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Guideline recommendations and the positioning of newer drugs in type 2 diabetes care

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Cardiovascular outcome trials in patients with type 2 diabetes at high cardiovascular risk have led to remarkable advances in our understanding of the effectiveness of GLP-1 receptor agonists and SGLT2 inhibitors to reduce cardiorenal events. In 2019, the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), and European Society of Cardiology (ESC) published updated recommendations for the management of such patients. We are concerned that ongoing discussions focusing on the differences between the endocrinologists' consensus report from the ADA and EASD and cardiologists' guidelines from the ESC are contributing to clinical inertia, thereby effectively denying evidence-based treatments advocated by both groups to patients with type 2 diabetes and cardiorenal disease. A subset of members from the writing groups of the ADA–EASD consensus report and the ESC guidelines was convened to emphasise where commonalities exist and to propose an integrated framework that encompasses the views incorporated in management approaches proposed by the ESC and the ADA and EASD. Coordinated action is required to ensure that people with type 2 diabetes, cardiovascular disease, heart failure, or chronic kidney disease are treated appropriately with an SGLT2 inhibitor or GLP-1 receptor agonist. In our opinion, this course should be initiated independent of background therapy, current glycaemic control, or individualised treatment goals.

Introduction

Type 2 diabetes is a complex metabolic disease characterised by the presence of hyperglycaemia that can lead to the development of microvascular and macrovascular complications. Overall, there is a two to three times increased risk of cardiovascular disease in people with type 2 diabetes, which is further magnified in the presence of chronic renal impairment.[1,2] In addition to atherosclerotic cardiovascular disease, patients with type 2 diabetes have an increased risk of heart failure, which is associated with further increases in morbidity and mortality.[3] Glycaemic control has been shown to effectively reduce the incidence and worsening of microvascular complications such as retinopathy—but has, at best, moderate effects on the development of macrovascular complications and heart failure,[4,5] which have remained resistant to therapeutic innovations.[6]

However, in the past decade, several large cardiovascular outcome trials have provided data on the efficacy of GLP-1 receptor agonists and SGLT2 inhibitors to reduce cardiorenal events in people with type 2 diabetes at high cardiovascular risk. In 2019, the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), and the European Society of Cardiology (ESC) published strong recommendations for the prescription of these drugs to this patient group.[7–9] The differences between the recommendations in the endocrinologists' consensus report from the ADA and EASD[7,8] and the cardiologists' guidelines from the ESC,[9] which largely centre on how high risk is defined and the role of metformin as first-line therapy, have been widely discussed and debated. Over the past 5 years, there has been a growth in clinical evidence for the beneficial cardiovascular effects of SGLT2 inhibitors and GLP-1 receptor agonists in people with type 2 diabetes and it is of major concern that the number of patients receiving these drugs remains low.[10,11]

We fear that these discussions about differences between specific recommendations, as well as regulatory issues and limitations with respect to health-care reimbursements, have led to clinical inertia to the detriment of patient care. A subset of the writing group members from the updated ADA–EASD consensus report[8] and the ESC guidelines[9] was convened to find common ground and to explore opportunities to integrate our efforts. Here, we propose an integrated framework that encompasses the views incorporated in the ESC guidelines and the ADA–EASD consensus report in their different approaches to the management of type 2 diabetes, and which we developed after roundtable discussions between members of the two writing groups. We propose a message of awakening, encouraging the medical community to apply to their clinical practice the evidence that originated from large studies and was taken up in the ESC guidelines and the ADA–EASD consensus report.

Evidence for SGLT2 inhibitors

The effect of SGLT2 inhibitors on cardiovascular endpoints has been examined in five placebo-controlled cardiovascular or cardiorenal outcome trials in patients with type 2 diabetes, providing consistent, strong evidence for the amelioration of both cardiovascular and renal complications. In the EMPA-REG OUTCOME trial, empagliflozin,[12] and in the CANVAS Program, canagliflozin,[13] significantly reduced three-point major adverse cardiovascular events (a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) in a population of patients with type 2 diabetes and increased cardiovascular risk (table 1). Additionally, in the CREDENCE trial, canagliflozin[14] significantly reduced three-point major adverse cardiovascular events in a population of patients with type 2 diabetes and chronic

