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Special article

The year in cardiovascular medicine 2021: diabetes and metabolic disorders

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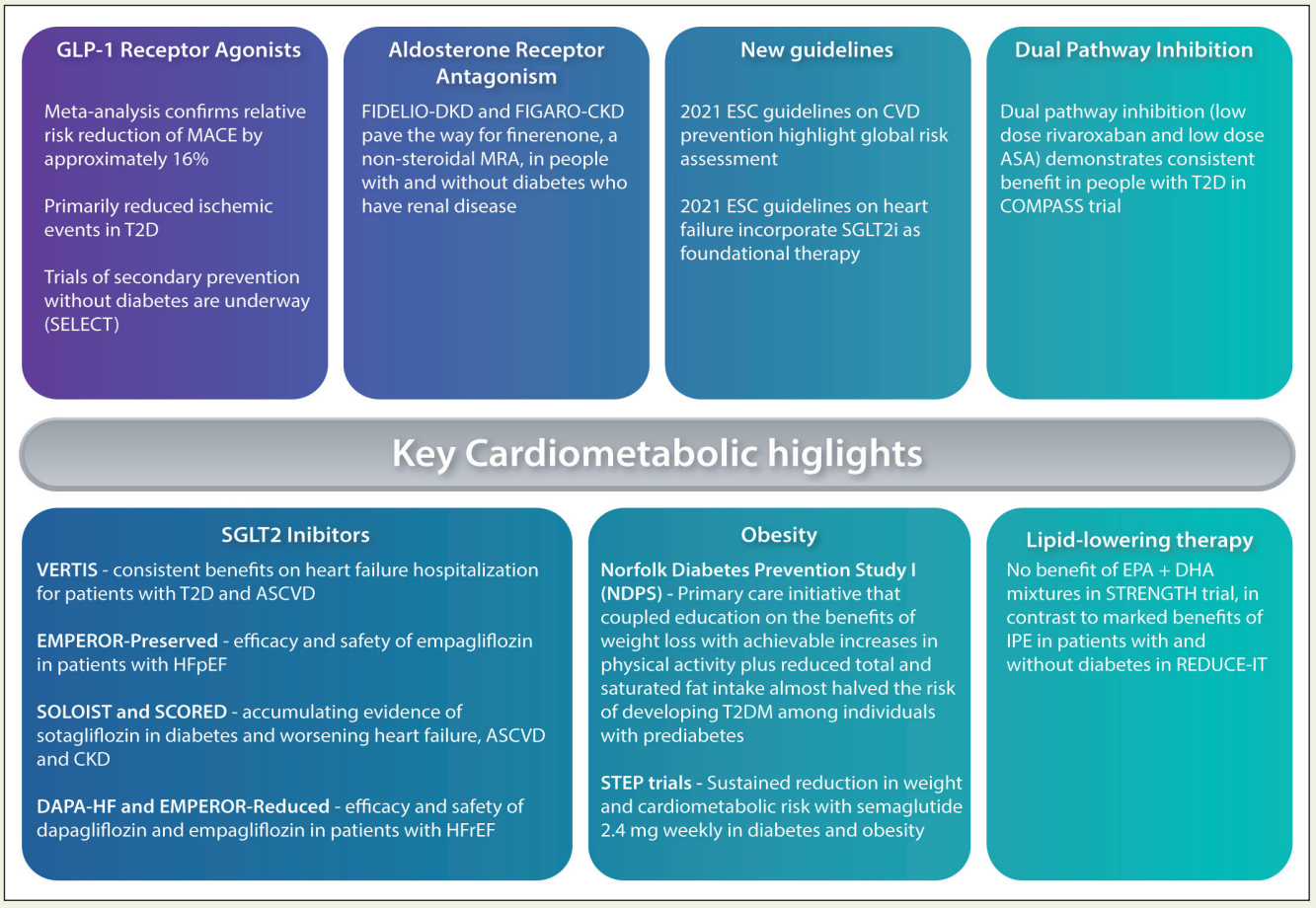

Graphical Abstract Key cardiometabolic highlights.

Abstract

In the current paper, we review recently published studies that are helping us to understand how the treatment landscape for glucagon-like peptide-1 receptor agonists and sodium glucose cotransporter 2 inhibitors is moving forward. We have also included relevant articles related to cardiovascular disease prevention in the setting of obesity, atherogenic dyslipidaemia and chronic kidney disease.

