
بسم الله الرحمن الرحیم

DIABETES MELLITUS

دکتر تورج واله
فوق تخصص بیماری های غدد و متابولیسم
استادیار دانشگاه علوم پزشکی اراک

Table 2.2—Criteria for the diagnosis of diabetes

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Classification and Diagnosis of Diabetes:
Standards of Medical Care in Diabetes - 2020. *Diabetes Care* 2020;43(Suppl. 1):S14-S31

Classification

Diabetes can be classified into the following general categories:

1. Type 1 diabetes (due to autoimmune ß-cell destruction, usually leading to absolute insulin deficiency)
2. Type 2 diabetes (due to a progressive loss of ß-cell insulin secretion frequently on the background of insulin resistance)
3. Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)
4. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)

Table 2.3—Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) adults who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of CVD
   - Hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - Women with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. Patients with prediabetes (A1C ≥5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.
3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other patients, testing should begin at age 45 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

CVD, cardiovascular disease; GDM, gestational diabetes mellitus.

Classification and Diagnosis of Diabetes:
Standards of Medical Care in Diabetes - 2020. *Diabetes Care* 2020;43(Suppl. 1):S14-S31

Discordance between A1C and plasma glucose levels

- Hemoglobin variants (i.e., hemoglobinopathies)
- Sickle cell disease
- Pregnancy (second and third trimesters and the post partum period)
- Glucose-6-phosphate dehydrogenase deficiency
- HIV
- Hemodialysis
- Recent blood loss or transfusion
- Erythropoietin therapy

Immunizations

- Annual vaccination against influenza
- Vaccination against pneumococcal disease
- Administer a 2- or 3-dose series of hepatitis B vaccine to unvaccinated adults with diabetes ages 18 through 59 years
- Consider administering a 3-dose series of hepatitis B vaccine to unvaccinated adults with diabetes ≥60 years of age.

A1C Testing

- Perform the A1C test at least two times a year
- Perform the A1C test quarterly in patients whose therapy has changed or who are not meeting glycemic goal

GLYCEMIC TARGETS

Table 6.3—Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C	<7.0% (53 mmol/mol)*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

Glycemic Targets:
Standards of Medical Care in Diabetes - 2020. *Diabetes Care* 2020;43(Suppl. 1): S66-S76

Table 7.1—Interfering substances for glucose readings

Glucose oxidase monitors
Uric acid
Galactose
Xylose
Acetaminophen
L-dopa
Ascorbic acid
Glucose dehydrogenase monitors
Icodextrin (used in peritoneal dialysis)

Screening and Diagnosis

- Blood pressure should be measured at every routine clinical visit.If blood pressure ≥140/90 mmHg should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension

- All hypertensive patients with diabetes should monitor their blood pressure at home

Treatment Goals

- For individuals with diabetes and hypertension at higher cardiovascular risk existing ASCVD or 10-year ASCVD risk ≥15%), a blood pressure target of <130/80 mmHg may be appropriate, if it can be safely attained

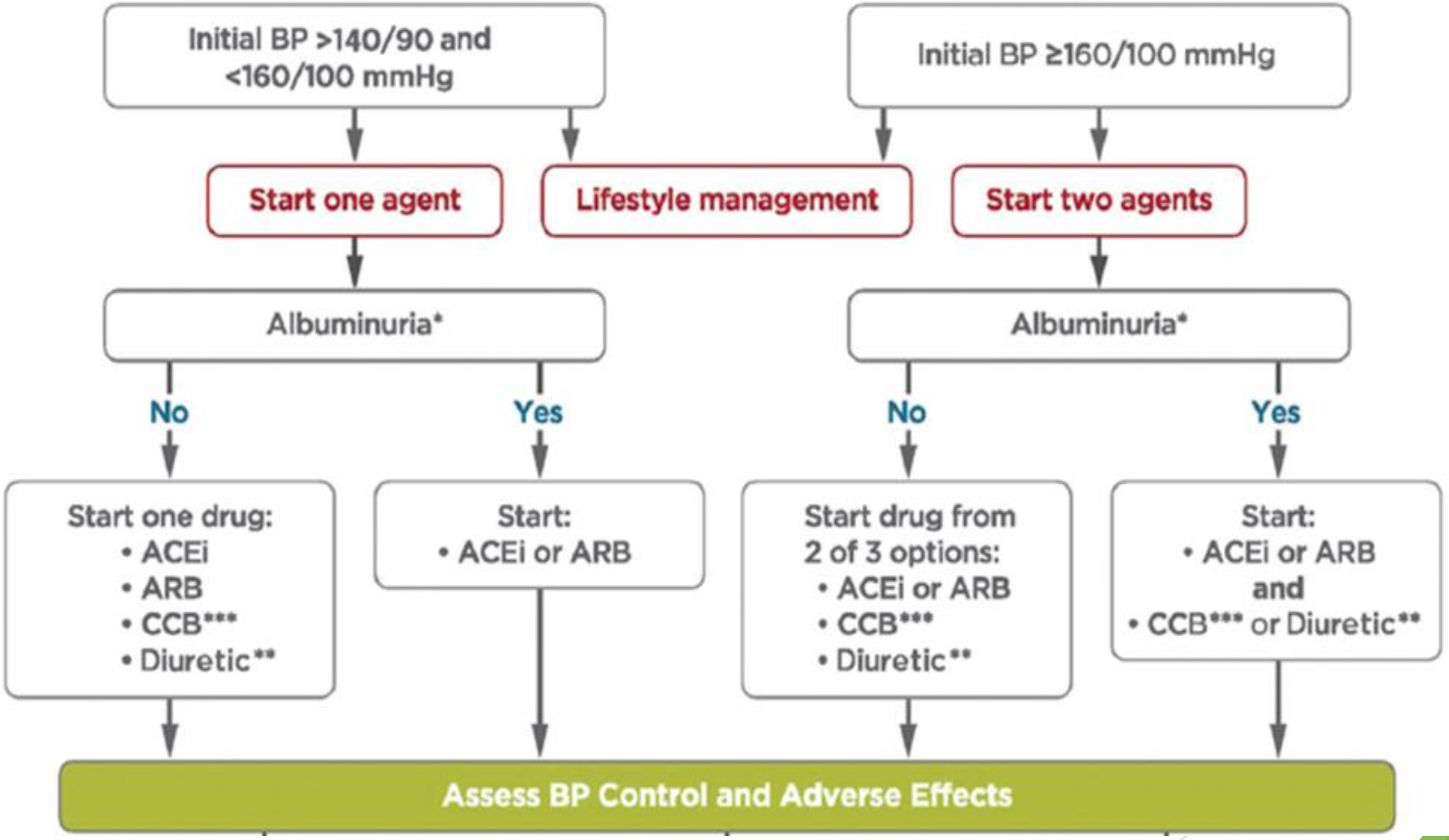
- For individuals with diabetes and hypertension at lower risk for cardiovascular disease (10-year ASCVD risk <15%), treat to a blood pressure target of <140/90 mmHg