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	EMPA-REG OUTCOME (empagliflozin)[12]	CANVAS Program (canagliflozin)[13]	CREDENCE (canagliflozin)[14]	DECLARE–TIMI 58 (dapagliflozin)[15]	VERTIS CV (ertugliflozin)[16]
Three-point MACE*	0·86 (0·74–0·99; p=0·04)	0·86 (0·75–0·97; p=0·02)	0·80 (0·67–0·95; p=0·01)	0·93 (0·84–1·03; p=0·17)	0·97 (0·85–1·11)
Hospital admission for heart failure	0·65 (0·50–0·85; p=0·002†)	0·67 (0·52–0·87)	0·61 (0·47–0·80; p<0·001)	0·73 (0·61–0·88)	0·70 (0·54–0·90)
Cardiovascular death	0·62 (0·49–0·77; p<0·001†)	0·87 (0·72–1·06)	0·78 (0·61–1·00; p=0·05)	0·98 (0·82–1·17)	0·92 (0·77–1·11)

Data are hazard ratio (95% CI; p value [if available]). MACE=major adverse cardiovascular events. *Three-point MACE consists of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. †Nominal p value.

Table 1: **Cardiovascular outcome trials with SGLT2 inhibitors in type 2 diabetes**

kidney disease.[14] The DECLARE–TIMI 58 trial, which assessed the cardiovascular effects of dapagliflozin versus placebo in 17 160 patients with type 2 diabetes, did not show a significant reduction of three-point major adverse cardiovascular events.[15] However, this finding was possibly due to the low cardiovascular risk profile of the study population, with 10 186 participants (60%) without prevalent cardiovascular disease, but with multiple risk factors. The VERTIS CV trial with ertugliflozin did not show a significant reduction in major adverse cardiovascular events, despite a study population consisting of patients with established atherosclerotic cardiovascular disease.[16]

Notably, in all of these trials, the SGLT2 inhibitors investigated showed a convincing significant reduction in the composite endpoint of hospital admission for heart failure or cardiovascular death. The beneficial effect of SGLT2 inhibitors on events related to heart failure has been supported by data from the DAPA-HF trial examining the effects of dapagliflozin[17] and from the EMPEROR-Reduced trial[18] investigating the effects of empagliflozin in patients with heart failure with reduced ejection fraction. In both of these studies, SGLT2 inhibition led to a significant reduction in the combined endpoint of heart failure worsening or cardiovascular death compared with placebo, even in individuals without type 2 diabetes.[17,18] Furthermore, despite use of different definitions of renal endpoints, all studies assessing SGLT2 inhibitors showed protection against progression of diabetic kidney disease. In cardiovascular outcome trials, these findings were secondary endpoints; however, the CREDENCE study showed a significant 30% reduction in the primary cardiorenal composite endpoint of end-stage kidney disease, doubling of serum creatinine concentration, death from kidney causes, or cardiovascular death in people with type 2 diabetes and chronic kidney disease.[14] Additionally, DAPA-CKD, a dedicated trial in patients with chronic kidney disease (with or without type 2 diabetes), showed a significant reduction in the primary composite endpoint of sustained decrease in estimated glomerular filtration rate (eGFR) of at least 50%, end-stage kidney disease, and renal or cardiovascular death, as well as reductions in cardiovascular death or hospital admission for heart failure and all-cause mortality, independent of diabetes status.[19]

Evidence for GLP-1 receptor agonists

GLP-1 receptor agonists are arguably among the most effective glucose-lowering medications and weight-loss drugs indicated for the treatment of type 2 diabetes. To date, in a series of seven cardiovascular outcome trials, four drugs in the class have shown significant reductions in the first occurrence of the three-point major adverse cardiovascular events composite outcome (liraglutide,[20] subcutaneous semaglutide,[21] albiglutide,[22] and dulaglutide;[23] table 2), two have shown non-significant reductions in three-point major adverse cardiovascular events (exenatide once weekly[24] and oral semaglutide[25]), and one was effectively neutral (lixisenatide[26]), without evidence of cardiovascular harms or benefits. Meta-analyses of the trial results (56 004 participants) show a 12% reduction in three-point major adverse cardiovascular events, a 12% reduction in cardiovascular death, an 11% reduction in all-cause mortality, a 9% reduction in fatal or non-fatal myocardial infarction, a 16% reduction in fatal or non-fatal stroke, a 9% reduction in hospital admission for heart failure, and a 17% reduction in a broad composite kidney outcome mainly driven by effects on albuminuria.[27,28]

The 2019 ADA–EASD and ESC recommendations

It is important to understand the context in which the ADA–EASD consensus report[7,8] and ESC guidelines[9] were written. The ADA–EASD consensus report is based on a structured review of published evidence of pharmacological and non-pharmacological interventions in type 2 diabetes over a defined time period (January, 2014–February, 2018). However, this review did not formally grade the evidence and is aimed at health-care providers in Europe and the USA. The ESC document is a guideline that weighed and graded evidence according to ESC criteria, leading to 138 recommendations in 14 areas of practice, and is targeted at practitioners in Europe (panel).