Keywords: Diabetes mellitus; Obesity; Heart failure; GLP-1 receptor agonists; SGLT2 inhibitors; Aldosterone receptor antagonism; Omega-3 fatty acid mixtures

Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) and sodium–glucose cotransporter 2 inhibitors (SGLT2i), introduced as glucose-lowering agents for type 2 diabetes (T2D) treatment during the last decade, continue their journey as ground-breaking cardiovascular (CV) protective agents. Given the results emerging from the most recent trials with GLP-1 RA and SGLT2i, we are undoubtedly witnessing a shift in trials' design and patient selection for these two drug classes, the trials with GLP-1 RA being ischaemia-centred and the ones with SGLT2i becoming more cardiorenal focused. In the current paper, we review recently published studies that are helping us to understand how the treatment landscape for GLP-1 RA and SGLT2i is moving forward. We have also included relevant articles related to cardiovascular disease (CVD) prevention in the setting of diabetes and metabolic disorders.

Obesity

Obesity is a chronic, relapsing disease, which represents a global public health challenge. The difficulty of adhering to lifestyle interventions makes hard the maintenan-

ce of long-term weight loss, with weight regain often following initial weight loss.

Bariatric surgery is invasive and eventually followed by weight regain. Important CV side effects have been observed among drugs approved for obesity treatment. The clutch that diabetes and obesity have on the world continues to grow and it is in this regard that the Norfolk Diabetes Prevention Study (NDPS)[1] and STEP 1 trial[1] have offered sparks of new hope to potential patients and healthcare systems.

The NDPS, with a mean follow-up of 24.7 months, demonstrated that a low-cost group-based primary care initiative that coupled education on the benefits of weight loss with achievable increases in physical activity plus reduced total and saturated fat intake almost halved the risk of developing T2D among individuals with pre-diabetes.[1] The improvements were sustained for at least 2 years, there was no weight regain, and for every 11 individuals who underwent the intervention, one was prevented from getting T2D. These extremely positive 'real world' results lend support to the global call for diabetes prevention programmes to promote long-term behavioural changes with the caveat that successful implementation will likely be defined by costs and appropriate cultural adaptions.

STEP 1, alongside its sibling STEP 2, 3, and 4 trials, was pivotal in positioning the glucagon-like peptide 1 receptor agonist (GLP-1RA) semaglutide as an approved medication for chronic weight management in adults with general obesity or who are overweight—a first in nearly two decades. While it needs to be acknowledged that ~15% of the cohort experienced <5% weight loss, it is noteworthy that over half lost at least 15% of their body weight and that weight only reached nadir around 60 weeks.[2] These are clinically meaningful data, and despite the relatively short duration and lack of a bariatric surgery arm, the efficacy data do suggest that in at least some cases of excess weight, we may now have a medical option that could rival bariatric surgery to manage obesity and its comorbidities.

The SELECT trial, which is currently recruiting ~17 500 subjects with BMI ≥ 27 kg/m^2 and established CVD without T2D to semaglutide (2.4 mg) vs. placebo (follow-up: 31–59 months; primary composite endpoint: CV death, non-fatal MI, non-fatal stroke), will expand our understanding of obesity management with GLP-1 RA.[3]

GLP-1 receptor agonists

GLP-1 RA have been shown to reduce major CV events in patients with T2D in various large cardiovascular outcomes trials (CVOTs). Many of these trials included patients with CVD or multiple risk factors and it remained unclear to what extent GLP-1 RA treatment leads to CV benefits in both risk groups. Marsico *et al.*[4] published a trial-level meta-analysis including seven large outcome trials with GLP-1 RA and could show that these agents significantly reduce major adverse cardiovascular events (MACE), CV and total mortality, stroke, and hospitalization for heart failure (HHF). There was a non-significant trend for the reduction of myocardial infarction (MI) in patients with T2D. Interestingly, three P-MACEs were reduced by 12% with the number needed to treat (NNT) to prevent one event of 73, while the NNT to prevent one death was 118. The NNT to prevent one admission due to heart failure was 300, suggesting that these agents—in contrast to SGLT2i—mainly exhibit their benefit by reducing arteriosclerosis-related events. Five of these trials enrolled patients with established CVD and CV risk factors only. No difference was observed for 3P-MACE between the two groups, also suggesting a benefit of GLP-1 RA in patients without established CVD. These data support the 2019 ESC guidelines for the treatment of patients with T2D and CVD as well as those with T2D and multiple risk factors recommending GLP-1 RA with proven CV benefit to reduce morbidity.