- In pregnant patients with diabetes and preexisting hypertension, BP target of ≤135/85 mmHg is suggested

Treatment Strategies

- For patients with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss if overweight or obese, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, and increased physical activity
- Patients with BP ≥140/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals
- Patients with confirmed BP ≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single-pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes

Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes



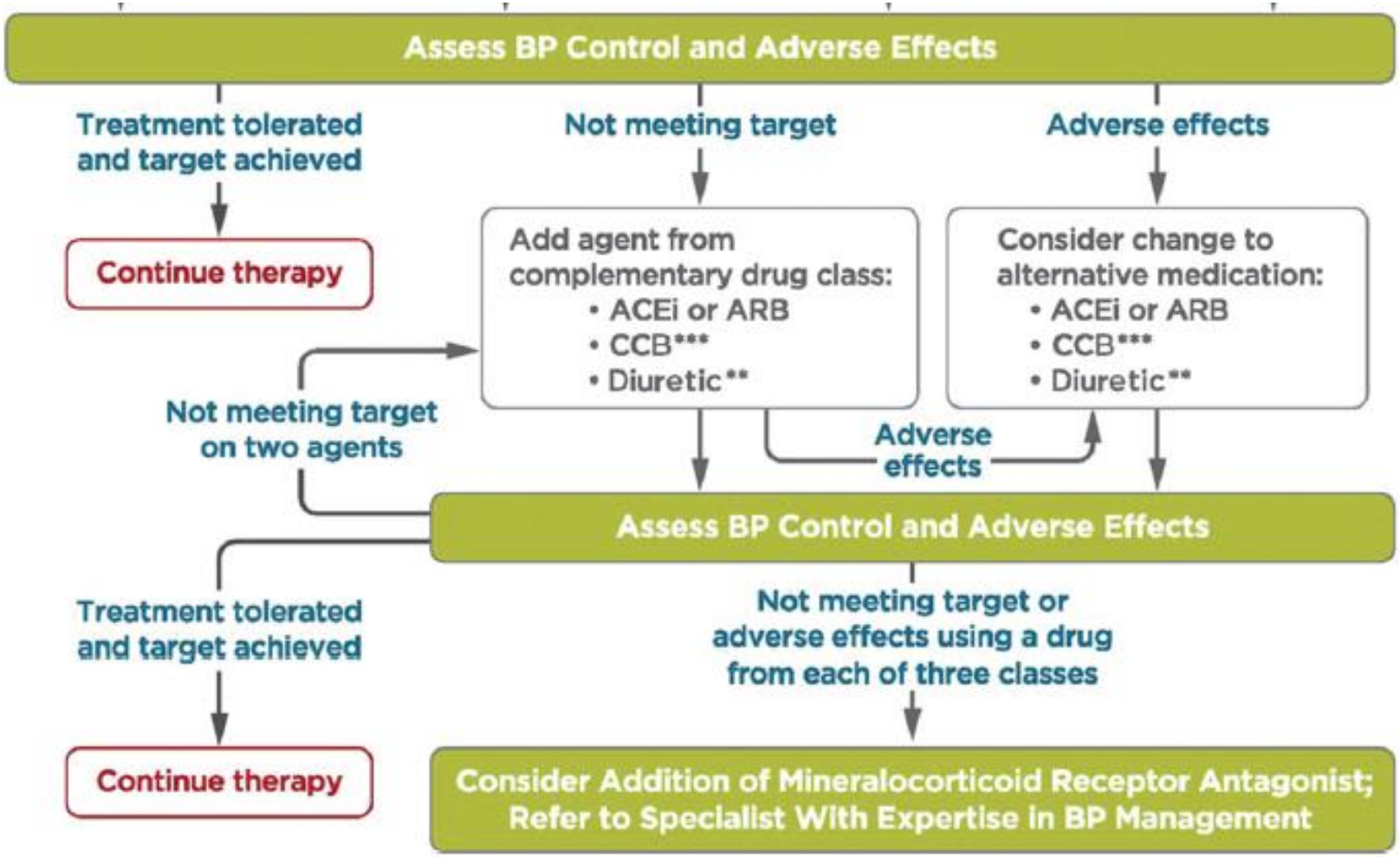


Figure 10.1—Recommendations for the treatment of confirmed hypertension in people with diabetes. *An ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) is suggested to treat hypertension for patients with urine albumin-to-creatinine ratio 30–299 mg/g creatinine and strongly recommended for patients with urine albumin-to-creatinine ratio ≥300 mg/g creatinine. **Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred. ***Dihydropyridine calcium channel blocker (CCB). BP, blood pressure. Adapted from de Boer et al. (17).

Lipid Management—Lifestyle Intervention

- Lifestyle modification focusing on weight loss (if indicated); reduction of saturated fat and trans fat; increase of dietary n-3 fatty acids, viscous fiber, and plant stanols/sterols intake; and increased physical activity

- Intensify lifestyle therapy and optimize glycemic control for patients with elevated triglyceride levels ≥150 mg/dL and/or low HDL cholesterol (<40 mg/dL for men, <50 mg/dL for women)

Lipid Management and Monitoring

- In adults not taking statins or other lipid-lowering therapy, it is reasonable to obtain a lipid profile at
  - the time of diabetes diagnosis,
  - at an initial medical evaluation,
  - and every 5 years thereafter if under the age of 40 years, or more frequently if indicated
- Obtain a lipid profile at initiation of statins or other lipid-lowering therapy, 4–12 weeks after initiation or a change in dose, and annually thereafter

Statin Treatment—Primary Prevention

- For patients with diabetes aged 40–75 years without atherosclerotic cardiovascular disease, use moderate-intensity statin therapy in addition to lifestyle therapy
- For patients with diabetes aged 20–39 years with additional atherosclerotic cardiovascular disease risk factors, initiate statin therapy in addition to lifestyle therapy