In 2018, the ADA–EASD consensus report on management of hyperglycaemia in type 2 diabetes recommended that, in the setting of type 2 diabetes, established cardiovascular disease was a compelling indication for treatment with a GLP-1 receptor agonist or an SGLT2 inhibitor.[7] In the 2019 update,[8] the ADA–EASD consensus

	LEADER (liraglutide)[20]	SUSTAIN 6 (subcutaneous semaglutide)[21]	Harmony Outcomes (albiglutide)[22]	REWIND (dulaglutide)[23]	EXSCEL (exenatide)[24]	PIONEER 6 (oral semaglutide)[25]	ELIXA (lixisenatide)[26]
Three-point MACE*	0·87 (0·78–0·97; p=0·01)	0·74 (0·58–0·95; p=0·02)	0·78 (0·68–0·90; p=0·0006)	0·88 (0·79–0·99; p=0·026)	0·91 (0·83–1·00; p=0·06)	0·79 (0·57–1·11; p=0·17)	1·02 (0·89–1·17; p=0·81)
Stroke	0·89‡ (0·72–1·11; p=0·3†)	0·61‡ (0·38–0·99; p=0·04†)	0·86 (0·66–1·14; p=0·3†)	0·76‡ (0·61–0·95; p=0·017†)	0·85 (0·70–1·03)	0·74‡ (0·35–1·57)	1·12 (0·72–1·58; p=0·54†)
Myocardial infarction	0·88§ (0·75–1·03; p=0·11†)	0·74§ (0·51–1·08; p=0·12†)	0·75 (0·61–0·90; p=0·003†)	0·96§ (0·79–1·16; p=0·65†)	0·97 (0·85–1·10)	1·18§ (0·73–1·90)	1·03 (0·87–1·22; p=0·71†)
Cardiovascular death	0·78 (0·66–0·93; p=0·007†)	0·98 (0·65–1·48; p=0·92†)	0·93 (0·73–1·19; p=0·21†)	0·91 (0·78–1·06; p=0·21†)	0·88 (0·76–1·02)	0·49 (0·27–0·92)	0·98 (0·78–1·22; p=0·85†)

Data are hazard ratio (95% CI; p value [if available]). MACE=major adverse cardiovascular events. *Three-point major adverse cardiovascular events consists of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. †Nominal p value. ‡Non-fatal stroke only. §Non-fatal myocardial infarction only.

Table 2: **Cardiovascular outcome trials with GLP-1 receptor agonists in type 2 diabetes**

suggested several further recommendations. First, in appropriate individuals with established type 2 diabetes and at high cardiovascular risk, the decision to treat with a GLP-1 receptor agonist or an SGLT2 inhibitor to reduce major adverse cardiovascular events, hypertensive heart failure, cardiovascular death, or progression of chronic kidney disease should be considered, independently of baseline HbA_{1c} or individualised HbA_{1c} target. Second, health-care providers should engage in shared decision making around initial combination therapy in patients with new-onset type 2 diabetes. Third, for patients with type 2 diabetes and established atherosclerotic cardiovascular disease (eg, previous myocardial infarction, ischaemic stroke, unstable angina with electrocardiogram changes, myocardial ischaemia on imaging or stress test, or revascularisation of coronary, carotid, or peripheral arteries), for whom major adverse cardiovascular events are the gravest threat, the level of evidence for benefit with respect to major adverse cardiovascular events is greater for GLP-1 receptor agonists than for SGLT2 inhibitors. Fourth, to reduce risk of major adverse cardiovascular events, GLP-1 receptor agonists can also be considered in patients with type 2 diabetes without established cardiovascular disease but with indicators of high cardiovascular risk (specifically, patients aged 55 years or older with >50% coronary, carotid, or lower-extremity artery stenosis; those with left ventricular hypertrophy; and those with an eGFR below 60 mL/min per 1·73 m² or with albuminuria). Fifth, for patients with or without established atherosclerotic cardiovascular disease, but with heart failure with reduced ejection fraction (<45%) or chronic kidney disease (eGFR 30 to ≤60 mL/min per 1·73 m² or urine albumin-to-creatinine ratio >30 mg/g, particularly >300 mg/g), the level of evidence for benefit with respect to major adverse cardiovascular events is greater for SGLT2 inhibitors than for GLP-1 receptor agonists. Sixth, SGLT2 inhibitors are recommended in patients with type 2 diabetes and heart failure, particularly those with reduced ejection fraction, to reduce heart failure, major adverse cardiovascular events, and cardiovascular death. Seventh, SGLT2 inhibitors are recommended to prevent the progression of chronic kidney disease, heart failure, major adverse cardiovascular events, and cardiovascular death in patients with type 2 diabetes with chronic kidney disease. Finally, patients with foot ulcers or at high risk of amputation should only be treated with SGLT2 inhibitors after careful shared decision making around risks and benefits, with comprehensive education on foot care and amputation prevention.

