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;43:487–493 | https://doi.org/10.2337/dci19-0066

The American Diabetes Association and the European Association for the Study of Diabetes have briefly updated their 2018 recommendations on management of hyperglycemia, based on important research findings from large cardiovascular outcomes trials published in 2019. Important changes include: 1) the decision to treat high-risk individuals with a glucagon-like peptide 1 (GLP-1) receptor agonist or sodium–glucose cotransporter 2 (SGLT2) inhibitor to reduce major adverse cardiovascular events (MACE), hospitalization for heart failure (hHF), cardiovascular death, or chronic kidney disease (CKD) progression should be considered independently of baseline HbA1c or individualized HbA1c target; 2) GLP-1 receptor agonists can also be considered in patients with type 2 diabetes without established cardiovascular disease (CVD) but with the presence of specific indicators of high risk; and 3) SGLT2 inhibitors are recommended in patients with type 2 diabetes and heart failure, particularly those with heart failure with reduced ejection fraction, to reduce hHF, MACE, and CVD death, as well as in patients with type 2 diabetes with CKD (estimated glomerular filtration rate 30 to ≤60 mL min⁻¹ [1.73 m⁻²] or urinary albumin-to-creatinine ratio >30 mg/g, particularly >300 mg/g) to prevent the progression of CKD, hHF, MACE, and cardiovascular death.

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) requested a brief update of the 2018 recommendations on management of hyperglycemia (1,2), based on the important research findings published in 2019, with a particular focus on new data from large cardiovascular outcomes trials (CVOTs). The authors began work on the brief update in July 2019 and submitted it for publication in Diabetes Care and Diabetologia in October 2019. Work was conducted over a series of phone calls and by electronic interactions. This brief update provides a summary of the implications of this new evidence on recommendations for the management of hyperglycemia in type 2 diabetes (see text box), which will be addressed more fully in the ADA Standards of Medical Care in Diabetes—2020 (https://professional.diabetes.org/SC). It should be considered in conjunction with the 2018 consensus report (1,2).

The Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial of the glucagon-like peptide 1 (GLP-1) receptor agonist dulaglutide
Changes to consensus recommendations

We previously recommended that, in the setting of type 2 diabetes, established CVD was a compelling indication for treatment with a GLP-1 receptor agonist or SGLT2 inhibitor. We now further suggest the following:

General consideration
- In appropriate high-risk individuals with established type 2 diabetes, the decision to treat with a GLP-1 receptor agonist or SGLT2 inhibitor to reduce MACE, hHF, CV death, or CKD progression should be considered independently of baseline HbA1c, or individualized HbA1c, target.
- Providers should engage in shared decision making around initial combination therapy in new-onset cases of type 2 diabetes.

GLP-1 receptor agonist recommendations
- For patients with type 2 diabetes and established atherosclerotic CV disease (such as those with prior myocardial infarction, ischemic stroke, unstable angina with ECG changes, myocardial ischemia on imaging or stress test, or revascularization of coronary, carotid, or peripheral arteries) where MACE is the greatest threat, the level of evidence for MACE benefit is greatest for GLP-1 receptor agonists.
- To reduce risk of MACE, GLP-1 receptor agonists can also be considered in patients with type 2 diabetes without established CVD with indicators of high risk, specifically, patients aged 55 years or older with coronary, carotid, or lower extremity artery stenosis >50%, left ventricular hypertrophy, eGFR <60 mL min⁻¹ [1.73 m]⁻², or albuminuria.

SGLT2 inhibitor recommendations
- For patients with or without established atherosclerotic CVD, but with HFrEF (EF <45%) or CKD (eGFR 30 to ≤60 mL min⁻¹ [1.73 m]⁻² or UACR >30 mg/g, particularly UACR >300 mg/g), the level of evidence for benefit is greatest for SGLT2 inhibitors.
- SGLT2 inhibitors are recommended in patients with type 2 diabetes and HF, particularly those with HFrEF, to reduce hHF, MACE, and CV death.
- SGLT2 inhibitors are recommended to prevent the progression of CKD, hHF, MACE, and CV death in patients with type 2 diabetes with CKD.
- Patients with foot ulcers or at high risk for 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.