- In patients with diabetes at higher risk, especially those with multiple atherosclerotic cardiovascular disease risk factors or aged 50–70 years, it is reasonable to use high-intensity statin therapy
- In adults with diabetes and 10-year ASCVD risk of 20% or higher, it may be reasonable to add ezetimibe to maximally tolerated statin therapy to reduce LDL cholesterol levels by 50% or more

Statin Treatment

- For patients of all ages with diabetes and ASCVD, high-intensity statin therapy should be added to lifestyle therapy
- For very high risk patients using specific criteria, if LDL cholesterol is ≥70 mg/dL on maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor). A Ezetimibe may be preferred due to lower cost
- In adults with diabetes aged >75 years, it may be reasonable to initiate statin therapy after discussion of potential benefits and risks
- Statin therapy is contraindicated in pregnancy

Table 10.2—High-intensity and moderate-intensity statin therapy*

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30–49%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 1–4 mg

*Once-daily dosing. XL, extended release.

Treatment of elevated TG

- For patients with fasting TG levels ≥500 mg/dL, evaluate for secondary causes of hypertriglyceridemia and consider medical therapy to reduce the risk of pancreatitis.
- In adults with moderate hypertriglyceridemia (fasting or non-fasting TG 175–499 mg/dL), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that raise triglycerides
- In patients with atherosclerotic cardiovascular disease or other cardiovascular risk factors on a statin with controlled LDL cholesterol but elevated TG (135–499 mg/dL), the addition of icosapentethyl can be considered to reduce cardiovascular risk

Combination Therapy

- Statin plus fibrate combination therapy has not been shown to improve atherosclerotic cardiovascular disease outcomes and not recommended

- Statin plus niacin combination therapy has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and not recommended

Antiplatelet Agents

- Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of atherosclerotic CVD
- For patients with atherosclerotic CVD and documented aspirin allergy, clopidogrel (75 mg/day) should be used
- Dual antiplatelet therapy (with low-dose aspirin and a P2Y12 inhibitor) is reasonable for a year after an ACS
- Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk

