

FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)



INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF*

CONSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE*

+ASCVD Indicators of High Risk

- Established ASCVD
- Indicators of high ASCVD risk (age ≥ 65 years with coronary, cerebral, or lower extremity artery disease $>50\%$, or LVD)

GLP-1 RA with proven CVD benefit¹ **OR** SGLT2 with proven CVD benefit²

If A1C above target

If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2, choose agents demonstrating CV benefit and/or safety:

- For patients on a GLP-1 RA, consider adding SGLT2 with proven CVD benefit and vice versa³
- TZD⁴
- DPP-4 if not on GLP-1 RA
- Basal insulin⁵
- SU⁶

+HF

Particularly HF⁷ (LVEF $<45\%$)

SGLT2 with proven benefit in this population^{8,9}

+CKD

DKD and Albuminur¹⁰

PREFERABLY

SGLT2 with primary evidence of reducing CKD progression

OR

SGLT2 with evidence of reducing CKD progression in CVT¹¹

OR

GLP-1 RA with proven CKD benefit¹² if SGLT2 not tolerated or contraindicated

For patients with T2D and CKD (e.g., eGFR <60 mL/min^{1.73} m²) and those at increased risk of cardiovascular events

GLP-1 RA with proven CVD benefit¹ **OR** SGLT2 with proven CVD benefit²

NO

IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4	GLP-1 RA	SGLT2	TZD
If A1C above target	If A1C above target	If A1C above target	If A1C above target
SGLT2 OR TZD	SGLT2 OR TZD	GLP-1 RA OR DPP-4 OR TZD	SGLT2 OR DPP-4 OR GLP-1 RA

If A1C above target

Continue with addition of other agents as outlined above

If A1C above target

Consider the addition of SU⁶ OR basal insulin:

- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia¹³

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

GLP-1 RA with good efficacy for weight loss¹⁴ **OR** SGLT2

If A1C above target

If A1C above target

If A1C above target

If quadruple therapy required, or SGLT2 and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain

PREFERABLY

DPP-4 (if not on GLP-1 RA) based on weight neutrality

If DPP-4 not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

- SU⁶ + TZD⁴ + Basal insulin

COST IS A MAJOR ISSUE¹⁵

SU⁶ **OR** TZD⁴

If A1C above target

TZD⁴ **OR** SU⁶

If A1C above target

Health therapy based insulin with lowest acquisition cost

OR

Consider other therapies based on cost

1. Proven CVD benefit means it has label indication of reducing CVD events

2. Low dose may be better tolerated though less well studied for CVD effects

3. Dapagliflozin or Glibenclamide have demonstrated CVD safety

4. Choose later generation SU to lower risk of hypoglycemia; glibenclamide has shown similar CV safety to DPP-4

5. Be aware that SGLT2 labeling varies by region and individual agent with regard to individual level of eGFR for initiation and continued use

6. Dapagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVT¹¹. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have others have heart failure outcome data.

7. Refer to Section 11: Microvascular Complications and Foot Care

8. Dapagliflozin / glimepiride (D-900 + glimepiride) (D-100) / dulcinate + DPP-4 insulin

9. Semagliflozin + empagliflozin + dapagliflozin + canagliflozin + tolazamide

10. For specific considerations (e.g., in established CKD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidity)

11. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4 are relatively cheaper

12. Activated whenever these become new clinical considerations regardless of background glucose lowering medications.

13. Most patients enrolled in the relevant trials were on metformin or baseline or glucose lowering therapy.

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**Ada Van Stone Harris, Charles Benajah
Gilbert**

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