**GOALS OF CARE**
- Prevent complications
- Optimise quality of life

**REVIEW AND AGREE ON MANAGEMENT PLAN**
- Review management plan
- Mutual agreement on changes
- Ensure agreed modification of therapy is implemented in a timely fashion to avoid clinical inertia
- Decision cycle undertaken regularly (at least once/twice a year)

**ONGOING MONITORING AND SUPPORT INCLUDING:**
- Emotional well-being
- Check tolerability of medication
- Monitor glycaemic status
- Biofeedback including SMBG, weight, step count, HbA1c, BP, lipids

**ASSESS KEY PATIENT CHARACTERISTICS**
- Current lifestyle
- Comorbidities i.e. ASCVD, CKD, HF
- Clinical characteristics i.e. age, HbA1c, weight
- Issues such as motivation and depression
- Cultural and socio-economic context

**CONSIDER SPECIFIC FACTORS WHICH IMPACT CHOICE OF TREATMENT**
- Individualised HbA1c target
- Impact on weight and hypoglycaemia
- Side effect profile of medication
- Complexity of regimen i.e. frequency, mode of administration
- Choose regimen to optimise adherence and persistence
- Access, cost and availability of medication

**IMPLEMENT MANAGEMENT PLAN**
- Patients not meeting goals generally should be seen at least every 3 months as long as progress is being made; more frequent contact initially is often desirable for DSMES

**AGREE ON MANAGEMENT PLAN**
- Specify SMART goals:
  - Specific
  - Measurable
  - Achievable
  - Realistic
  - Time limited

**SHARED DECISION-MAKING TO CREATE A MANAGEMENT PLAN**
- Involves an educated and informed patient (and their family/caregiver)
- Seeks patient preferences
- Effective consultation includes motivational interviewing, goal setting and shared decision-making
- Empowers the patient
- Ensures access to DSMES

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ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

**GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH**

### FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)

**IF HbA1c ABOVE TARGET PROCEED AS BELOW**

- **ESTABLISHED ASCVD OR CKD**
  - **ASCVD PREDOMINATES**
    - GLP-1 RA with proven CVD benefit
    - SGLT2i with proven CVD benefit
  - HF OR CKD PREDOMINATES
    - **PREFERABLY**
      - SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate
      - OR
        - DPP-4i
      - If SGLT2i not tolerated or contraindicated or if eGFR less than adequate, add GLP-1 RA with proven CVD benefit
  - **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 insulin

- **WITHOUT ESTABLISHED ASCVD OR CKD**
  - **COMPPELLING NEED TO MINIMISE HYPOGLYCAEMIA**
    - GLP-1 RA with good efficacy for weight loss
    - SGLT2i
    - TZD
  - **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
      - DPP-4i (if not on GLP-1 RA) based on weight neutrality
  - **COMPPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS**
    - **PREFERABLY**
      - SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate
      - OR
        - If SGLT2i not tolerated or contraindicated or if eGFR less than adequate, add GLP-1 RA with proven CVD benefit
  - **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 insulin
  - **IF HbA1c above target**
    - Consider the addition of SU or basal insulin:
      - Choose later generation SU with lower risk of hypoglycaemia
      - Consider basal insulin with lower risk of hypoglycaemia

### COST IS A MAJOR ISSUE

- GLP-1 RA with good efficacy for weight loss
- SGLT2i
- TZD
- SU

### ESTABLISHED ASCVD OR CKD

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liiraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly 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 CKD progression in CVOTs.
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 < NPH insulin.
8. SGLT2i with proven CVD benefit
9. If no specific comorbidities (i.e. 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.