Cardiovascular Disease—Treatment

- In patients with known ASCVD, consider ACE inhibitor or ARB therapy to reduce the risk of cardiovascular events
- In patients with prior myocardial infarction, b-blockers should be continued for at least 2 years after the event
- In patients with type 2 diabetes with stable heart failure, metformin may be continued for glucose lowering if eGFR remains >30 mL/min but should be avoided in unstable or hospitalized patients with heart failure
- Among patients with type 2 diabetes who have established ASCVD or established kidney disease, a SGLT2 inhibitor or GLP-1 receptor agonist with demonstrated cardiovascular disease benefit is recommended

Pharmacologic Therapy for Type 2 Diabetes

Pharmacologic Therapy for Type 2 Diabetes

- Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes
- Metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin
- The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or A1C levels (>10%) or blood glucose levels (≥300 mg/dl) are very high

Pharmacologic Therapy for Type 2 Diabetes (continued)

- A patient-centered approach should be used to guide the choice of pharmacologic agents include cardiovascular comorbidities, hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences
- Among patients with type 2 diabetes who have established atherosclerotic CVD or indicators of high risk, established kidney disease, or heart failure, an SGLT2 inhibitor or GLP-1 receptor agonist with demonstrated cardiovascular disease benefit is recommended

Pharmacologic Therapy for Type 2 Diabetes (continued)

- In patients with type 2 diabetes who need greater glucose lowering than can be obtained with oral agents, glucagon-like peptide 1 receptor agonists are preferred to insulin when possible
- Intensification of treatment for patients with type 2 diabetes not meeting treatment goals should not be delayed
- The medication regimen and medication-taking behavior should be reevaluated at regular intervals (every 3–6months) and adjusted as needed to incorporate specific factors that impact choice of treatment

	MECHANISM OF ACTION	EXAMPLES[a]	HBA_{1c} REDUCTION (%)[b]	AGENT-SPECIFIC ADVANTAGES	AGENT-SPECIFIC DISADVANTAGES	CONTRAINDICATIONS
Oral						
Biguanides[c*]	↓ Hepatic glucose production	Metformin	1–2	Weight neutral, do not cause hypoglycemia, inexpensive, extensive experience, ↓ CV events	Diarrhea, nausea, lactic acidosis, vitamin B12 deficiency	Renal insufficiency (see text for GFR <45 mL/min), CHF, radiographic contrast studies, hospitalized patients, acidosis
α-Glucosidase inhibitors[c**]	↓ GI glucose absorption	Acarbose, miglitol, voglibose	0.5–0.8	Reduce postprandial glycemia	GI flatulence, liver function tests	Renal/liver disease
Dipeptidyl peptidase IV inhibitors[c***]	Prolong endogenous GLP-1 action; ↑ Insulin, ↓ glucagon	Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin	0.5–0.8	Well tolerated, do not cause hypoglycemia	Angioedema/ urticarial and immune-mediated dermatologic effects	Reduced dose with renal disease
Insulin secretagogues: Sulfonylureas[c*]	↑ Insulin secretion	Glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glyburide, glyclopyramide	1–2	Short onset of action, lower postprandial glucose, inexpensive	Hypoglycemia, weight gain	Renal/liver disease
Insulin secretagogues: Nonsulfonylureas[c***]	↑ Insulin secretion	Mitiglinide nateglinide, repaglinide	0.5–1.0	Short onset of action, lower postprandial glucose	Hypoglycemia	Renal/liver disease

Antidiabetic therapies

- Metformin
- Should be avoided on maintenance haemodialysis
- Increased risk of lactic acidosis in this setting
- Doses should be reduced [eGFR] <45 mL/min) or then stopped (eGFR <30 mL/min)
- Acarbose
- Can be given in CKD stage 1–3 without dose adjustments
- It should not be used in patients with a creatinine clearance of less than 25 mL/min/1.73m^2
- Is not licensed for patients on maintenance haemodialysis

Antidiabetic therapies

- Sulfonylureas
  - Not licensed for use in patients on maintenance haemodialysis
  - Increased incidence of hypoglycaemia
  - Glibenclamide is contraindicated in CKD stages≥3 (eGFR<60 mL/min)
  - Gliclazid lower risk for severe hypoglycaemia than glibenclamide and glimepiride, should be used with caution when GFR is <40 mL/min

Antidiabetic therapies

Glinides

- Glinides exhibit insulinotropic effects by stimulating pancreatic SU receptors. Receptor activation is more rapid and shorter than for SU
- *Repaglinide*
- Metabolised in the liver, eliminated via the faeces
- May be given in all stages of renal failure
- Dose adjustments should be considered at CKD stages 4–5
- Can be considered in the haemodialysis patient
- Experience in this group is limited
- Monitoring required