Another GLP-1RA that garnered attention in the CV community is the exendin-4-based efpeglenatide. Akin to its GLP-1 homologue cousins, efpeglenatide was shown in the AMPLITUDE-O trial to lower CV event risk in people with T2D.[5,6] Despite having the greatest prevalence of kidney disease among the GLP-1RA CVOT cohorts, AMPLITUDE-O showed efpeglenatide significantly reducing the incidence of the composite kidney outcome that comprised new macroalbuminuria, an increase in the urinary albumin-to-creatinine ratio of ≥30% from baseline, a sustained estimated glomerular filtration rate (eGFR) decline of ≥40%, renal replacement therapy, or a persistent eGFR of <15 mL/min/1.73 m^2. Importantly, the cardiorenal benefits of efpeglenatide occurred independent of baseline SGLT2 inhibitor use and eGFR thereby lending credence to the use of GLP-1RA–SGLT2 inhibitor combination therapy to leverage the different advantages that each of these classes confer.

SGLT2 inhibitors

The past year has been a momentous one for the class of SGLT2 inhibitors. The long-term effects of the SGLT2 inhibitor ertugliflozin on CV and kidney outcomes were assessed in VERTIS CV.[7] This CV safety trial found that patients with T2D with ASCVD randomly assigned to ertugliflozin 5 or 15 mg achieved the primary objective of non-inferiority to placebo in time to the first major adverse CV event, a composite endpoint of CV death, non-fatal myocardial infarction, or non-fatal stroke [hazard ratio (HR) 0.97 (95.6% CI, 0.85–1.11); $P < 0.001$ for non-inferiority]. The first secondary outcome in the hierarchical testing sequence was superiority for the time to the composite of CV death or HHF, which was not met [HR, 0.88 (95.8% CI, 0.75–1.03); $P = 0.11$ for superiority]; therefore, formal hypothesis testing ended with this endpoint. Since VERTIS CV enrolled a large proportion of participants with a history of HF and known pre-trial ejection fraction, results from pre-specified analyses of the effect of ertugliflozin vs. placebo on a series of HF-related outcomes were recently published.[8] Ertugliflozin treatment reduced the first and total HHF events. This suggests that the effect was not only on delaying the time to the first decompensation, but also thereafter. The effect of ertugliflozin on relative risk for first HHF event was similarly beneficial in those with and

without a history of HF, and in those with a history of HF, with reduced ejection fraction ≤45% or preserved ejection fraction >45%. The effect on risk for the first HHF was consistent across most baseline subgroups, but a greater benefit of ertugliflozin was observed in three populations: eGFR < 60 mL/min/1.73 m^2, albuminuria, and diuretic use.

Other studies also provide convincing evidence of HF benefit with SGLT2 inhibition. The SOLOIST trial studied the SGLT1/2 inhibitor sotagliflozin in patients with diabetes and acute decompensated heart failure.[9] The trial showed that in-hospital initiation of SGLT2i—once the patient was medically stabilized—was safe. This has obvious implications for better patient adherence to therapy. More importantly, there was a very large and significant reduction in total CV deaths, HHF, and urgent heart failure visits [HR 0.67, relative risk reduction (RRR) 33%, absolute risk reduction (ARR) 25 events per 100 patient-years, $P = 0.0009$]. This benefit was apparent very early and statistically significant by 28 days. The SOLOIST data provide strong support for the initiation of SGLT2i in patients with diabetes and heart failure prior to discharge, assuming there are no contraindications.

An additional analysis of SOLOIST examined the important patient-centred metric of days alive out of hospital (DAOH).[10] There was a significant improvement in DAOH, including a significant increase in days alive. There was also a significant difference in favour of sotagliflozin vs. placebo in the Kansas City Cardiomyopathy Questionnaire score, a measure of how patients feel.[8] Future trials will increasingly incorporate such patient-centred outcomes.

