pramlintide) are not commonly used in the USA and most are not licensed in Europe. There was no new evidence that impacts clinical practice.

Comparative efficacy of glucose-lowering agents

In a network meta-analysis of 453 trials assessing glucose-lowering medications from nine drug classes, the greatest reductions in HbA_{1c} were seen with insulin regimens and GLP-1 RA [223]. A network meta-analysis comparing the effects of glucose-lowering therapy on body weight and blood pressure indicates that the greatest efficacy for reducing body weight is seen with subcutaneous semaglutide followed by the other GLP-1 RA and SGLT2i, and the greatest reduction in blood pressure is seen with the SGLT2i and GLP-1 RA classes [224]. As discussed above, the novel GIP and GLP-1 RA tirzepatide was associated with greater glycaemic and weight loss efficacy than semaglutide 1 mg weekly [185].

Combination therapy

The underlying pathophysiology of type 2 diabetes is complex, with multiple contributing abnormalities resulting in a naturally progressive disease and increasing HbA_{1c} over time in many. While traditional recommendations have focused on the stepwise addition of therapy, allowing for clear delineation of positive and negative effects of new drugs, there are data to suggest benefits of combination approaches in diabetes care. Combination therapy has several potential advantages, including (1) increased durability of the glycaemic effect [225–227], addressing therapeutic inertia, (2) simultaneous targeting of the multiple pathophysiological processes characterised by type 2 diabetes, (3) impacts on medication burden, medication-taking behaviour and treatment persistence and (4) complementary clinical benefits (e.g. on glycaemic control, weight and cardiovascular risk profiles) [215, 228–244].

The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) was a multicentre open-label RCT designed to test four different diabetes medication classes in people with type 2 diabetes and compare their ability to achieve and maintain HbA_{1c} levels <53 mmol/mol (<7%). Eligible participants had their metformin therapy optimised and were randomly assigned to receive a sulfonylurea (glimepiride), a DPP-4 inhibitor (sitagliptin), a GLP-1 RA (liraglutide) or basal insulin (insulin glargine), with the primary outcome being the time to metabolic failure, defined as the time to an initial HbA_{1c} level ≥53 mmol/mol (≥7%), if it was confirmed at the next visit to remain above that threshold. Starting with a mean baseline HbA_{1c} level of 58 mmol/mol (7.5%) before the addition of one of the four medications, over 5 years of follow-up, 71% of the cohort reached the primary metabolic outcome. Insulin glargine and liraglutide were significantly, albeit modestly, more effective at achieving and maintaining HbA_{1c} targets. Liraglutide exhibited a lower risk than the pooled effect of the other three medications on a composite cardiovascular outcome comprising MACE, revascularisation, or HF or unstable angina requiring hospitalisation [245, 246].

Personalised approach to treatment based on individual characteristics and comorbidities: recommended process for glucose-lowering medication selection

People with cardiorenal comorbidities

The 2018 ADA/EASD consensus report and 2019 update focused on the consideration of clinically important factors when choosing glucose-lowering therapy. In people with established CVD or with a high risk for CVD, GLP-1 RA were prioritised over SGLT2i. Given their favourable drug class effect in reducing HHF and progression of CKD, SGLT2i were prioritised in people with HF, particularly those with a reduced ejection fraction, or CKD. Since 2019, additional cardiovascular, kidney and HF outcomes trials have been completed, particularly with SGLT2i. In addition, updated meta-analyses have been published that compare subgroup populations based on clinically relevant characteristics, such as presence of CVD, use of background therapy with metformin, stage of CKD, history of HF and age. Collectively, this new evidence was systematically retrieved and appraised to be incorporated into these clinical practice recommendations (Fig. 3).

New evidence from cardiorenal outcomes studies since the last consensus report

In the Evaluation of Ertugliflozin Efficacy and Safety CVOT (VERTIS CV), which recruited exclusively people with established CVD and type 2 diabetes, ertugliflozin was similar to placebo with respect to the primary MACE outcome and all key secondary outcomes (including a composite kidney outcome) except for HHF [146]. The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study included adults with type 2 diabetes with an eGFR from 30 to <90 ml/min per 1.73 m^2 and albuminuria (30–500 mg/mmol [300–5000 mg/g] creatinine) [152]. In CREDENCE, canagliflozin treatment significantly reduced the risk of a composite primary outcome of progression to renal replacement therapy, eGFR of <15 ml/min per 1.73 m^2, a doubling