Sodium-glucose cotransporter 2 inhibitors[***]	↑ renal glucose excretion	Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	0.5–1.0	do not cause hypoglycemia, ↓ weight and BP; see text for CVD effect	Urinary and genital infections, polyuria, dehydration, exacerbate tendency to hyperkalemia and DKA; see text	Moderate renal insufficiency, insulin-deficient DM
Thiazolidinediones[c,***]	↓ Insulin resistance, ↑ glucose utilization	Pioglitazone, rosiglitazone	0.5–1.4	Lower insulin requirements	Peripheral edema, CHF, weight gain, fractures, macular edema	CHF, liver disease
Parenteral						
Amylin agonists[c,d,***]	Slow gastric emptying, ↓ glucagon	Pramlintide	0.25–0.5	Reduce postprandial glycemia, weight loss	Injection, nausea, ↑ risk of hypoglycemia with insulin	Agents that also slow GI motility
GLP-1 receptor agonists[c,***]	↑ Insulin, ↓ glucagon, slow gastric emptying, satiety	Albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide	0.5–1.0	Weight loss, do not cause hypoglycemia; see text for CVD effect	Injection, nausea, ↑ risk of hypoglycemia with insulin secretagogues	Renal disease, agents that also slow GI motility; medullary carcinoma of thyroid, pancreatic disease
Insulin[c,d,****]	↑ Glucose utilization, ↓ hepatic glucose production, and other anabolic actions	See text and Table 397-4	Not limited	Known safety profile	Injection, weight gain, hypoglycemia	
Medical nutrition therapy and physical activity[c,*]	↓ Insulin resistance, ↑ insulin secretion	Low-calorie, low-fat diet, exercise	1–3	Other health benefits	Compliance difficult, long-term success low	

Thiazolidinedione

- Pioglitazone
- Risk of hypoglycaemia is low
- Hepatic metabolism
- Has no renal elimination and is unaffected by haemodialysis
- Can be used in CKD stage 1–5
- No dose adjustment is needed for for impaired renal function
- not licensed for use in patients with maintenance haemodialysis

GLP-1 agents

- Liraglutide
- long-acting GLP-1 agonist
- No dose adjustment is required for(creatinine clearance 30< mL/min)
- No therapeutic experience with liraglutide in severe renal impairment (creatinine clearance<30 mL/min)
- Caution in severe renal impairment including those with ESRD
- Insufficient experience of the use in patients on maintenance haemodialysis

GLP-1 agents

- In patients with CKD who are at increased risk for cardiovascular events, use of a GLP 1 receptor agonist may reduce risk of progression of albuminuria, cardiovascular events
- liraglutide reduced the risk of new or worsening nephropathy (persistent macroalbuminuria,doubling of serum creatinine, ESRD,or death from ESRD) by 22%
- Semaglutide reduced the risk nephropathy by 36%

DPP4 inhibitors

Sitagliptin

- Not removed by conventional dialysis, but is removed by high flux dialysis (13.5% of the drug is removed by a 3–4 hour dialysis session)
- Mild renal impairment (creatinine clearance ≥50 mL//min) – no dose adjustment
- Moderate renal impairment (creatinine clearance 30–50 mL/min) – use sitagliptin 50 mg QD.
- Severe renal impairment (creatinine clearance <30 mL/min or ESRF requiring haemodialysis or peritoneal dialysis) – use sitagliptin 25 mg QD.
- Administered without regard to the timing of dialysis

DPP4 inhibitors

- Linagliptin
- 80% is eliminated in the faeces and 5% in the urine
- Not removed by dialysis
- No dose adjustment is required and linagliptin 5 mg QD is suitable for patients on MHDx
- Linagliptin, sitagliptin, vildagliptin and alogliptin can be used in patients on maintenance haemodialysis
- Dose reductions for sitagliptin,vildagliptin and alogliptin are required

SGLT2 inhibitors

- Sodium-glucose co-transporter-2 inhibitors:
- Inhibit glucose reabsorption in the proximal renal tubules
- Weight loss
- Low risk of hypoglycaemia
- Antihypertensive effect due to simultaneous urinary excretion of sodium
- Reduce intraglomerular pressure
- Reduce albuminuria

SGLT2 inhibitors

- Slow GFR loss that independent of glycemia
- Reduce oxidative stress in the kidney by>50%
- Reduce inflammasome activity
- Dapagliflozin, Canagliflozin and Empagliflozin
- In CKD (stages 1–2) with no dose adjustment CKD (stages4–5) they are to be avoided

SGLT2 inhibitors

- Patients with DM2 and DKD, consider use of a SGL2 inhibitor in patients with an eGFR >30 and urinary albumin>30mg/g cr, particularly in those with urinary albumin >300 mg/g cr, to reduce risk of CKD progression CVD

- SGLT2 inhibitors may promote AKI through volume depletion particularly when combined with diuretics or other medications that reduce glomerular filtration

Complication of SGL2 Inhibitors

- Risk of amputation
- Bone fracture
- DKA
- Genitourinary infections
- Volume depletion
- Hypotension
- Elevation LDL
- Fournier’s gangrene

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i	GLP-1 RA	SGLT2i	TZD
If A1C above target	If A1C above target	If A1C above target	If A1C above target
SGLT2i **OR** TZD	SGLT2i **OR** TZD	GLP-1 RA **OR** DPP-4i **OR** TZD	SGLT2i **OR** DPP-4i **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 SU[4] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia[9]

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

GLP-1 RA with good efficacy for weight loss[10]	**EITHER/ OR**	SGLT2i

If A1C above target

SGLT2i	GLP-1 RA with good efficacy for weight loss[10]