The 2019 ESC guidelines on type 2 diabetes, prediabetes, and cardiovascular disease[9] recommend that patients with diabetes should be classified according to three accepted levels of cardiovascular risk and treated accordingly, independent of baseline HbA_{1c}. Patients at very high risk include individuals with type 2 diabetes and established cardiovascular disease or with other target organ damage (proteinuria, renal impairment [defined as eGFR <30 mL/min per 1·73 m²], left ventricular hypertrophy, or retinopathy), those with three or more major risk factors, and those with early-onset type 1 diabetes of long duration (>20 years). Patients at high risk are defined as individuals with a diabetes duration of at least 10 years without target organ damage, but with any other additional risk factor. Patients at moderate risk are young patients (aged <35 years for type 1 diabetes; aged <50 years for type 2 diabetes) with a diabetes duration of up to 10 years, without other risk factors. The major risk factors consist of age 50 years or older, hypertension, dyslipidaemia, smoking, and obesity.

In patients at moderate risk, the ESC guidelines[9] recommend that metformin be should be considered as first-line therapy. Patients with atherosclerotic cardiovascular disease and individuals at high or very high risk should be treated with an SGLT2 inhibitor or a GLP-1 receptor agonist; if HbA_{1c} values are not meeting targets in these patients, metformin should be added. Glucose control should be further intensified with additional glucose-lowering drugs to reduce the risk of microvascular events.

Differences between the ADA–EASD and ESC recommendations

The original ADA–EASD consensus report[7] was published

***Panel:* Differences of emphasis between the ADA–EASD consensus recommendations and ESC guidelines[7-9]**

Type 2 diabetes with established atherosclerotic cardiovascular disease

- According to the ADA–EASD consensus report, for patients with type 2 diabetes and established atherosclerotic cardiovascular disease, in which major adverse cardiovascular events are the gravest threat, the level of evidence for benefit with respect to major adverse cardiovascular events is greater for GLP-1 receptor agonists than for SGLT2 inhibitors. However, SGLT2 inhibitors are a good alternative choice, independent of HbA_{1c}. In patients with heart failure with reduced ejection fraction or chronic kidney disease, SGLT2 inhibitors are preferred over GLP-1 receptor agonists.
- According to the ESC guidelines, patients with type 2 diabetes and atherosclerotic cardiovascular disease should be treated with an SGLT2 inhibitor or a GLP-1 receptor agonist, independent of HbA_{1c}.

Type 2 diabetes without established atherosclerotic cardiovascular disease

- According to the ADA–EASD consensus report, to reduce the risk of major adverse cardiovascular events, GLP-1 receptor agonists or, alternatively, SGLT2 inhibitors should be considered in patients with type 2 diabetes without established cardiovascular disease but with indicators of high risk. Specifically, patients at high risk are those aged 55 years or older with more than 50% coronary, carotid, or lower-extremity artery stenosis; those with left ventricular hypertrophy; and those with an eGFR below 60 mL/min per 1·73 m^2 or with albuminuria, independent of HbA_{1c}. In patients with heart failure with reduced ejection fraction or chronic kidney disease, SGLT2 inhibitors are preferred over GLP-1 receptor agonists.
- According to the ESC guidelines, patients with type 2 diabetes without atherosclerotic cardiovascular disease but with other target organ damage (proteinuria, renal impairment defined as eGFR <30 mL/min per 1·73 m^2, left ventricular hypertrophy, or retinopathy), three or more major risk factors (aged 50 years or older, hypertension, dyslipidaemia, smoking, and obesity), early onset type 1 diabetes of long duration (>20 years), or at high risk (diabetes duration ≥10 years without target organ damage, plus any other additional risk factor) should be treated with an SGLT2 inhibitor or a GLP-1 receptor agonist, independent of HbA_{1c}.