Analysis of two SGLT2 inhibitor CVOTs, DECLARE–TIMI 58 (6) and the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program (7), suggests that the benefits of SGLT2 inhibitors for hHF, MACE, and CV death are greatest for those individuals with preexisting heart failure with reduced ejection fraction (HFrEF) compared with those without HFrEF. It is important to note that hHF was a secondary outcome, relatively low numbers of patients had HF at baseline, and data on ejection fraction (EF) were only available for a proportion of patients. In DECLARE–TIMI 58, individuals with HF but no reduction of EF as well as those without HF did not seem to benefit from dapagliflozin treatment to lower MACE and CV death outcomes. The benefit for hHF was strongest for those who at baseline had an EF <30%, strong for those with an EF <45%, and marginal for those with an EF ≥45% or those without HF. The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial of dapagliflozin was the first heart failure outcome trial of a diabetes medication (8). Recruitment included patients with and without type 2 diabetes with heart failure and an EF ≤40% and demonstrated benefits for reduction of the primary composite end point of CV death, hHF, and urgent HF visits, as well as for HF events and mortality (CV and total) considered separately. We now suggest that SGLT2 inhibitors are recommended in patients with type 2 diabetes and HF, particularly those with HFrEF, to reduce hHF, MACE, and CV death.
Figure 1—Glucose-lowering medication in type 2 diabetes: overall approach. RA, receptor agonist; SU, sulfonylureas; T2D, thiazolidinediones. Adapted from Davies et al. (1). © American Diabetes Association and European Association for the Study of Diabetes, 2018.
Choosing glucose-lowering medication in those with indicators of high-risk or established atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD) or heart failure (HF)

Use principles in Figure 1

To avoid clinical inertia, reassess and modify treatment regularly* (3–6 months)

Use metformin unless contraindicated or not tolerated
- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add an SGLT2i or GLP-1 RA with proven CVD benefit† (consider adding independently of individualized HbA1c target)
- If individualized HbA1c target achieved and already on dual therapy or multiple glucose-lowering therapies when adding SGLT2i or GLP-1 RA, consider stopping or reducing dose of other glucose-lowering therapy to reduce the risk of hypoglycemia

ASCVD predominates
- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years + LVH or coronary, carotid, lower extremity artery stenosis >50%)

PREFERABLY
GLP-1 RA with proven CVD benefit†

OR

SGLT2i with proven CVD benefit† if eGFR adequate²

If HbA1c above target
- Avoid TZD in the setting of HF
Choose agents demonstrating CV safety:
- For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit†
- DPP-4i if not on GLP-1 RA
- Basal insulin⁴
- SU⁷

HF or CKD predominates
- Particularly HFrEF (LVEF <45%)
- CKD: Specifically eGFR 30–60 mL min⁻¹(1.73m²)⁴ or UACR >30 mg/g, particularly UACR >300 mg/g

PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate¹

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate² add GLP-1 RA with proven CVD benefit†⁴

If HbA1c above target
- Avoid TZD in the setting of HF
Choose agents demonstrating CV safety:
- For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit†
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin⁴
- SU⁷

1. Proven CVD benefit means it has label indication of reducing CVD events.
2. Be aware that SGLT2i labeling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use.
3. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozin has primary heart failure outcome data from DAPA-HF.

