2021 American Diabetes Association Glucose Lowering Medications in Type 2 Diabetes Diabetes Care 2021 Jan;44 (Supplement 1): S111-124 (Used with permission from Diabetes Care, August 2021)

FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity) TO AVOID THERAPEUTIC NO **INERTIA REASSESS** AND MODIFY INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HFT TREATMENT CONSIDER INDEPENDENTLY OF BASELINE A1C, **INDIVIDUALIZED A1C TARGET, OR METFORMIN USE\*** IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW +ASCVD/Indicators +HF +CKD of High Risk **COMPELLING NEED TO** COMPELLING NEED TO MINIMIZE **COST IS A MAJOR**  Established ASCVD Particularly HFrEF Indicators of high MINIMIZE WEIGHT GAIN OR ISSUE11,12 **HYPOGLYCEMIA** (LVEF <45%) ASCVD risk (age ≥55 DKD and NO PROMOTE WEIGHT LOSS years with coronary, Albuminuria<sup>8</sup> carotid, or lower-extremity DPP-4i GLP-1 RA SGLT2i TZD EITHER/ artery stenosis >50%, SU<sup>4</sup> TZD12 or LVH) SGLT2i with proven GLP-1 RA with benefit in this HA1C H A1C If A1C If A1C good efficacy population5.6.7 SGLT2i for weight ETTHER/ **PREFERABLY** target loss10 If A1C above target GLP-1 SGLT2i SGLT2i with primary evidence RA with GLP-1 RA SGLT2i of reducing CKD proven proven SGLT2i SGLT2i If A1C above target OR CVD CVD progression DPP-4i DPP-4i OR benefit1 benefit1 OR OR TZD12 SU<sup>4</sup> OR OR TZD TZD SGLT2i with TZD GLP-1 RA GLP-1 RA with evidence of If A1C above target good efficacy reducing CKD SGLT2 for weight progression in If A1C above target If further intensification CVOTs5,8,8 If A1C above target is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose GLP-1 RA with Continue with addition of other agents as outlined above If A1C above target agents demonstrating proven CVD CV benefit and/or safety: benefit1 if SGLT2i Insulin therapy basal insulin not tolerated or If A1C above target with lowest acquisition cost · For patients on a contraindicated If quadruple therapy required. GLP-1 RA, consider or SGLT2i and/or GLP-1 RA not adding SGLT2i with tolerated or contraindicated, use Consider other therapies proven CVD benefit For patients with T2D regimen with lowest risk of Consider the addition of SU4 OR basal insulin: based on cost and vice versa and CKDs (e.g., eGFR weight gain Choose later generation SU with TZD² <60 mL/mln/1.73 m²) and PREFERABLY lower risk of hypoglycemia thus at increased risk of DPP-4i if not on cardiovascular events Consider basal insulin with lower risk of hypoglycemia<sup>6</sup> GLP-1 RA DPP-4i (if not on GLP-1 RA) based on weight neutrality Basal insulin<sup>3</sup> · SU4 7. Proven benefit means it has label indication of ETHER/ reducing heart failure in this population 1. Proven CVD benefit means it has label indication of reducing CVD events If DPP-4i not tolerated or 8. Refer to Section 11: Microvascular Complications and Foot Care 2. Low dose may be better tolerated though less well studied for CVD effects GLP-1 SGLT2i contraindicated or patient already 9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin RA with 3. Degludec or U-100 glargine have demonstrated CVD safety with on GLP-1 RA, cautious addition of: 10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide proven proven Choose later generation SU to lower risk of hypoglycemia; SU<sup>4</sup> • TZD<sup>2</sup> • Basal insulin 11. If no specific comorbidities (i.e., no established CVD, low risk of CVD CVD glimepiride has shown similar CV safety to DPP-4i hypoglycemia, and lower priority to avoid weight gain benefit1,7 benefit1 5. Be aware that SGLT2i labelling varies by region and individual agent or no weight-related comorbidities) with regard to indicated level of eGFR for initiation and continued use 12. Consider country- and region-specific cost of drugs. In some

countries TZDs are relatively more expensive and DPP-4i are

relatively cheaper.

6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction

in HF and to reduce CKD progression in CVOTs. Canagliflozin and

dapagliflozin have primary renal outcome data. Dapagliflozin and empaglificzin have primary heart fallure outcome data.

<sup>†</sup> Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

## **GLP-1** Receptor Agonists

Product	Dosing	FDA Indications
Exenatide (Byetta®)	5-10mg twice daily	Adjunct in T2DM
Exenatide ER (Bydureon®)	2mg once weekly	Adjunct in T2DM
Dulaglutide (Trulicity®)	0.75-4.5mg once weekly	Adjunct in T2DM, risk reduction of CV events with DM & CVD or multiple risk factors
Liraglutide (Victoza®)	0.6 x 1 week, 1.2-1.8mg daily	Adjunct in T2DM, risk reduction of CV events with DM & CVD
Lixisenatide (Adlyxin®)	10mg x 2 week, 20mg daily	Adjunct in T2DM
Semaglutide (Ozempic®)	0.25 once weekly x 1 month, 0.5-1mg weekly	Adjunct in T2DM, risk reduction of CV events with DM & CVD
Semaglutide (Rybelsus®)	3mg daily x 1 month, 7- 14mg daily (ORAL)	Adjunct in T2DM
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## Adverse Effects:

- Nausea, vomiting, diarrhea-minimize fatty/greasy foods, plan smaller meals
- black box warning against use in patients with family history of medullary thyroid cancer or multiple endocrine neoplasia-2

## **SGLT-2 Inhibitors**

Product	Dosing	eGFR Dose Adjustment	FDA Indications
Canagliflozin (Invokana®)	100mg daily 300mg daily	eGFR 45-60 ml/min: 100mg/d eGFR <45 ml/min + >300 mg/d urine albumin: 100mg/d eGFR <45 ml/min + <300 mg/d urine albumin: do not use	<ul> <li>Adjunct in T2DM</li> <li>Risk reduction of major cardiovascular events in T2DM and established CV disease</li> <li>Risk reduction of ESRD, doubling of SCr, CV death, and hospitalization for HF in T2DM &amp; diabetic nephropathy</li> </ul>
Dapagliflozin (Farxiga®)	5mg daily 10mg daily	Discontinue if eGFR <45 ml/min	<ul> <li>Adjunct in T2DM</li> <li>Risk reduction of HF         hospitalization with T2DM and CV         disease or multiple risk factors</li> <li>Reduce risk of CV death and         hospitalization for HF in HFrEF</li> </ul>
Empagliflozin (Jardiance®)	10mg daily 25mg daily	Discontinue if eGFR <30 ml/min	<ul> <li>Adjunct in T2DM</li> <li>Risk reduction of CV mortality with DM &amp; established CV disease</li> </ul>
Ertugliflozin (Steglatro®)	5mg daily 15mg daily	Discontinue if eGFR <60 ml/min	Adjunct in T2DM
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## Adverse Effects:

Genital mycotic infections, urinary tract infections, hypotension, volume depletion Encourage appropriate hygiene and hydration)