Metformin use

- According to the ADA–EASD consensus report, metformin should be baseline therapy in all patients with type 2 diabetes.
- According to the ESC guidelines, in patients with type 2 diabetes at moderate risk (young patients with type 1 diabetes [aged <35 years] or type 2 diabetes [aged <50 years] with diabetes duration <10 years, without other risk factors), metformin should be considered as first-line therapy. In patients at higher risk, an SGLT2 inhibitor or a GLP-1 receptor agonist should be used, with metformin added if HbA_{1c} targets are not met.

ADA=American Diabetes Association. EASD=European Association for the Study of Diabetes. ESC=European Society of Cardiology. eGFR=estimated glomerular filtration rate.

in December, 2018, before the full reporting of several of the larger cardiovascular and cardiorenal outcome trials, including REWIND (dulaglutide),[23] DECLARE–TIMI 58 (dapagliflozin),[15] and CREDENCE (canagliflozin).[14] These trials added evidence, particularly in patients with multiple cardiovascular risk factors, and provided primary outcome data for cardiovascular and renal outcomes and data for patients with HbA_{1c} below or at the target range. The ESC guidelines[9] were published in September, 2019, and were able to consider this additional evidence. The ADA–EASD consensus was subject to a brief update[8] in December, 2019, to reflect these additional data.

The definition and consideration of groups at risk differ between the two documents. The updated ADA–EASD consensus report[8] identifies specific groups at high risk on the basis of inclusion criteria used in the cardiovascular outcome trials, whereas the ESC guidelines[9] use their own definition of cardiovascular risk categories modified from the 2016 ESC guidelines on cardiovascular disease prevention[29] and include people with type 1 diabetes. The ESC definition of high cardiovascular risk is based on the duration of diabetes plus an additional risk factor (older age, hypertension, dyslipidaemia, smoking, or obesity) and therefore includes most people with type 2 diabetes.[30] However, it is difficult to judge how closely this group reflects those participants recruited to the cardiovascular outcome trials, such as DECLARE–TIMI 58 and REWIND.[30]

The positioning of the use of glucose-lowering therapies in cardiovascular protection also differs. The ADA–EASD consensus report gives preference to use of GLP-1 receptor agonists with regard to reduction in major adverse cardiovascular events in patients with established atherosclerotic cardiovascular disease and in patients with high-risk indicators; however, SGLT2 inhibitors are preferred in those with chronic kidney disease or heart failure. The ESC guidelines suggest the use of either GLP-1 receptor agonists or SGLT2 inhibitors in patients with atherosclerotic cardiovascular disease, or in those with high or very high cardiovascular risk, but does not differentiate between use of classes in specific subgroups.

The area of difference that has attracted the most attention is the positioning of metformin. In many of the cardiovascular outcome trials, patients were given metformin as baseline therapy; however, there is no evidence to suggest that the presence of metformin

might have influenced the results.[31] The ADA–EASD consensus[8] retains metformin as foundational treatment for type 2 diabetes, but explicitly questions whether or not this is a quirk of history rather than being truly evidence-based. Additionally, the consensus report highlights that GLP-1 receptor agonists, SGLT2 inhibitors, or both, should be added to the treatment regimen in patients at high risk of established atherosclerotic cardiovascular disease, chronic kidney disease, or heart failure, irrespective of HbA_{1c}. By contrast, the ESC guidelines remove the requirement to start with metformin as first-line therapy in drug-naive patients who have atherosclerotic cardiovascular disease or are at high or very high cardiovascular risk, preferring initial therapy with either a GLP-1 receptor agonist or an SGLT2 inhibitor.