Updates to the 2018 consensus report are indicated in magenta font

Figure 2—Choosing glucose-lowering medication in those with indicators of high-risk or established atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), or heart failure (HF). RA, receptor agonist; SU, sulfonylureas; TZD, thiazolidinediones. Adapted from Davies et al. (1). © American Diabetes Association and European Association for the Study of Diabetes, 2018.
The REWIND trial of the GLP-1 receptor agonist dulaglutide had no lower limit to HbA1c for eligibility and demonstrated equivalent efficacy for reduction of MACE above and below the median HbA1c of 55 mmol/mol (7.2%) (3). None of the CVOTs of SGLT2 inhibitors with primary MACE end points have recruited patients with an HbA1c <48 mmol/mol (<6.5%), and there is little data to inform clinical decision making for patients with an HbA1c <53 mmol/mol (<7%) (9). However, the outcome benefits observed in the CVOTs do not appear restricted to patients with an elevated HbA1c. That said, the DAPA-HF trial recruited patients with HFrEF with and without diabetes (8). The benefit for reduction of mortality and HF events with dapagliflozin was significant in both subgroups, suggesting that the effects of dapagliflozin on these end points is independent of HbA1c (8). We now recommend that in appropriate high-risk individuals with established type 2 diabetes, the decision to treat with a GLP-1 receptor agonist or SGLT2 inhibitor to reduce MACE, hHF, cardiovascular death, or CKD progression should be considered independently of baseline HbA1c, or individualized HbA1c target. That said, there are no specific analyses addressing HbA1c <48 mmol/mol (<6.5%). We continue to recommend that substituting a drug with known CVD, CKD, and hHF benefit for one without known benefit in high-risk patients is reasonable when patients are at individualized glycemic targets.

The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial of the SGLT2 inhibitor canagliflozin was the first renal outcome trial of a diabetes medication (10) with a primary composite end point of end-stage kidney disease (dialysis, transplantation, or a sustained eGFR of <15 mL min^-1 [1.73 m]^2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes. The trial recruited patients with type 2 diabetes and CKD on the maximally tolerated dose of ACE inhibitors or angiotensin receptor blockers with a urinary albumin-to-creatinine ratio (UACR) of 300–5,000 mg/g and an eGFR of 30 to 90 mL min^-1 [1.73 m]^2. This trial demonstrated a clear benefit of canagliflozin (100 mg) on multiple renal end points, including progression to end-stage kidney disease, and on cardiovascular mortality, MACE, and hHF. Furthermore, the CREDENCE results demonstrated that the benefits conferred by canagliflozin in terms of reducing MACE, hHF, cardiovascular mortality, and renal end points were similar regardless of baseline status for cardiovascular or CKD grade 2–3 (11). We now recommend that SGLT2 inhibitors should be used to prevent hHF, MACE, and CV death and the progression of CKD in patients with type 2 diabetes with CKD. The benefits are clear-cut for those with UACR >300 mg/g and eGFR 30–90 mL min^-1 [1.73 m]^2 and less well established for lesser grades of CKD based on secondary end point analyses of the CVOT.

A concern in the CANVAS Program was the increased risk of amputation with canagliflozin compared with placebo (7). In CREDENCE (10), although the risk of amputation was higher overall than in other SGLT2 inhibitor trials, no significant increase in risk was observed with canagliflozin 100 mg versus placebo (HR 1.11; 95% CI 0.79, 1.56). This may be due to the risk mitigation strategies employed: exclusion of patients with a history of a traumatic amputation within 12 months of screening, or an active foot ulcer, osteomyelitis, gangrene, or critical ischemia of the lower extremity within 6 months of screening; and interruption of therapy for emergence of any of the above with careful consideration of the individual risks and benefits prior to restarting canagliflozin after resolution of the event. We now recommend that patients with foot ulcers or at high risk for 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.

Based on the studies published thus far, we believe that for patients with type 2 diabetes and established atherosclerotic CVD (such as those with prior myocardial infarction, ischemic stroke, unstable angina with ECG changes, myocardial ischemia on imaging or stress test, or revascularization of coronary, carotid, or peripheral arteries) where MACE is the greatest threat, that the level of evidence for MACE benefit is greatest for GLP-1 receptor agonists. The Peptide Innovation for Early Diabetes Treatment 6 (PIONEER 6) cardiovascular safety trial of oral semaglutide, a GLP-1 receptor agonist, involved 3,183 patients with type 2 diabetes followed for only a median of 16 months, but it provided adequate demonstration of cardiovascular safety (HR 0.79; 95% CI 0.57, 1.11) and a strong signal for reduction of CV mortality rate (HR 0.49; 95% CI 0.27, 0.92) (12). This formulation of semaglutide has been approved for marketing in the U.S. and a decision in the European Union is expected soon.

