davies M, Færch L, Jeppesen OK, et al; STEP 2 Study Group. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet* 2021;397:971-84. DOI
70. Rosenstock J, Wysham C, Frías JP, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. *Lancet* 2021;398:143-55. DOI
71. Frías JP, Davies MJ, Rosenstock J, et al; SURPASS-2 Investigators. Tirzepatide versus semaglutide Once weekly in patients with type 2 diabetes. *N Engl J Med* 2021;385:503-15. DOI
72. Ludvik B, Giorgino F, Jódar E, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or

without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. *Lancet* 2021;398:583-98. DOI PubMed

73. Battelino T, Bergenstal RM, Rodríguez A, et al. Efficacy of once-weekly tirzepatide versus once-daily insulin degludec on glycaemic control measured by continuous glucose monitoring in adults with type 2 diabetes (SURPASS-3 CGM): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. *Lancet Diabetes Endocrinol* 2022;10:407-17. DOI
74. Gastaldelli A, Cusi K, Fernández Landó L, Bray R, Brouwers B, Rodríguez Á. Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. *Lancet Diabetes Endocrinol* 2022;10:393-406. DOI PubMed
75. Available from: https://clinicaltrials.gov/ct2/show/NCT04166773 [Last accessed on 24 May 2023].
76. Parker VER, Robertson D, Wang T, et al. Efficacy, safety, and mechanistic insights of cotadutide, a dual receptor glucagon-like peptide-1 and glucagon agonist. *J Clin Endocrinol Metab* 2020;105:803-20. DOI
77. Prato S, Kahn SE, Pavo I, et al. SURPASS-4 investigators. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *Lancet* 2021;398:1811-24. DOI PubMed
78. Sattar N, McGuire DK, Pavo I, et al. Tirzepatide cardiovascular event risk assessment: a pre-specified meta-analysis. *Nat Med* 2022;28:591-8. DOI PubMed PMC
79. Available from: https://clinicaltrials.gov/ct2/show/NCT04255433 [Last accessed on 24 May 2023].
80. Gerstein HC, Hart R, Colhoun HM, et al. The effect of dulaglutide on stroke: an exploratory analysis of the REWIND trial. *Lancet Diabetes Endocrinol* 2020;8:106-14. DOI PubMed
81. Strain WD, Frenkel O, James MA, et al. Effects of semaglutide on stroke subtypes in type 2 diabetes: post hoc analysis of the randomized SUSTAIN 6 and PIONEER 6. *Stroke* 2022;53:2749-57. DOI PubMed PMC
82. Available from: https://clinicaltrials.gov/ct2/show/NCT04777396 [Last accessed on 24 May 2023].
83. Available from: https://clinicaltrials.gov/ct2/show/NCT05394519 [Last accessed on 24 May 2023].
84. Available from: https://clinicaltrials.gov/ct2/show/NCT03574597 [Last accessed on 24 May 2023].
85. Jastreboff AM, Aronne LJ, Ahmad NN, et al; SURMOUNT-1 Investigators. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med* 2022;387:205-16. DOI
86. Kuchay MS, Krishan S, Mishra SK, et al. Effect of dulaglutide on liver fat in patients with type 2 diabetes and NAFLD: randomised controlled trial (D-LIFT trial). *Diabetologia* 2020;63:2434-45. DOI
87. Newsome PN, Buchholtz K, Cusi K, et al; NN9931-4296 Investigators. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med* 2021;384:1113-24. DOI
88. Available from: https://clinicaltrials.gov/ct2/show/NCT04822181 [Last accessed on 24 May 2023].
89. Available from: https://clinicaltrials.gov/ct2/show/NCT05013229 [Last accessed on 24 May 2023].
90. Heikkala E, Mikkola I, Jokelainen J, Timonen M, Hagnäs M. Multimorbidity and achievement of treatment goals among patients with type 2 diabetes: a primary care, real-world study. *BMC Health Serv Res* 2021;21:964. DOI PubMed PMC
91. Chiang JI, Hanlon P, Li TC, et al. Multimorbidity, mortality, and HbA1c in type 2 diabetes: a cohort study with UK and Taiwanese cohorts. *PLoS Med* 2020;17:e1003094. DOI PubMed PMC
92. Xie F, Chan JC, Ma RC. Precision medicine in diabetes prevention, classification and management. *J Diabetes Investig* 2018;9:998-1015. DOI PubMed PMC
93. Available from: https://www.fda.gov/medical-devices/in-vitro-diagnostics/precision-medicine [Last accessed on 24 May 2023].
94. Nathan DM, Lachin JM, Balasubramanyam A, et al; GRADE Study Research Group. Glycemia reduction in type 2 diabetes - glycemic outcomes. *N Engl J Med* 2022;387:1063-74. DOI
95. Tye SC, Denig P, Heerspink HJL. Precision medicine approaches for diabetic kidney disease: opportunities and challenges. *Nephrol Dial Transplant* 2021;36:3-9. DOI PubMed PMC