The SCORED trial examined sotagliflozin vs. placebo in patients with diabetes and chronic kidney disease.[10] This trial also found a significant reduction in total CV deaths, hospitalizations for heart failure, and urgent heart failure visits (HR 0.74, RRR 26%, ARR 1.9 events per 100 patient-years, $P = 0.0004$). This trial extended the benefits of SGLT2 inhibitors across the full range of proteinuria in patients with diabetes, including microalbuminuria. Of note, there was also a significant reduction in total CV deaths, myocardial infarctions, and strokes. Prior trials of SGLT2i had been inconsistent with respect to reductions in myocardial infarction, and none had previously shown a significant reduction in stroke. Whether the significant benefits in ischaemic endpoints in SCORED were due to the SGLT1 inhibition provided by that drug beyond the SGLT2 inhibition will require further basic science investigation.

Despite the prognostic importance of kidney disease for CV outcomes, patients with T2D are rarely risk-stratified by kidney parameters in cardiology practice, with these parameters being absent from commonly used CV risk prediction algorithms.

Results from pre-specified exploratory analyses from VERTIS CV highlight the potential value of stratifying kidney disease risk by both UACR and measures of kidney function in patients with T2D to predict CV risk and putative response to SGLT2i.[11] A recent meta-analysis of six outcomes trials in patients with T2D was performed to assess the CV and kidney outcomes across the class of SGLT2i overall and by the presence or absence of prevalent CV and chronic kidney disease.[12] The results suggest a reduced risk of MACEs and heterogeneity of CV death. The greatest magnitude of benefit was for a reduction in the risk for HHF and kidney disease progression, with estimates of HHF risk outcome the most consistent observation across the trials.

Based on the initial data from CVOTs with SGLT2i in patients with diabetes showing a reduction in HF-related endpoints, dedicated HF trials were conducted in patients with heart failure with reduced ejection fraction (HFrEF). Dapagliflozin and prevention of adverse outcomes in heart failure (DAPA-HF) as well as EMPEROR-Reduced trials unequivocally established the benefit of SGLT2i in HFrEF. An extremely insightful analysis of DAPA-HF separated the patients into those with and without diabetes.[13] The substantial benefits were consistent in each of these subgroups (HR for patients without diabetes 0.73, HR for patients with diabetes 0.75; *P*-value for interaction = 0.80). Furthermore, the safety was excellent in both subgroups. Another subgroup analysis of the EMPEROR-Reduced assessed to what extent the beneficial effects of empagliflozin on CV and renal endpoints differed between patients with or without diabetes.[14] This work showed that both CV and renal outcomes in patients with HFrEF were independent of baseline diabetes status and across the continuum of HbA1c. A priori, some doctors were very worried about giving SGLT2i to patients without diabetes, but in fact, the risks of hypoglycaemia and diabetic ketoacidosis were negligible.

A very interesting clinical study conducted by Brown *et al*.[15] examined whether dapagliflozin may regress left ventricular hypertrophy in patients with T2D. In this randomized study, treatment with dapagliflozin of 66 patients with T2D for 12 months compared with placebo significantly reduced left ventricular mass (LVM) as assessed by cardiac MRI. This reduction in LVM was accompanied by a reduction in systolic blood pressure, body weight, visceral and subcutaneous adipose tissue, insulin resistance, as well as hsCRP. Two recent reports have provided further insights on SGLT2 inhibition. In SUGAR-DM-HF,[16] empagliflozin treatment significantly reduced left ventricular volumes in individuals with heart failure with reduced ejection fraction and either T2D or pre-diabetes. These observations align with those from similar studies in different patient types that point to reverse cardiac remodelling[17,18] as the root for the SGLT2 inhibitor-mediated reductions in HHF observed in the EMPEROR-Reduced and DAPA-HF trials. The EMPERIAL trial evaluated the effect of empagliflozin on exercise ability and patient-reported outcomes in HFrEF and HF with preserved ejection fraction (HFpEF) in patients with and without T2D.[19] Three hundred and twelve HFrEF patients and 315 patients with HFpEF were randomized to empagliflozin 10 mg or placebo for 12 weeks and the primary endpoint was a 6 min walk test distance change at week 12. In this trial, the primary outcome in both patient populations was neutral. However, exploratory pre-specified analyses of KCCQ–TSS responder rates, congestion score, and diuretic use showed a benefit in SGLT2i-treated patients, generating the hypothesis that SGLT2i treat-