For patients with or without established atherosclerotic CVD, but with HFrEF or CKD (eGFR 30 to ≤60 mL min^-1 [1.73 m]^2 or UACR >30 mg/g, particularly UACR >300 mg/g), the level of evidence for benefit is greatest for SGLT2 inhibitors. For patients with type 2 diabetes at low cardiovascular risk and without CKD, there have been no studies to examine the cardiovascular or renal benefit of GLP-1 receptor agonists or SGLT2 inhibitors.

Some meta-analyses (5,13,14) suggest the presence of heterogeneity in estimates for MACE and CV death with GLP-1 receptor agonists, although this is mostly due to the results of a single trial with lixisenatide. Likewise, there is some heterogeneity in the estimate for CV death with SGLT2 inhibitors. Whether differences in point estimates of benefits and harms are the result of differences in the effects of the medications, the design and conduct of the trials, or chance effects is uncertain. Attention to patient-specific factors and preferences, product labeling, meta-analyses, and the primary research reports should drive individualized clinical decision making with regard to prescribing particular medications within a class. For many patients, treatment with a GLP-1 receptor agonist or SGLT2 inhibitor in some health care settings involves considerable direct cost to them, and the impact of this on their overall well-being needs to be factored into decision making.

The Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA) trial randomized adults at high cardiovascular risk to receive the dipeptidyl peptidase 4 (DPP-4) inhibitor linagliptin or to receive the sulfonylurea glimepiride to evaluate a primary MACE end point. No between-group difference in the primary end point was demonstrated (HR 0.98; 95% CI 0.84, 1.14). At trial end, for linagliptin as compared with glimepiride, there was a 1.5-kg
weight loss benefit, no difference in HbA1c or introduction of glucose-lowering medications postbaseline, and substantial benefits in terms of reductions in hypoglycemia, though serious hypoglycemic events were rare with glimepiride (0.45/100 patient-years) (15). Paired with other DPP-4 inhibitor CVOTs, including Cardiovascular and Renal Microvascular Outcome Study with Linagliptin (CARmELINA) (16), which demonstrated the CV safety of linagliptin, this is a reassuring safety signal for glimepiride, an inexpensive and effective sulfonylurea. It is unclear whether these findings extend to other sulfonylureas.

Whereas we previously stated that there was limited evidence for initial combination therapy, the Vildagliptin Efficacy in Combination with Metformin for Early Treatment of Type 2 Diabetes (VERIFY) trial provides additional information. The initial combination of the DPP-4 inhibitor vildagliptin and metformin was shown to provide for a lower rate of secondary failure of glycemic control to HbA1c ≥53 mmol/mol (≥7%) versus metformin alone or the sequential addition of metformin and vildagliptin (17). We now suggest that providers should engage in shared decision making around initial combination therapy in new-onset cases of type 2 diabetes.

There are several major questions regarding the optimal application of new diabetes drugs. One obvious question arising from recent trial results is whether combined use of GLP-1 receptor agonists and SGLT2 inhibitors provides additional benefit for the prevention of MACE, CV death, hHF, and CKD progression. Three trials have demonstrated the HbA1c-lowering and weight-reduction efficacy of the combination (18–20), but none addresses the impact of the combination of the two on cardiorenal end points. A second question that arises from the recent secondary analyses of SGLT2 inhibitor studies is whether there are subsets of patients who benefit disproportionately, or very little, from treatment with the newer diabetes drugs. The emerging evidence that SGLT2 inhibitors may be particularly useful in preventing adverse outcomes in patients with diabetes with HFrEF raises the possibility of more targeted use of these agents. Finally, the mechanism(s) of action by which GLP-1 receptor agonists and SGLT2 inhibitors confer cardiorenal benefit in diabetes are not understood. Research in this area will be very useful in optimizing the now clear potential of drugs for diabetes to mitigate the cardiovascular and renal complications of the disease.

