

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



**FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
IF HbA_{1c} ABOVE TARGET PROCEED AS BELOW**

ESTABLISHED ASCVD OR CKD

NO

WITHOUT ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

HF OR CKD PREDOMINATES

COMPPELLING NEED TO MINIMIZE HYPOLYCAEMIA

COMPPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

COST IS A MAJOR ISSUE¹⁰

GLP-1 RA with proven CVR benefit¹

GLP-1 RA with proven CVR benefit¹, if eGFR adequate²

If HbA_{1c} above target

If further intensification is required or patient is new stable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVR benefit
- SPP-4i if not on GLP-1 RA
- Basal insulin³
- GLP-1
- GLP-1

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVRs if eGFR adequate²

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate² add GLP-1 RA with proven CVR benefit¹

If HbA_{1c} above target

- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety
- Consider adding the other class with proven CVR benefit¹
- SPP-4i (not recommended in the setting of HF if not on GLP-1 RA)
- Basal insulin³
- GLP-1

SPP-4i

GLP-1 RA

SGLT2i

TZD

If HbA_{1c} above target

If HbA_{1c} above target

If HbA_{1c} above target

If HbA_{1c} above target

SGLT2i OR TZD

SGLT2i OR TZD

GLP-1 RA OR SPP-4i OR TZD

SGLT2i OR SPP-4i OR GLP-1 RA

If HbA_{1c} above target

Continue with addition of other agents as outlined above

If HbA_{1c} above target

- Consider the addition of SPP-4i OR basal insulin:
- Choose later generation SGLT2i with lower risk of hypoglycaemia
 - Consider basal insulin with lower risk of hypoglycaemia³

GLP-1 RA with good efficacy for weight loss⁴

SGLT2i

If HbA_{1c} above target

SGLT2i

GLP-1 RA with good efficacy for weight loss⁴

If HbA_{1c} above target

If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain

PREFERABLY

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

If SPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, continue addition of:

- GLP-1
- GLP-1
- Basal insulin

GLP-1

TZD

If HbA_{1c} above target

TZD

GLP-1

If HbA_{1c} above target

- Insulin therapy (total insulin with lowest acquisition cost)
- OR
- Consider SPP-4i OR SGLT2i with lowest acquisition cost¹⁰

1. Proven CVR benefit means it has label indication of reducing CVR events for GLP-1 RA (strongest evidence for semaglutide + empagliflozin + canagliflozin) whereas the SGLT2i evidence extends stronger for empagliflozin + canagliflozin.

2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use.

3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CVR progression in CVRs.

4. Semaglutide + liraglutide have demonstrated CVR safety.

5. Low dose may be better tolerated through less well studied for CVR effects.

6. Choose later generation SGLT2i with lower risk of hypoglycaemia.

7. Semaglutide + liraglutide (CVR) + liraglutide (CVR) + liraglutide + SPP-4i insulin.

8. Semaglutide + liraglutide + canagliflozin + canagliflozin + liraglutide.

9. If no specific contraindications (i.e. no established CVR, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight related contraindications).

10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and SPP-4i relatively cheaper.

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L Cohen

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