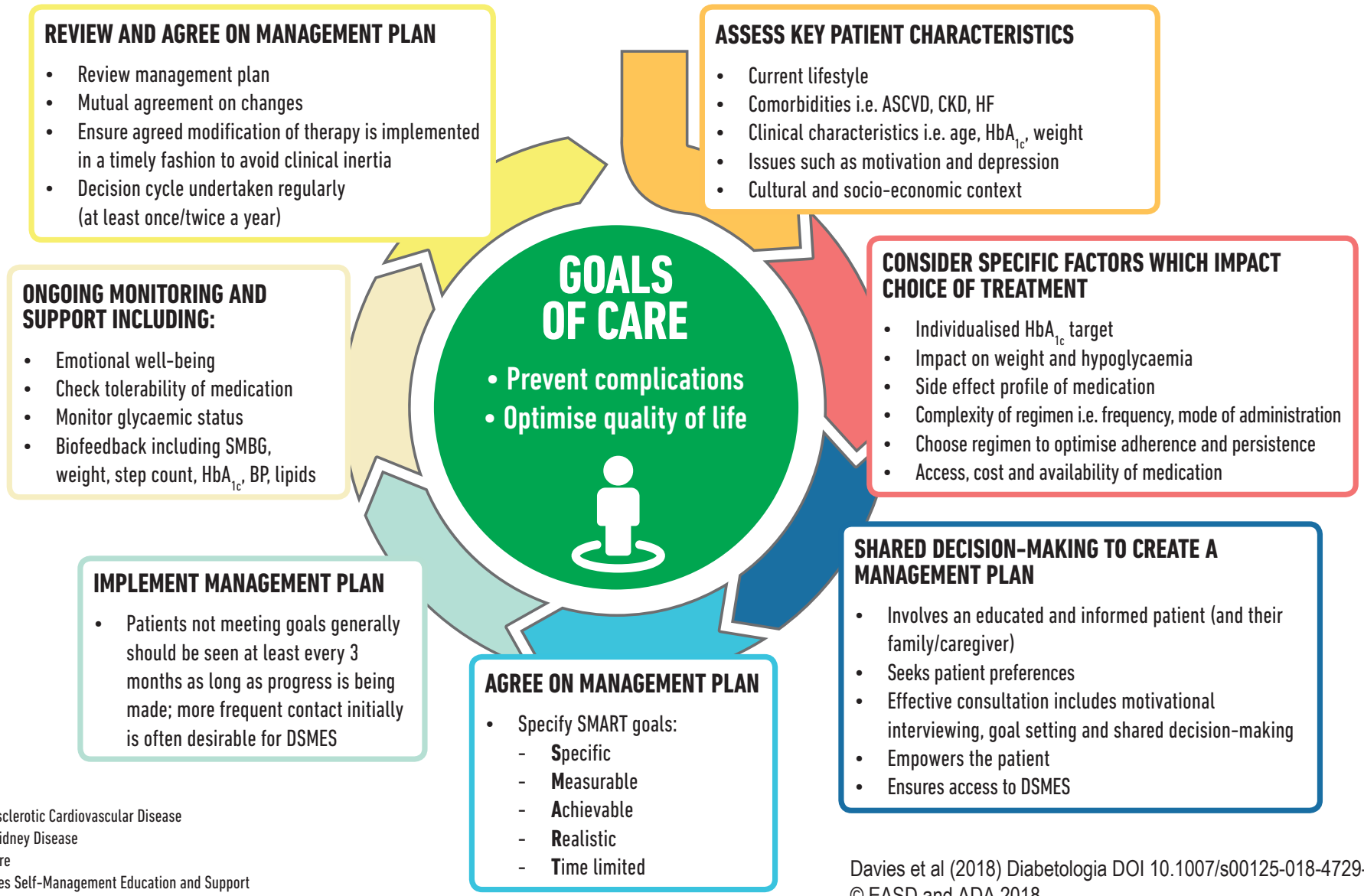
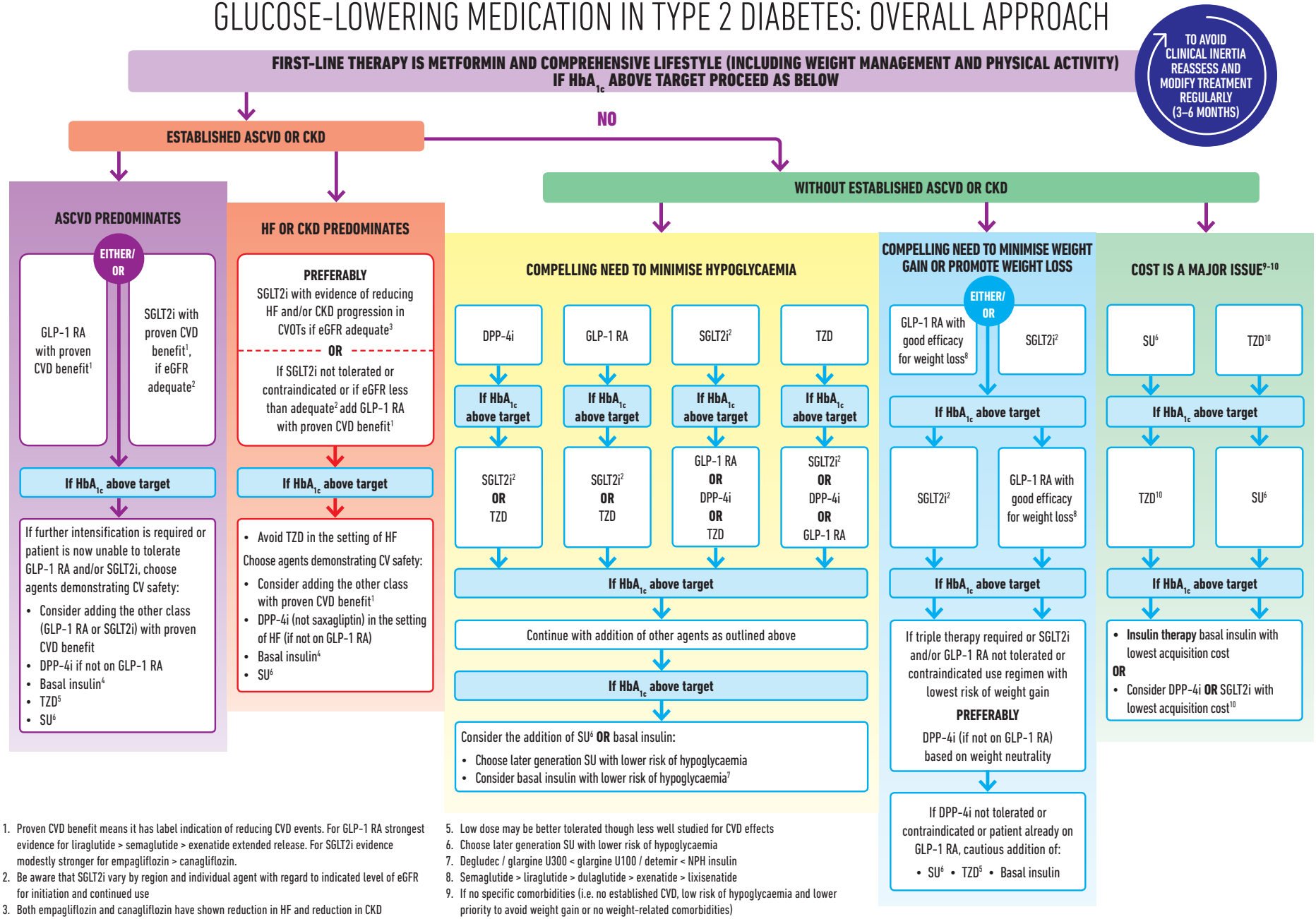
DECISION CYCLE FOR PATIENT-CENTRED GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES



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

Davies et al (2018) Diabetologia DOI 10.1007/s00125-018-4729-5

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > 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. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
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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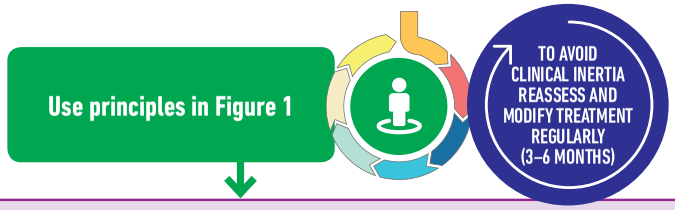
CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)



Use metformin unless contraindicated or not tolerated

If not at HbA_{1c} target:

- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add SGLT2i or GLP-1 RA with proven cardiovascular benefit[1] (See below)

If at HbA_{1c} 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 with proven cardiovascular benefit[1] (See below)

OR reconsider/lower individualised target and introduce SGLT2i or GLP-1 RA

OR reassess HbA_{1c} at 3 month intervals and add SGLT2i or GLP-1 RA if HbA_{1c} goes above target

ASCVD predominates

GLP-1 RA with proven CVD benefit[1]

EITHER/ OR

SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

If HbA_{1c} 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 CVD benefit[1]
- DPP-4i if not on GLP-1 RA
- Basal insulin[5]
- TZD[6]
- SU[7]

HF or CKD predominates

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1,4]

If HbA_{1c} above target

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[5]
- SU[7]

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > 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 to reduce CKD progression in CVOTs
4. Caution with GLP-1 RA in ESRD
5. Degludec or U100 glargine have demonstrated CVD safety
6. Low dose may be better tolerated though less well studied for CVD effects
7. Choose later generation SU to lower risk of hypoglycaemia

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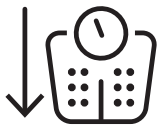
CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS



In those WITHOUT established ASCVD OR CKD

Use principles in Figure 1

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

First-line therapy is metformin

If HbA_{1c} is ≥ 17 mmol/mol (1.5%) above individualised HbA_{1c} target consider early combination therapy

If HbA_{1c} above target

EITHER/ OR

GLP-1 RA with good efficacy for weight loss[1]

SGLT2i if eGFR adequate[2]

If HbA_{1c} above target

SGLT2i if eGFR adequate[2]

GLP-1 RA with good efficacy for weight loss[1]

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

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:

• SU[3] • TZD[4] • Basal insulin

Implement strategies for maximising weight loss

General lifestyle advice

• Medical nutritional therapy
• Eating patterns
• Physical activity

Non-surgical energy restriction for weight loss

Weight loss of 15kg can lead to remission of T2DM in patient <6 years' duration, **consider evidence-based weight loss programmes**

Consider medication for weight loss

Consider metabolic surgery

1. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Choose later generation SU with lower risk of hypoglycaemia
4. Low dose may be better tolerated though less well studied for CVD effects

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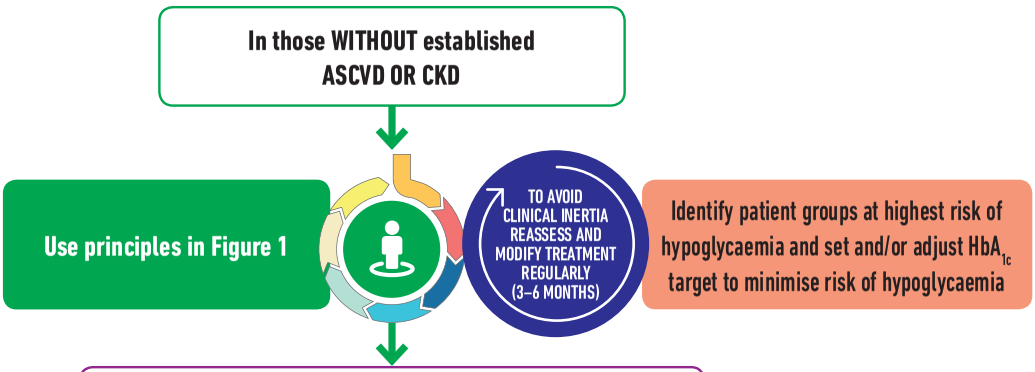
CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA



1. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
2. Low dose TZDs are better tolerated
3. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin

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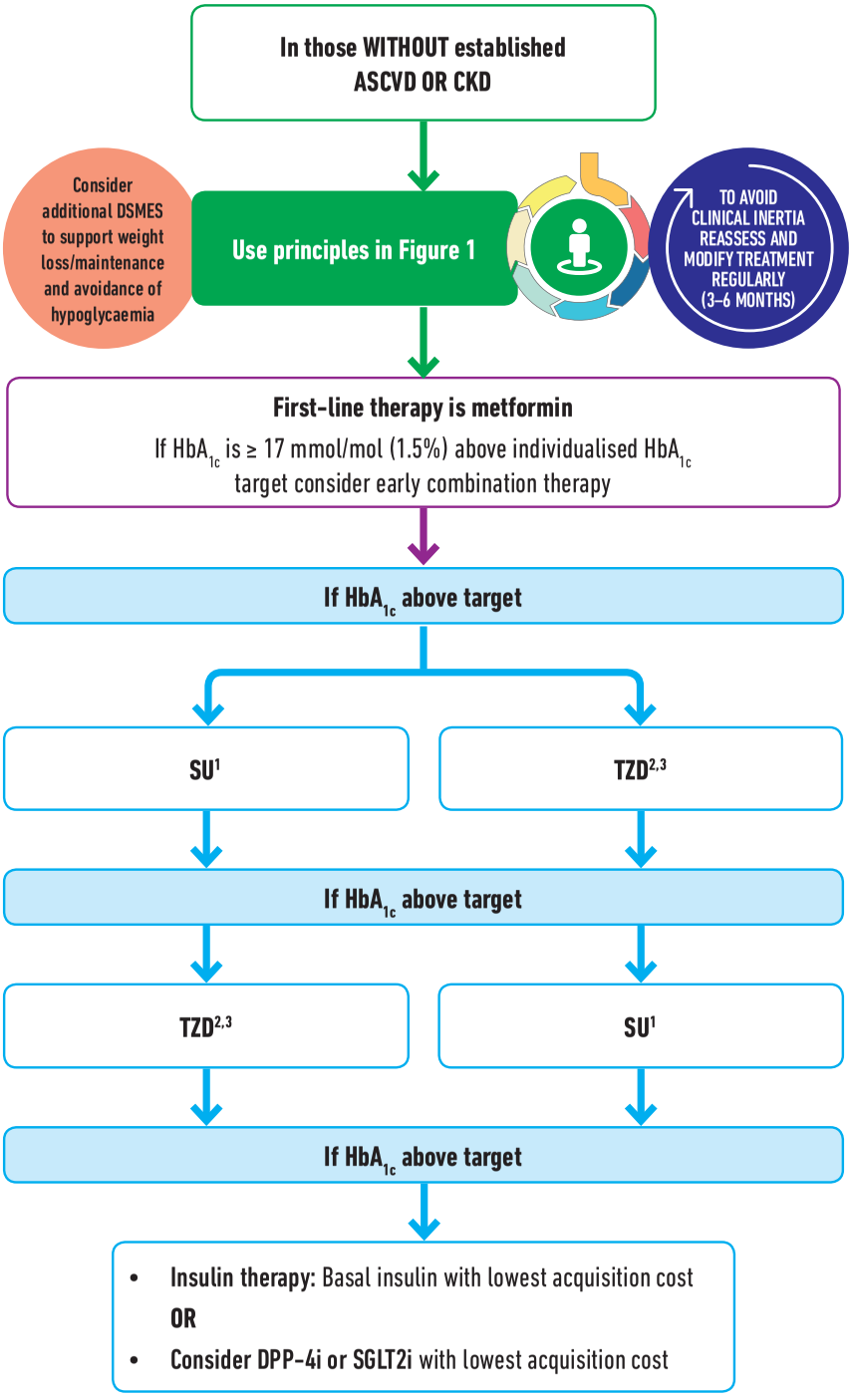
CHOOSING GLUCOSE-LOWERING MEDICATION IF COST IS A MAJOR ISSUE



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-4i relatively cheaper
3. Low-dose TZDs are better tolerated