Similarities between the ADA–EASD and ESC recommendations

The main common point between the two documents[8,9] is that both expert groups put the patient at the centre of the care pathway and derive their guidance on drug treatments from evidence provided by major clinical trials in people with type 2 diabetes, with the ADA–EASD consensus report[8] also taking into account real-world evidence. Both documents attempt to integrate care to manage the high levels of morbidity and mortality associated with type 2 diabetes and to emphasise the importance of a multifactorial approach, including not only glucose-lowering drugs but also blood pressure control, statins, and, in patients at very high cardiovascular risk, antiplatelet therapy. The importance of diet and lifestyle is emphasised in both documents and both expert groups recognise that choices of drugs in the treatment of people with diabetes need to be based on evidence that moves beyond HbA_{1c}. Both groups recognise the strong evidence for agents from GLP-1 receptor agonist and SGLT2 inhibitor classes and prioritise these drugs in their treatment algorithms. Both documents clearly state that the concept of individualised care is central to the management of diabetes and that therapeutic decisions depend on many factors, including comorbidities and other patient characteristics, as well as patients' own preferences and priorities.

Both documents recommend metformin as first-line therapy in newly diagnosed type 2 diabetes; however, the ADA–EASD consensus recommends this for all patients with newly diagnosed type 2 diabetes, whereas the ESC guidelines indicate that SGLT2 inhibitors or GLP-1 receptor agonists should be offered first in the presence of cardiovascular disease and in patients at high or very high cardiovascular risk. This difference is not as great as it sounds because the ADA–EASD consensus report insists that patients at high risk of cardiorenal disease should be treated with SGLT2 inhibitors or GLP-1 receptor agonists, independent of HbA_{1c}. Furthermore, most patients with type 2 diabetes rapidly progress to requiring combination therapy; therefore, in the context of the ESC treatment approach, the addition of metformin to initial SGLT2 inhibitor or GLP-1 receptor agonist therapy will often be required soon after diagnosis.

A call to action for clinicians

It is obvious from clinical trial findings and prescription data that there is an urgent need to provide clear messages to patients with diabetes and their health-care providers. Only a small proportion of patients with diabetes and cardiovascular disease are currently treated with GLP-1 receptor agonists or SGLT2 inhibitors[32] and, most astonishingly, prescription of these potentially life-saving medications by cardiologists is very low (1–5%).[11,33] Both the ADA–EASD consensus report and the ESC guidelines agree on several compelling indications for the use of GLP-1 receptor agonists and SGLT2 inhibitors, which should be urgently implemented in clinical practice by cardiologists, endocrinologists, nephrologists, primary care providers, pharmacists, and other licensed health-care professionals.[8,9] First, people with type 2 diabetes and prevalent cardiovascular disease or at high cardiovascular risk (eg, previous myocardial infarction, stroke, or revascularisation of any arterial bed; evidence of cardiac ischaemia on any stress imaging procedure; a >50% arterial stenosis of presumed atherosclerotic origin; or left ventricular hypertrophy) should be treated with a GLP-1 receptor agonist or an SGLT2 inhibitor. Second, patients with type 2 diabetes and heart failure, particularly those with reduced ejection fraction, should be treated with an SGLT2 inhibitor. Third, patients with type 2 diabetes and chronic kidney disease, particularly those with an eGFR of 25–75 mL/min per 1·73 m^2 or a urine albumin-to-creatinine ratio greater than 200 mg/g, should be treated with an SGLT2 inhibitor; if this therapy is not tolerated or not preferred, a GLP-1 receptor agonist should be considered. Finally, these treatment decisions should be made independent of background therapy, current glycaemic control, or individualised treatment goals. The SGLT2 inhibitor or GLP-1 receptor agonist prescribed should have shown outcome benefit in the relevant clinical trials.

Notably, treatment with GLP-1 receptor agonists and SGLT2 inhibitors does not mean that the patient's and their health-care provider's work is done. Focusing on lifestyle management, reaching appropriate glycaemic targets to minimise risk of microvascular disease and decrements in quality of life, and the full panoply of strategies to reduce cardiovascular risk were foundational therapies implemented in all of the trials that showed the benefits of GLP-1 receptor agonists and SGLT2 inhibitors. Additionally, an integrated approach to patient care is needed, involving clinicians with backgrounds in diabetes, cardiovascular disease, and chronic kidney disease, to individualise overall care and harmonise use of these drug classes.