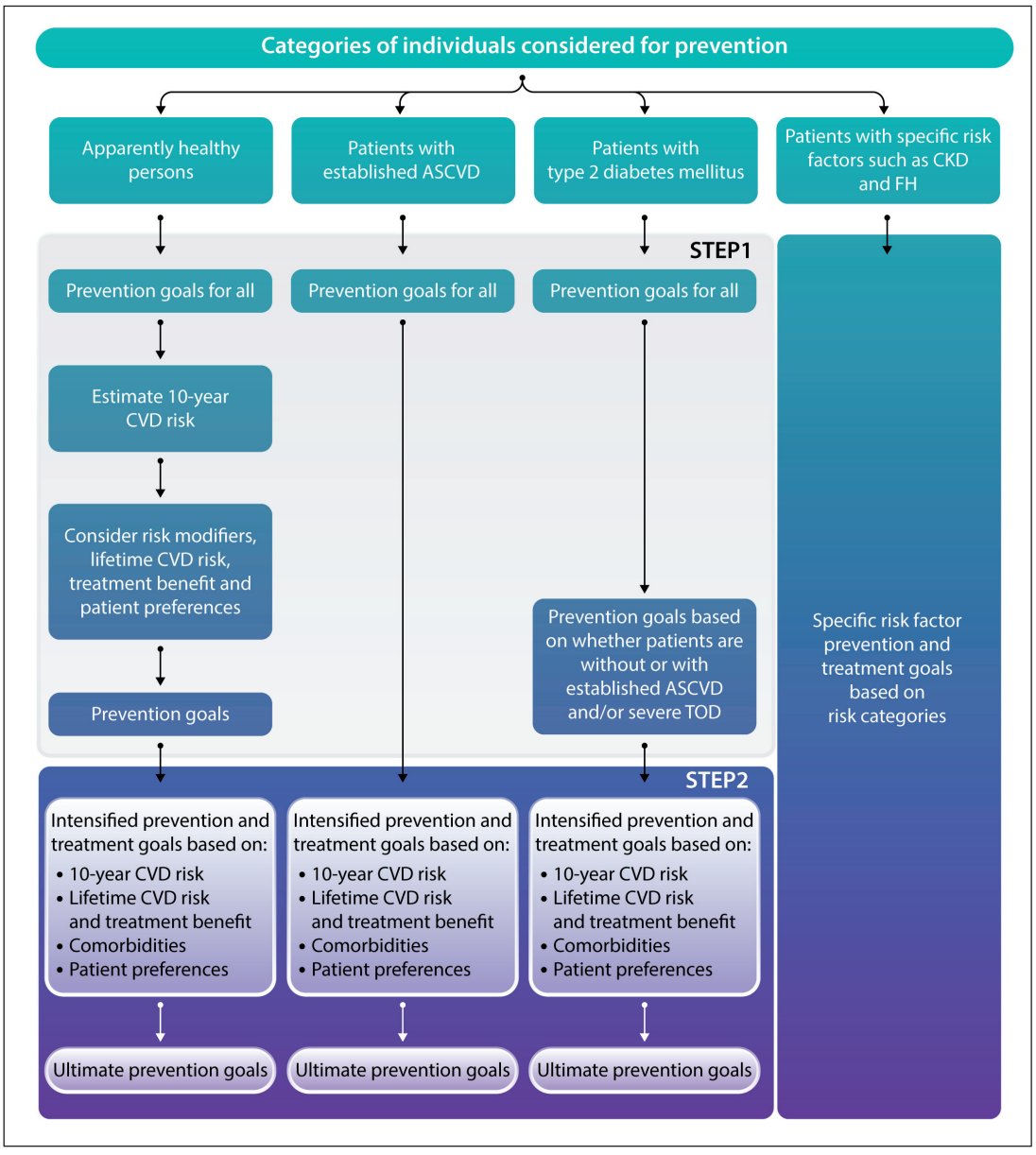

Figure 1 Stepwise approach to risk stratification and treatment options. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; FH, familial hypercholesterolaemia; TOD, target organ damage. Modified with permission from Visseren *et al.*,[27] by permission of OUP on behalf of ESC.

ment may have an effect on these factors. Interestingly, recent analyses from both DAPA-HF[20] and EMPEROR-Reduced[21] suggest an improvement in health status, assessed by KCCQ, in SGLT2i-treated patients.