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Use metformin unless contraindicated or not tolerated

If not at HbA1c target:
- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add SGLT2i or GLP-1 RA with proven cardiovascular benefit

If at HbA1c target:
- If already on dual therapy, or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents
- OR reconsider/lower individualised target and introduce SGLT2i or GLP-1 RA
- OR reassess HbA1c at 3 month intervals and add SGLT2i with proven cardiovascular benefit

Avoid TZD in the setting of HF

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

If HbA1c above target
- If further intensification is required or patient is 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 cardiovascular benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin

If HbA1c above target
- PREFERABLY SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate
- OR If SGLT2i not tolerated or contraindicated or if eGFR less than adequate add GLP-1 RA with proven cardiovascular benefit

If ASCVD predominates
- GLP-1 RA with proven cardiovascular benefit
- SGLT2i with proven cardiovascular benefit, if eGFR adequate

If CKD predominates
- GLP-1 RA with proven cardiovascular benefit

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD) WITH ESTABLISHED ATHROSCLEROTIC CARDIOVASCULAR CHOOSEING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHROSCLEROTIC CARDIOVASCULAR
CHOOSING GLUCOSE-LOWERING MEDICATION

IF COMPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

In those WITHOUT established ASCVD OR CKD
First-line therapy is metformin
If HbA1c is ≥ 17 mmol/mol (1.5%) above individualised HbA1c target consider early combination therapy

General lifestyle advice
• Medical nutritional therapy
• Eating patterns
• Physical activity
• Medication adherence
• Restraint for weight loss
• Non-social energy restriction

Choose outcomes for maximalising weight loss

- Use principles in Figure 1
- In those WITHOUT established ASCVD OR CKD
- Gain OR Promote weight loss

If HbA1c above target

SGLT2i if eGFR adequate
GLP-1 RA with good efficacy for weight loss

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:
• SU
• TZD
• Basal insulin
- already on DPP-4i. A cautious addition of DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA

Implement strategies for maximising weight loss

If HbA1c above target

GLP-1 RA with good efficacy for weight loss
SGLT2i if eGFR adequate

Use principles in Figure 1

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First-line therapy is metformin

If HbA1c is ≥ 17 mmol/mol (1.5%) above individualised HbA1c target consider early combination therapy

If HbA1c above target
- GLP-1 RA
- DPP-4i
- SGLT2i
- TZD

SGLT2i or TZD

Continue with addition of other agents as outlined above

Consider the addition of sulfonylurea or basal insulin:
- Choose later generation SU with lower risk of hypoglycaemia
- Consider basal insulin with lower risk of hypoglycaemia

If HbA1c ≥ target
- Continue with addition of other agents as outlined above

Consider the addition of sulfonylurea or basal insulin

CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA

In those WITHOUT established ASCVD OR CKD

HbA1c ≥ target consider early combination therapy

If HbA1c ≥ 7 mmol/mol (53%) above individualised target and/or if age 75+ years consider reducing to target 6.5% or lower

If HbA1c ≥ 17 mmol/mol (1.5%) above individualised target consider basal insulin with lower risk of hypoglycaemia

Identify patient groups at highest risk of hypoglycaemia and set individualised HbA1c targets

To minimise hypoglycaemia use principles in Figure 1

ASCVD OR CKD

In those WITHOUT established ASCVD OR CKD
CHOOSING GLUCOSE-LOWERING MEDICATION IF COST IS A MAJOR ISSUE

1. Choose later-generation SU to minimise risk of hypoglycaemia
2. Consider country- and region-specific cost of drugs. In some countries, TZD relatively more expensive and DPP-4 relatively cheaper
3. Consider DPP-4 or SGLT2i with lowest acquisition cost
4. If HbA1c above target
   • Basal insulin with lowest acquisition cost
   • Consider DPP-4 or SGLT2i with lowest acquisition cost
5. First-line therapy is metformin
6. If HbA1c ≥ 17 mmol/mol (1.5%) above individualised HbA1c
   - Consider early combination therapy

TO AVOID CLINICAL INERTIA
REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Consider additional DSMES to support weight loss/maintenance and avoidance of hypoglycaemia

ACSD OR RCD
In those without established ASCVD OR CKD
Consider insulin as first injectable if:

- HbA1c very high > 97 mmol/mol (11%)
- Symptoms or evidence of catabolism: weight loss, polyuria, polydipsia which suggest insulin deficiency
- If type 1 diabetes is a possibility

Consider initial injectable combination (i.e. GLP-1 RA + basal insulin or prandial/basal insulin) if HbA1c > 86 mmol/mol (10%) and/or > 23 mmol/mol (2%) above target.