If A1C above target

If quadruple 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

COST IS A MAJOR ISSUE[11,12]

SU[4]	TZD[12]

If A1C above target

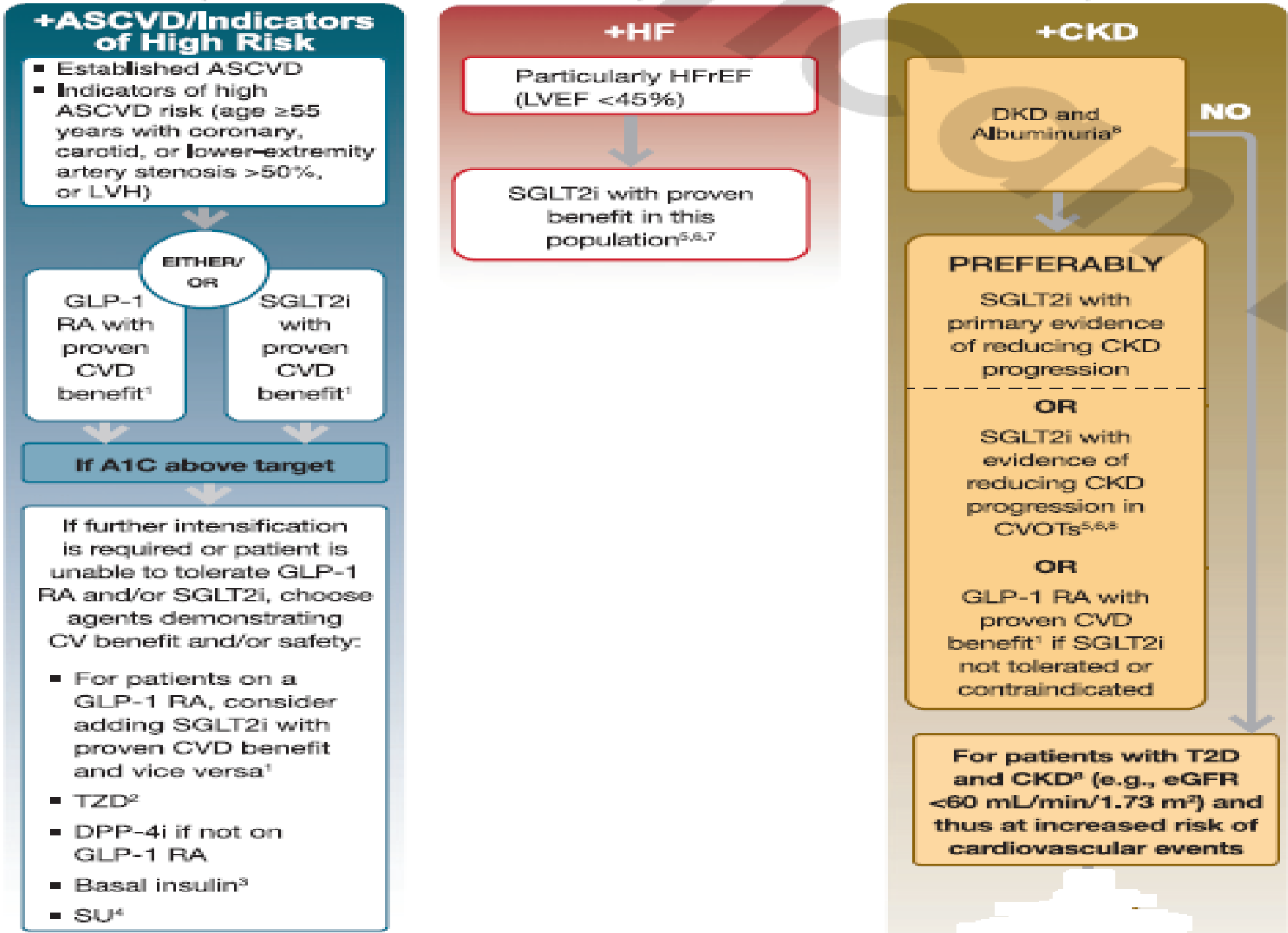
TZD[12]	SU[4]