Conclusions

It has been more than 50 years since the findings from the UGDP trial, the first attempt to improve cardiovascular outcomes in diabetes, were reported.[3,4] The conclusions from that trial were that macrovascular outcomes were unlikely to be improved solely by improving glycaemic control. Later studies, such as the UKPDS trial,[4] largely supported this view but suggested that good glycaemic control seems to generate metabolic memory and improved cardiovascular outcomes over 10–15 years. These findings contrast sharply with those reported in relation to the development of retinopathy, for which glycaemic control has been consistently shown to ameliorate risk. In summary, the glucocentric view of vascular complications works in relation to retinopathy, but is insufficient on its own with respect to the prevention and management of macrovascular disease in diabetes. The debate is over. It is time for action to ensure that patients with diabetes at high cardiorenal risk receive the benefits of GLP-1 receptor agonists and SGLT2 inhibitors through the collaboration of practitioners involved in their care.

Contributors

All authors contributed equally to the conception, preparation, drafting, and final approval of this Personal View.

Declaration of interests

NM, PJG, and FC were members of the writing group for the 2019 European Society of Cardiology guidelines. MJD, CM, and JBB were members of the writing group for the updated 2019 consensus report from the American Diabetes Association and European Association for the Study of Diabetes. NM has given lectures for Boehringer Ingelheim, Sanofi-Aventis, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, Lilly, and Novo Nordisk; has received unrestricted research grants from Boehringer Ingelheim; and has served as an advisor for Bayer, Boehringer Ingelheim, Sanofi-Aventis, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, and Novo Nordisk. NM has also served in trial leadership for Boehringer Ingelheim and Novo Nordisk. NM declines all personal compensation from pharmaceutical and device companies. MJD has served as a consultant, advisory board member, and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, and Janssen; an advisory board member for Servier and Gilead Sciences; and a speaker for the Napp Pharmaceuticals, Mitsubishi Tanabe Pharma Corporation, and Takeda Pharmaceuticals International. MJD has also received grants in support of investigator-initiated trials from Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim, AstraZeneca, and Janssen. PJG is diabetes advisor to Synexus and editor-in-chief of *Diabetes & Vascular Disease Research*. PJG also reports delivering presentations and serving on the advisory board for Boehringer Ingelheim, Bayer, AstraZeneca, Lilly, Merck, Janssen Pharmaceutica, and Novo Nordisk. CM serves or has served on advisory panels for Novo Nordisk, Sanofi, Merck Sharp & Dohme, Eli Lilly, Novartis, AstraZeneca, Boehringer Ingelheim, Hanmi Pharmaceuticals, Roche, Medtronic, ActoBio Therapeutics, Pfizer, and UCB, with financial compensation for these activities received by KU Leuven. KU Leuven has also received research support for CM from Medtronic, Novo Nordisk, Sanofi, Merck Sharp & Dohme, Eli Lilly, Roche, Abbott, ActoBio Therapeutics, and Novartis. CM also serves or has served on speakers' bureaux for Novo Nordisk, Sanofi, Merck Sharp & Dohme, Eli Lilly, Boehringer Ingelheim, AstraZeneca, and Novartis, with financial compensation for these activities received by KU Leuven. JRP reports personal fees via his employer (the University of Glasgow) for delivering presentations (for Merck KGaA, Novo Nordisk); serving on advisory boards (for Biocon, Novo Nordisk); and serving on ACI Clinical and IQVIA event adjudication committees for Boehringer Ingelheim. JRP has also received a research grant from Janssen to support an observational study and non-financial support (donation of study medication/ devices) from AstraZeneca, Dexcom, and Merck KGaA for investigator-initiated trials. FC reports delivering presentations and serving on the advisory board from Abbott, AstraZeneca, Bayer, Bristol-Myers Squibb, Merck Sharp & Dohme, Mundipharma, Novo Nordisk, and Pfizer. JBB's contracted consulting fees and travel support for contracted activities are paid to the University of North Carolina by Adocia, AstraZeneca, Dance Biopharm, Dexcom, Eli Lilly, Fractyl, GI Dynamics, Intarcia Therapeutics, Lexicon, MannKind, Metavention, NovaTarg, Novo Nordisk, Orexigen, PhaseBio, Sanofi, Senseonics, vTv Therapeutics, and Zafgen. JBB also reports grant support from AstraZeneca, Eli Lilly, Intarcia Therapeutics, Johnson & Johnson, Lexicon, Medtronic, NovaTarg, Novo Nordisk, Sanofi, Theracos, Tolerion, and vTv Therapeutics; is a consultant to Cirius Therapeutics, CSL Behring, Fortress Biotech, Mellitus Health, Neurimmune, Pendulum Therapeutics, Stability Health, and Zealand Pharma; and holds stock or stock options in Mellitus Health, Pendulum Therapeutics, PhaseBio, and Stability Health.