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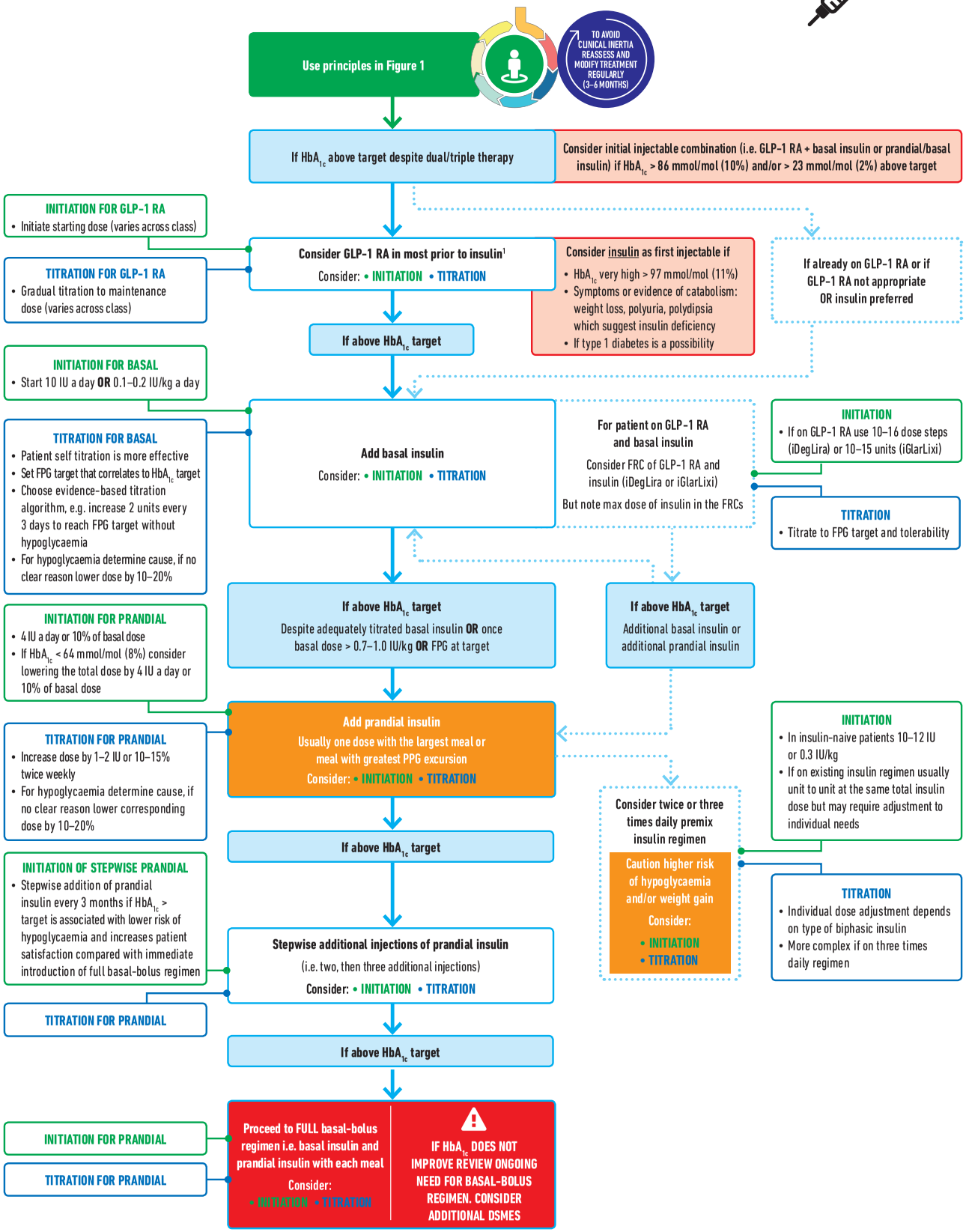
INTENSIFYING TO INJECTABLE THERAPIES



1. Consider choice of GLP-1 RA considering: patient preference, HbA_{1c} 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

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CONSIDERING ORAL THERAPY IN COMBINATION WITH INJECTABLE THERAPIES

METFORMIN

Continue treatment with metformin

SGLT2i

If on SGLT2i, continue treatment

Consider adding SGLT2i if

- Established CVD
- If HbA_{1c} above target or as weight reduction aid

Beware

- DKA (euglycaemic)
- Instruct on sick-day rules
- Do not down-titrate insulin over-aggressively

TZD[1]

Stop TZD when commencing insulin OR reduce dose

SULFONYLUREA

If on SU, stop or reduce dose by 50% when basal insulin initiated

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

DPP-4i

Stop DPP-4i if GLP-1 RA initiated

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

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