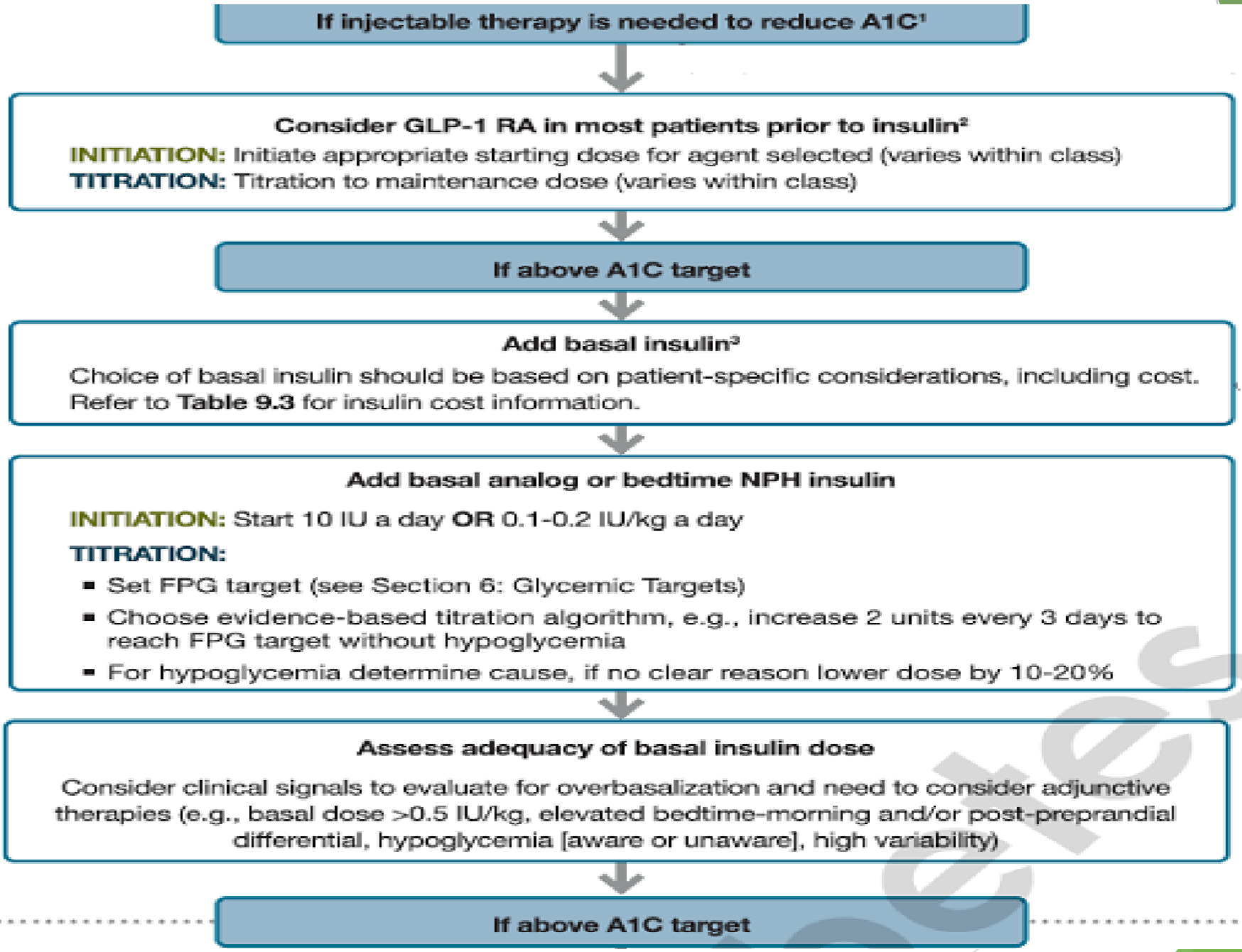
If A1C above target

Insulin therapy basal insulin with lowest acquisition cost

OR

Consider other therapies based on cost


+ASCVD/Indicators of High Risk
Established ASCVD
Indicators of high ASCVD risk (age ≥55 years with coronary, carotid, or lower-extremity artery stenosis >50%, or LVH)
EITHER/ OR
GLP-1 RA with proven CVD benefit[1]
SGLT2i with proven CVD benefit[1]
If A1C above target
If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety:
For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit and vice versa[1]
TZD[2]
DPP-4i if not on GLP-1 RA
Basal insulin[3]
SU[4]
+HF
Particularly HFrEF (LVEF <45%)
SGLT2i with proven benefit in this population[5,6,7]
+CKD
DKD and Albuminuria[8]
NO
PREFERABLY
SGLT2i with primary evidence of reducing CKD progression
OR
SGLT2i with evidence of reducing CKD progression in CVOTs[5,6,8]
OR
GLP-1 RA with proven CVD benefit[1] if SGLT2i not tolerated or contraindicated
For patients with T2D and CKD[8] (e.g., eGFR <60 mL/min/1.73 m²) and thus at increased risk of cardiovascular events


If injectable therapy is needed to reduce A1C[1]
Consider GLP-1 RA in most patients prior to insulin[2]
INITIATION: Initiate appropriate starting dose for agent selected (varies within class)
TITRATION: Titration to maintenance dose (varies within class)
If above A1C target
Add basal insulin[3]
Choice of basal insulin should be based on patient-specific considerations, including cost. Refer to Table 9.3 for insulin cost information.
Add basal analog or bedtime NPH insulin
INITIATION: Start 10 IU a day OR 0.1-0.2 IU/kg a day
TITRATION:
Set FPG target (see Section 6: Glycemic Targets)
Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
For hypoglycemia determine cause, if no clear reason lower dose by 10-20%
Assess adequacy of basal insulin dose
Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., basal dose >0.5 IU/kg, elevated bedtime-morning and/or post-preprandial differential, hypoglycemia [aware or unaware], high variability)
If above A1C target