Modifications to the main figures of the prior publication are suggested as shown in Figs. 1 and 2.

Acknowledgments. The authors would like to thank William T. Cefalu (Director of the Division of Diabetes, Endocrinology, and Metabolic Diseases at the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health) for his review. The authors would like to acknowledge M. Saraco (Managing Director, Scientific & Medical Affairs) from ADA, as well as M. Hata (Executive Assistant) and P. Niemann (Executive Assistant) from EASD for their assistance. The authors would also like to acknowledge M. Bonar (Creative Director) and C. Franklin (Design Assistant) from the Leicester Diabetes Centre, Leicester, U.K., who provided considerable support in drafting and amending the figures. The authors also acknowledge the careful review and helpful suggestions of the members of the ADA Professional Practice Committee and the EASD Committee on Clinical Affairs.

Funding. This activity was funded by the American Diabetes Association and the European Association for the Study of Diabetes.

Duality of Interest. J.B.B. has provided consultation to Adocia, AstraZeneca, Eli Lilly, MannKind, NovoTarg, Novo Nordisk, Senseonics, and vTv Therapeutics with fees paid to the University of North Carolina. He has received grant support from Novo Nordisk, Sanofi, and vTv Therapeutics. He is a consultant to Cirius Therapeutics Inc., CSL Behring, and Neurimmune AG. He holds stock options in Mellitus Health, PhaseBio, Stability Health, and Pendulum Therapeutics. He is supported by a grant from the National Institutes of Health (UL1TR002489). D.I.W. reports receiving a Data Monitoring Committee for Novo Nordisk. A.T. reports nonfinancial support from EASD during the conduct of the study, grants and other from Boehringer Ingelheim, grants and other from Novo Nordisk, other from Novartis, grants and other from Sanofi, grants and other from AstraZeneca, grants from GlaxoSmithKline, and grants and other from the European Foundation for the Study of Diabetes (EFSDF) outside the submitted work. P.A. reports grants, nonfinancial support, and other from AstraZeneca, grants from GlaxoSmithKline, and grants and other from the European Foundation for the Study of Diabetes (EFSDF) outside the submitted work. N.A. reports grants and other from Boehringer Ingelheim, other from Merck Sharp & Dohme, and other from Eli Lilly during the conduct of the study. G.M. reports grants and personal fees from Novo Nordisk, personal fees from Johnson & Johnson, and personal fees from Fractyl Inc. during the conduct of the study. C.M. reports grants and fees from Novo Nordisk, grants and fees from Sanofi, grants and fees from Merck Sharp & Dohme, grants and fees from Eli Lilly and Company, grants and fees from Novartis, fees from AstraZeneca, grants and fees from Boehringer Ingelheim, fees from Roche Diagnostics, and grants and fees from Medtronic, and grants and fees from Actelion Therapeutics outside the submitted work, with all fees paid to her university. D.A.D.A. reports personal fees from Eli Lilly, Merck, Novo Nordisk, and Intarcia and grants from Merck and Lindag during the conduct of the study, personal fees from Lilly, Merck, Novo Nordisk, and Intarcia, and grants from Merck and Lindag outside the submitted work. M.J.D. reports personal fees and grants from Boehringer Ingelheim, Janssen, Novo Nordisk, and Sanofi and personal fees from Astra-Zeneca, Eli Lilly, Gilead Sciences Ltd., Intarcia/Server, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma Corporation, and Takeda Pharmaceuticals International Inc. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. All authors were responsible for drafting the article and revising it critically for important intellectual content. All authors approved the version as published.

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