2025 ADA: Use of Glucose-lowering medications in the management of T2D *(Figure 9.3; S190)*

Health lifestyle behaviors; Diabetes Self-Management Education and Support (DSMES); Social Determinants of Health (SDOH)

To avoid therapeutic inertia, reassess and modify treatment regularly (3-6 months)

Goal: Cardiovascular and Kidney Risk Reduction in High-Risk Individuals with Type 2 Diabetes*

+ASCVD†

+Indicators of high CVD risk

+ASCVD/indicators of high CVD Risk≈

GLP-1 RA# with proven CVD benefit **OR** SGLT2i‡ with proven CVD benefit

If A1C is above goal

- For individuals on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- Pioglitazone^

+HF
Current or prior symptoms of HF with documented HFrEF or HFpEF

SGLT2i‡ with proven HF benefit in this population

+CKD
eGFR <60 mL/min/1.73 m2 OR albuminuria (ACR ≥3.0 mg/mmol [30mg/g]). Repeat measurement is required to confirm CKD

+CKD (on maximally tolerated dose of ACEi or ARB)

SGLT2i‡ with primary evidence of reducing CKD progression
- SGLT2i can be started with eGFR ≥20 mL/min/1.73 m^2
- Continue until initiation of dialysis or transplantation
- Glucose-lowering efficacy is reduced with eGFR <45 mL/min/1.73 m^2

OR

GLP-1 RA# with proven CKD benefit

If A1C is above goal, for individuals on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiovascular and kidney risk reduction, management of other metabolic comorbidities, and/or glycemic lowering is needed

+Mitigating risk of MASLD or MASH

Agents with potential benefit in MASLD or MASH
GLP-1RA, dual GIP and GLP-1 RA, pioglitazone, or combination of GLP-1RA with pioglitazone
Use insulin in the setting of decompensated cirrhosis

Goal: Achievement and Maintenance of Weight and Glycemic Goals

+Weight management

Efficacy for weight loss

Very high: Semaglutide, tirzepatide

High: Dulaglutide, liraglutide

Intermediate: GLP-1 RA (not listed above), SGLT2i

Neutral: Metformin, DPP-4i

+Achievement and maintenance of glycemic goals

Metformin or other agent (including combination therapy) that provides adequate EFFICACY to achieve and maintain glycemic treatment goals

Prioritize avoidance of hypoglycemia in high-risk individuals

Efficacy for glucose lowering

Very high: Dulaglutide (high dose), semaglutide, tirzepatide, insulin
Combination oral, combination injectable (GLP-1 RA and insulin)

High: GLP-1 RA (not listed above), metformin, pioglitazone, SGLT2i, sulfonylurea

Intermediate: DPP-4i

If A1C is above goal or significant hypoglycemia or hyperglycemia or barriers to care are identified

- Refer to DSMES to support self-efficacy in achievement of treatment goals
- Consider technology (e.g., diagnostic or personal CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of treatment goals

* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be made irrespective of background use of metformin or A1C.
† ASCVD: Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, and arterial revascularization procedure) and variably included conditions such as transient ischemic attack, unstable angina, amputation and symptomatic or asymptomatic coronary artery disease. Indicators of high risk: While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria).
≈ A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high-risk CVD. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details.
For GLP-1 RAs, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and kidney end points in individuals with T2D with established or high risk of CVD. One kidney outcome trial demonstrated benefit in reducing persistent eGFR reduction and CV death for a GLP-1 RA in individuals with CKD and T2D.
‡ For SGLT2is, CV and kidney outcomes trials demonstrate their efficacy in reducing the risks of composite MACE, CV death, all-cause mortality, MI, HHF, and kidney outcomes in individuals with T2D and established or high risk of CVD.
^ Low-dose pioglitazone may be better tolerated and similarly effective as higher doses
ACEi, angiotensin converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; DSMES, diabetes self-management education and support; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatoticliver disease; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T2D, type 2 diabetes.
Diabetes Care 2025;48(Suppl. 1):S181–S206 | doi: https://doi.org/10.2337/dc25-S009; Adapted from Davies et al Diabetes Care 2022;45:2753–2786

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