If above A1C target

Consider GLP-1 RA if not already in regimen

For addition of GLP-1 RA, consider lowering insulin dose dependent on current glycemic assessment and patient factors

Add prandial insulin[5]

Usually one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate

INITIATION:

- 4 IU a day or 10% of basal insulin dose
- If A1C <8% (64 mmol/mol) consider lowering the basal dose by 4 IU a day or 10% of basal dose

TITRATION:

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

If on bedtime NPH, consider converting to twice-daily NPH regimen

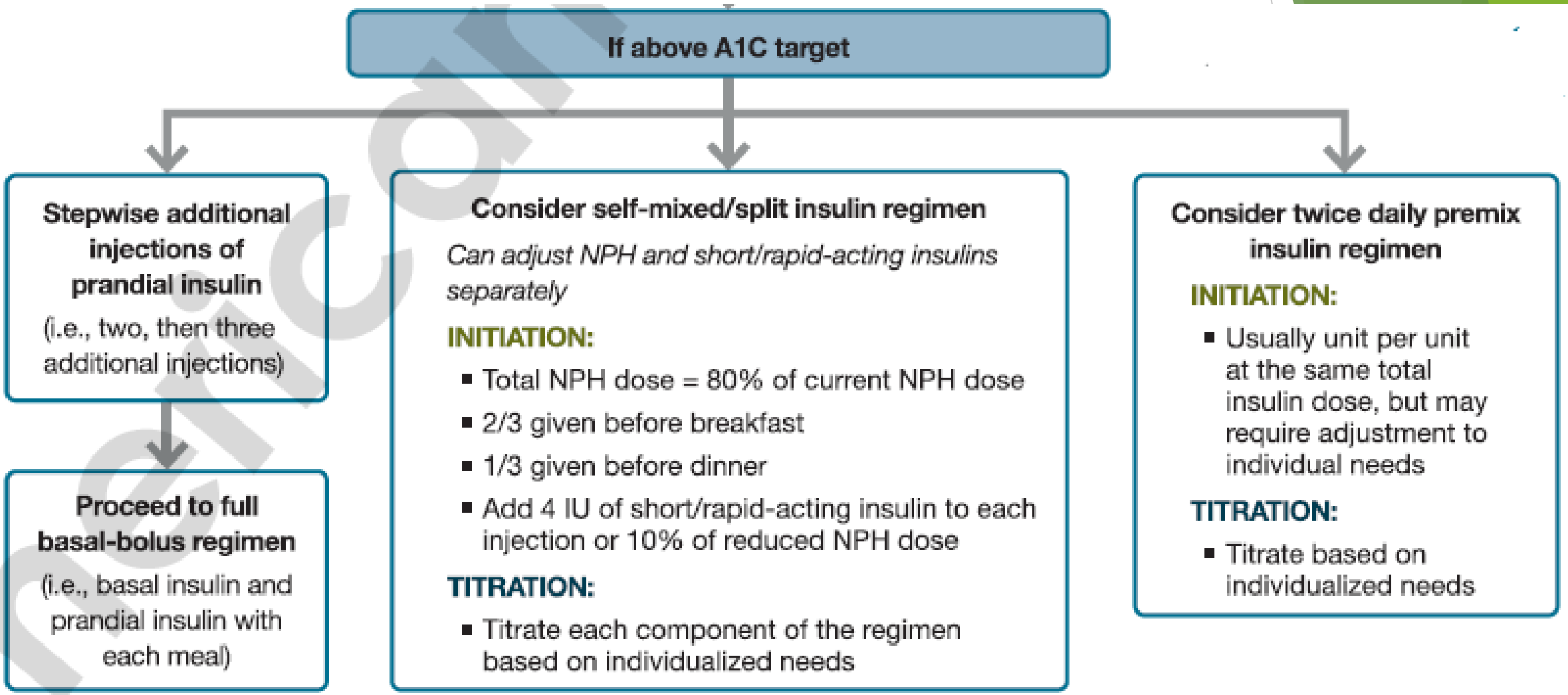
Conversion based on individual needs and current glycemic control. The following is one possible approach:

INITIATION:

- Total dose = 80% of current bedtime NPH dose
- 2/3 given in the morning
- 1/3 given at bedtime

TITRATION:

- Titrate based on individualized needs


If above A1C target
Stepwise additional injections of prandial insulin
(i.e., two, then three additional injections)
Proceed to full basal-bolus regimen
(i.e., basal insulin and prandial insulin with each meal)
Consider self-mixed/split insulin regimen
Can adjust NPH and short/rapid-acting insulins separately
INITIATION:
Total NPH dose = 80% of current NPH dose
2/3 given before breakfast
1/3 given before dinner
Add 4 IU of short/rapid-acting insulin to each injection or 10% of reduced NPH dose
TITRATION:
Titrate each component of the regimen based on individualized needs
Consider twice daily premix insulin regimen
INITIATION:
Usually unit per unit at the same total insulin dose, but may require adjustment to individual needs
TITRATION:
Titrate based on individualized needs