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References

1 Mulnier HE, Seaman HE, Raleigh VS, et al. Risk of myocardial infarction in men and women with type 2 diabetes in the UK: a cohort study using the General Practice Research Database. *Diabetologia* 2008; **51:** 1639–45.

2 Bell S, Fletcher EH, Brady I, et al. End-stage renal disease and survival in people with diabetes: a national database linkage study. *QJM* 2015; **108:** 127–34.

3 McAllister DA, Read SH, Kerssens J, et al. Incidence of hospitalization for heart failure and case-fatality among 3·25 million people with and without diabetes mellitus. *Circulation* 2018; **138:** 2774–86.

4 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352:** 837–53.

5 ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358:** 2560–72.

6 Udell JA, Cavender MA, Bhatt DL, Chatterjee S, Farkouh ME, Scirica BM. Glucose-lowering drugs or strategies and cardiovascular outcomes in patients with or at risk for type 2 diabetes: a meta-analysis of randomised controlled trials. *Lancet Diabetes Endocrinol* 2015; **3:** 356–66.

7 Davies MJ, D'Alessio DA, Fradkin J, et al. 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* 2018; **41:** 2669–701.

8 Buse JB, Wexler DJ, Tsapas A, et al. 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:** 487–93.

9 Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020; **41:** 255–323.

10 Dennis JM, Henley WE, McGovern AP, et al. Time trends in prescribing of type 2 diabetes drugs, glycaemic response and risk factors: a retrospective analysis of primary care data, 2010–2017. *Diabetes Obes Metab* 2019; **21:** 1576–84.

11 Dave CV, Schneeweiss S, Wexler DJ, Brill G, Patorno E. Trends in clinical characteristics and prescribing preferences for SGLT2 inhibitors and GLP-1 receptor agonists, 2013–2018. *Diabetes Care* 2020; **43:** 921–24.

12 Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; **373:** 2117–28.
13 Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; **377:** 644–57.
14 Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; **380:** 2295–306.
15 Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2018; **380:** 347–57.
16 Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med* 2020; **383:** 1425–35.
17 McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; **381:** 1995–2008.
18 Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020; **383:** 1413–24.
19 Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney kisease. *N Engl J Med* 2020; **383:** 1436–46.
20 Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016; **375:** 311–22.
21 Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016; **375:** 1834–44.
22 Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet* 2018; **392:** 1519–29.
23 Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019; **394:** 121–30.
24 Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2017; **377:** 1228–39.
25 Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2019; **381:** 841–51.
26 Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* 2015; **373:** 2247–57.
27 Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol* 2019; **7:** 776–85.
28 Marsico F, Paolillo S, Gargiulo P, et al. Effects of glucagon-like peptide-1 receptor agonists on major cardiovascular events in patients with type 2 diabetes mellitus with or without established cardiovascular disease: a meta-analysis of randomized controlled trials. *Eur Heart J* 2020; **41:** 3346–58.
29 Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016; **37:** 2315–81.
30 Caparrotta TM, Blackbourn LAK, McGurnaghan SJ, et al. Prescribing paradigm shift? Applying the 2019 European Society of Cardiology-led guidelines on diabetes, prediabetes, and cardiovascular disease to assess eligibility for sodium-glucose cotransporter 2 inhibitors or glucagon-like peptide 1 receptor agonists as first-line monotherapy (or add-on to metformin monotherapy) in type 2 diabetes in Scotland. *Diabetes Care* 2020; **43:** 2034–41.
31 Inzucchi SE, Fitchett D, Jurišić-Eržen D, et al. Are the cardiovascular and kidney benefits of empagliflozin influenced by baseline glucose-lowering therapy? *Diabetes Obes Metab* 2020; **22:** 631–39.
32 McCoy RG, Dykhoff HJ, Sangaralingham L, et al. Adoption of new glucose-lowering medications in the US—the case of SGLT2 inhibitors: nationwide cohort study. *Diabetes Technol Ther* 2019; **21:** 702–12.
33 Vaduganathan M, Patel RB, Singh A, et al. Prescription of glucagon-like peptide-1 receptor agonists by cardiologists. *J Am Coll Cardiol* 2019; **73:** 1596–98.
34 Goldner MG, Knatterud GL, Prout TE. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. III. Clinical implications of UGDP results. *JAMA* 1971; **218:** 1400–10.