If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred:

Proceed to FULL basal-bolus regimen i.e. basal insulin and prandial insulin with each meal.

Consider:

- INITIATION
- TITRATION

For patient on GLP-1 RA and basal insulin:

Consider FRC of GLP-1 RA and insulin (iDegLira or iGlarLixi), but note max dose of insulin in the FRCs.

If above HbA1c target:

- Stepwise additional injections of prandial insulin (i.e. two, then three additional injections)

Consider:

- INITIATION
- TITRATION

Add basal insulin.

Consider:

- INITIATION
- TITRATION

Consider GLP-1 RA in most prior to insulin.

Consider:

- INITIATION
- TITRATION

Add prandial insulin. Usually one dose with the largest meal or meal with greatest PPG excursion.

Consider:

- INITIATION
- TITRATION

Use principles in Figure 1.

If HbA1c above target despite dual/triple therapy:

INTENSIFYING TO INJECTABLE THERAPIES

INITIATION OF STEPWISE PRANDIAL

- Stepwise addition of prandial insulin every 3 months if HbA1c > target is associated with lower risk of hypoglycaemia and increases patient satisfaction compared with immediate introduction of full basal-bolus regimen.

1. Consider choice of GLP-1 RA considering: patient preference, HbA1c lowering, weight-lowering effect or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit.

FPG = Fasting Plasma Glucose
FRC = Fixed Ratio Combination
PPG = Post Prandial Glucose

† IF HbA1c DOES NOT IMPROVE REVIEW ONGOING NEED FOR BASAL-BOLUS REGIMEN. CONSIDER ADDITIONAL DSMES.

INITIATION FOR BASAL

- Start 10 IU a day OR 0.1–0.2 IU/kg a day

INITIATION FOR GLP-1 RA

- Initiate starting dose (varies across class)

TITRATION FOR BASAL

- Patient self titration is more effective
- Set FPG target that correlates to HbA1c target
- Choose evidence-based titration algorithm, e.g. increase 2 units every 3 days to reach FPG target without hypoglycaemia
- For hypoglycaemia determine cause, if no clear reason lower dose by 10–20%

TITRATION FOR GLP-1 RA

- Gradual titration to maintenance dose (varies across class)

TITRATION FOR PRANDIAL

- Increase dose by 1–2 IU or 10–15% twice weekly
- For hypoglycaemia determine cause, if no clear reason lower corresponding dose by 10–20%

TITRATION FOR PRANDIAL

INITIATION FOR PRANDIAL

- In insulin-naive patients 10–12 IU or 0.3 IU/kg
- If on existing insulin regimen usually unit to unit at the same total insulin dose but may require adjustment to individual needs

TITRATION

- Individual dose adjustment depends on type of biphasic insulin
- More complex if on three times daily regimen

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
CONSIDERING ORAL THERAPY IN COMBINATION WITH INJECTABLE THERAPIES

- **METFORMIN**
- **TZD1**
- **DPP-4i**
- **SULfonylurea**
- **SGLT2i**

**Continue treatment with metformin**

**Stop TZD when commencing insulin OR reduce dose by 50% when on SU.**

**Stop DPP-4i if GLP-1 RA initiated.**

**If on SGLT2i, continue treatment.**

**Consider stopping SU if prandial insulin initiated or on a premix regimen.**

**Beware**
- DKA (euglycaemic)
- Do not down-titrate insulin aggressively
- Instruct on sick-day rules
- Establish a premix regimen

1. Contraindicated in some countries. Consider lower dose. This combination has a high risk of fluid retention and weight gain.

**Combination with Injectable Therapies**

Combining oral therapy in