The EMPEROR-PRESERVED trial examined HFpEF patients with and without diabetes, finding a significant reduction in CV death or HHF (HR 0.79, RRR 21%, ARR 3.3%, $P<0.001$).[22] The trial confirmed the findings from SOLOIST and SCORED, each of which had demonstrated significant benefits in the subgroups of patients who had HFpEF. EMPEROR-PRESERVED extended those findings by demonstrating benefit in patients without diabetes as well.

The near doubling of amputation risk with canagliflozin in the CANVAS trial was disquieting and concerns around SGLT2 inhibition and increased risk of amputations have persisted despite the absence of this signal in the CREDENCE trial with canagliflozin and outcome trials with dapagliflozin, empagliflozin, and ertugliflozin. It has been speculated that amputation risk was not elevated in the SGLT2 inhibitor trials that reported after CANVAS because investigators were instructed to pay more attention to lower limb care. Using real-world data from over 3 million patients with T2D in the USA, Paul *et al.*[23] provide reassuring data demonstrating that the risk of a lower limb amputation with SGLT2 inhibitors was no higher than that with other antihyperglycaemic agents. In fact, a history of peripheral artery disease was the most likely contributor for amputation underscoring the importance of optimally managing T2D in a timely fashion to avoid the development and progression of peripheral artery disease.

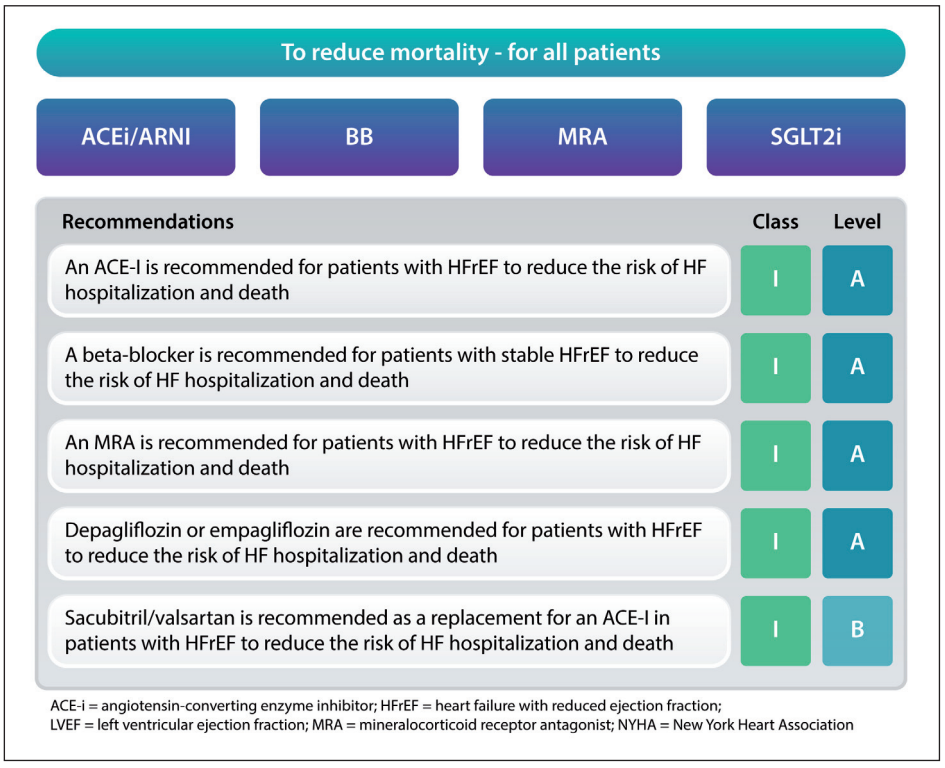

Figure 2 Pharmacological treatments indicated in patients with NYHA classes II–IV heart failure with reduced ejection fraction (left ventricular ejection fraction≤40%). Modified with permission from McDonagh *et al.*,[28] by permission of OUP on behalf of ESC.

