

The ADA Decision Pathway

First-Line Therapy if Metformin and Comprehensive Lifestyle (Including Weight Management and Physical Activity); If HbA1c Above Target Proceed as Below

Established ASCVD or CKD

No

Without established ASCVD or CKD

ASCVD Predominates

Either
/or

GLP-1 RA with proven CVD benefit¹
SGLT2i with proven CVD benefit¹, if eGFR adequate²

If HbA1c above target

If further intensification is required or patient is now unable 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 CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin⁴
- Thiazolidinedione (TZD)⁵
- Sulfonylurea (SU)⁶

HF or CKD Predominates

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate³

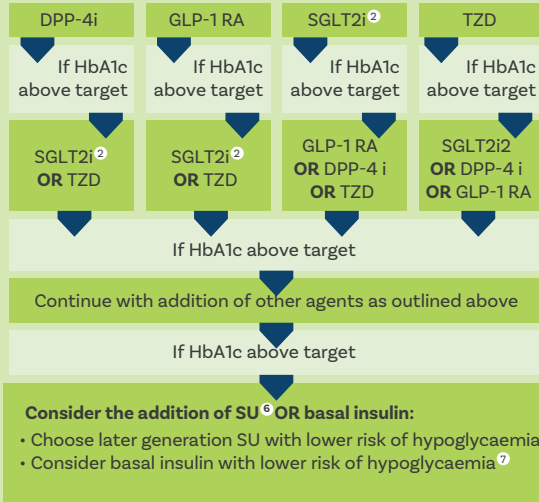
OR

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

If HbA1c above target

- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
- Consider adding the other class with proven CVD benefit¹
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin⁴
- SU⁶

Compelling Need to Minimize Hypoglycaemia



Compelling Need to Minimize Weight Gain or Promote Weight Loss

Either
/or

GLP-1 RA with good efficacy for weight loss⁸ SGLT2i²

If HbA1c above target

SGLT2i² GLP-1 RA with good efficacy for weight loss⁸

If HbA1c 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

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

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

- SU⁶
- TZD⁵
- Basal insulin

Cost is a Major Issue⁹⁻¹⁰

Either
/or

SU⁶ TZD¹⁰

If HbA1c above target

TZD¹⁰ SU⁶

If HbA1c above target

Insulin therapy basal insulin with lowest acquisition cost

OR

Consider DPP-4i OR SGLT2i with lowest acquisition cost

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence of liraglutide > semaglutide > exenatide. For SGLT2i evidence modestly stronger of empagliflozin > canagliflozin

3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs

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

4. Degludec or U100 glargine have demonstrated CVD safety

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

6. Choose later generation SU with lower risk of hypoglycaemia

7. Degludec/glargine U300 < glargine U100/detemir < neutral protamine hagedorn (NPH) insulin

8. Semaglutide > Liraglutide > dulaglutide > exenatide > lixisenatide

9. If no specific comorbidities (ie no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)

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