Aldosterone receptor antagonism and cardiovascular events in patients with type 2 diabetes and kidney disease

The long-term effects on the kidney and CV outcomes of finerenone, a non-steroidal, selective mineralocorticoid receptor antagonist, were investigated in the multicentre FIDELIO-DKD trial in patients with T2D and stage 3 and 4 chronic kidney disease (CKD).[24] The FIGARO CKD trial evaluated the use of finerenone in a wider range of CKD patients with T2D.[25] Stage 2–4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated proteinuria patients assigned to the finerenone group had a lower risk of the primary composite outcome of death from CV causes, non-fatal MI, non-fatal stroke, or HHF (HR: 0.87; 95% confidence interval: 0.76–0.98; $P=0.03$) than those assigned to placebo. The protective effect of finerenone therapy on CV outcomes was mainly driven by a lower incidence of HHF. Although the frequency of serious adverse events did not differ between groups, the incidence of hyperkalaemia-related discontinuation was higher with finerenone than with placebo.

Lipid-lowering therapy

The role of high-dose omega-3 fatty acid mixtures on CV events continues to be refined. The STRENGTH randomized clinical trial assessed the effect of a mixture of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (omega-3 carboxylic acid, CA) on CV outcomes in patients with atherogenic dyslipidaemia and high CV risk.[26] A total of 13 078 patients were randomized to receive 4 g/day of omega-3 CA or corn oil in addition to usual background therapies, including statins. In this trial, treatment with omega-3 CA compared with corn oil did not result in a significant difference in the composite outcome of CV death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, and hospitalization for unstable angina. These data do not support the use of this mixed omega-3 fatty acid formulation to reduce CV morbidity and mortality in high-risk patients. The data are in contrast to trials of EPA-only containing prescription formulations (i.e. icosapent ethyl), which have all been positive to date.

ESC guidelines on cardiovascular disease prevention in clinical practice

The 2021 ESC guidelines on CVD prevention in clinical practice[27] represent an update of the previous 2016 guidelines and address the role of risk factor modification. These guidelines suggest a stepwise approach in risk stratification and treatment options with an approach for all subjects and then a step 2 approach with intensified prevention and treatment goals based on 10-year CV risk, lifetime CV risk, treatment benefit, comorbidities, as well as patient preferences (*Figure 1*). The target values for blood pressure lowering and lipid-lowering remain unchanged, but the guidelines underscore the need for personalized treatment decision based on individual risk estimation.

ESC guidelines for the diagnosis and treatment of acute and chronic heart failure

New concepts in the 2021 HF guidelines[28] include a change of the HFmrEF term to heart failure with mildly reduced ejection fraction and a simplified treatment algorithm for HFrEF according to phenotypes for tailored management. The SGLT2i dapagliflozin and empagliflozin are recommended (IA), in addition to optimal medical therapy, for patients with HFrEF regardless of diabetes status. Dapagliflozin and empagliflozin added to therapy with ACE-I/ARNI, beta-blockers, and MRAs reduce the risk of CV death and worsening HF in patients with HFrEF (*Figure 2*). These four key drug therapies should be initiated as quickly and safely as possible.

Dual pathway inhibition

The COMPASS trial established the benefit of dual pathway inhibition with vascular dose rivaroxaban (2.5 mg twice daily) and low-dose aspirin in patients with coronary artery disease or peripheral artery disease. An analysis of patients from COMPASS showed consistent benefits in those with and without diabetes.[29] However, the ARRs were numerically larger, given the higher baseline CV risk of the patients with diabetes. While the overall COMPASS trial did find lower mortality with dual pathway inhibition, the mortality reduction in those with diabetes was approximately three-fold greater than in those without diabetes (ARR of 1.9 vs. 0.6%). When examining a mega-composite of CV outcomes consisting of CV death, myocardial infarction, stroke, major adverse limb events, or major vascular amputation, there was a 27% RRR and a 2.7% ARR in the patients with diabetes with dual pathway inhibition compared with aspirin monotherapy. Importantly, the excess bleeding hazard seen in the overall trial was not amplified in those with diabetes. While major bleeding was significantly increased, there was no significant increase in fatal or intracranial bleeding in the overall trial or in the patients with diabetes, though the number of events was relatively low and if using this regimen, patients with elevated bleeding risk should be carefully screened out. Of note, the COMPASS trial excluded patients with an indication for dual antiplatelet therapy, such as recent acute coronary syndrome or stenting, and, therefore, these results do not apply to such patients.

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