Type II Diabetes Mellitus Management

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Disclosure

- I have no relevant financial relationships to disclose

- One in 11 adults worldwide has diabetes
- Type 2 DM accounts for 90-95% of all diabetes
- Most, but not all, people with type2 diabetes have overweight or obesity
- Individuals who do not have obesity or overweight by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region

- Rates of impaired glucose tolerance and type 2 diabetes have increased significantly in the adolescent and young adult population, in concert with increases in obesity

- It is estimated that one in five adolescents and one in four young adults now have impaired glucose tolerance in the U.S., which in turn increases the risks of progression to type 2 diabetes, CKD, and cardiovascular complications

- Minority populations are particularly affected, with half or more of newly diagnosed cases of type 2 diabetes in childhood and adolescence occurring in Hispanic, non-Hispanic Black, Asian/Pacific Islander, and American Indian populations

- Most children and adolescents who develop type 2 diabetes will have microvascular complications by young adulthood; in addition, a recently identified 25% increase in the risks of hyperglycemic crises, acute myocardial infarction, stroke, and lower extremity amputation over a 5-year period was most notable in people with diabetes aged 18–44 years

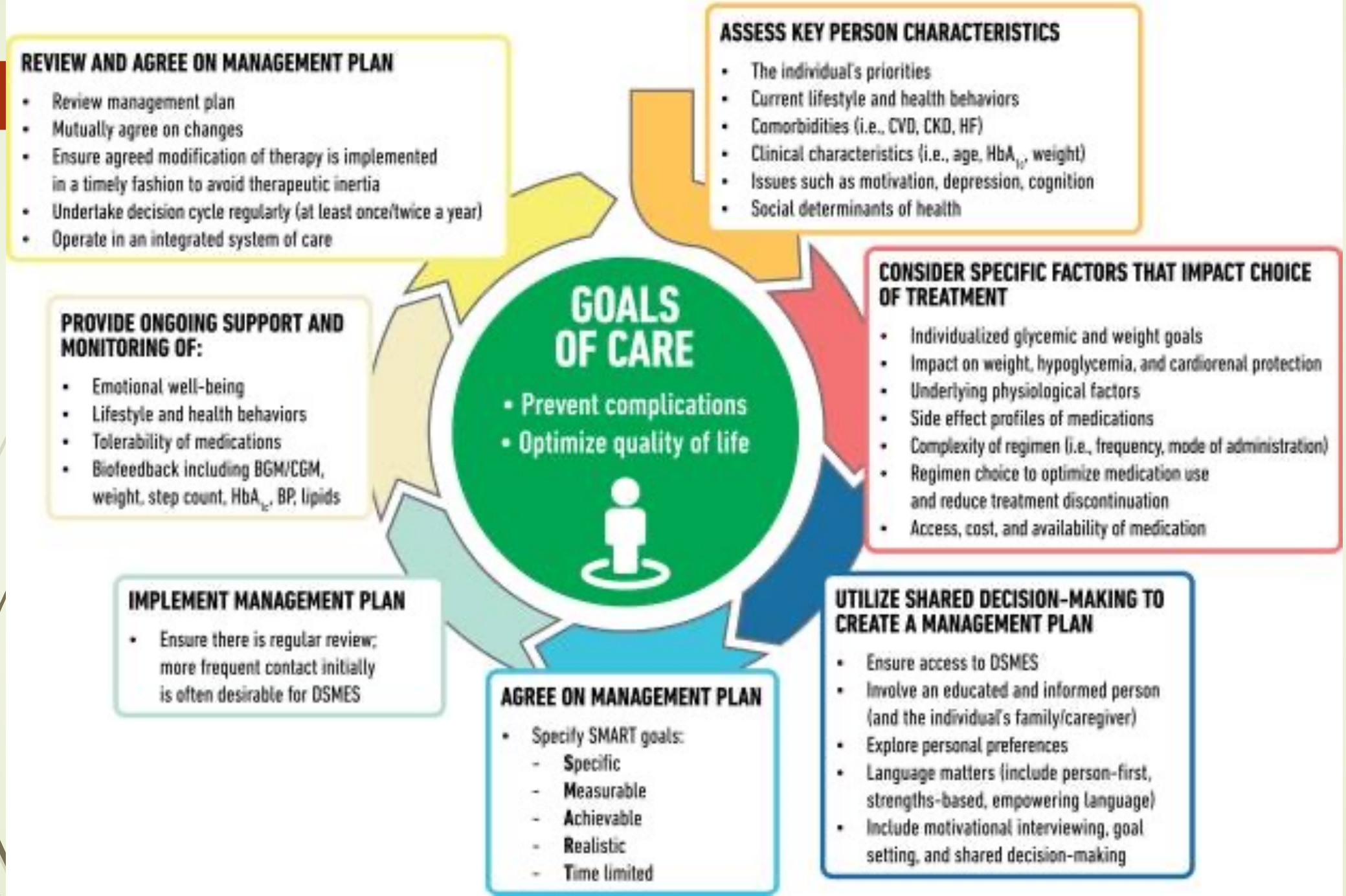
- Even undiagnosed people with diabetes are at increased risk of developing macrovascular and microvascular complications.
- It occurs more frequently in individuals with prior gestational diabetes mellitus (GDM) or polycystic ovary syndrome
- It is often associated with a strong genetic predisposition or family history in first-degree relatives (more so than type 1 diabetes)
- The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity

- People with type 2 diabetes may have insulin levels that appear normal or elevated
- Insulin resistance may improve with weight reduction, physical activity, and/or pharmacologic treatment of hyperglycemia but is seldom restored to normal
- Recent interventions with intensive diet and exercise or surgical weight loss have led to diabetes remission
- The duration of glycemic burden is a strong predictor of adverse outcomes

Diagnosis criteria

- Fasting blood sugar:126mg/dl or higher
- OGTT: 2hr plasma glucose 200mg/dl or higher
- HbA1c: 6.5% or higher
- Symptoms of Hyperglycemia plus Random blood glucose 200mg/dl or higher

DECISION CYCLE FOR PERSON-CENTERED GLYCEMIC MANAGEMENT IN TYPE 2 DIABETES



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10008140/

- A reasonable HbA_{1c} target for most nonpregnant adults with sufficient life expectancy to see microvascular benefits (generally ~10 years) is around 7% or less

- Aiming for a lower HbA_{1c} level than this may have value if it can be achieved safely without significant hypoglycemia or other adverse treatment effects.

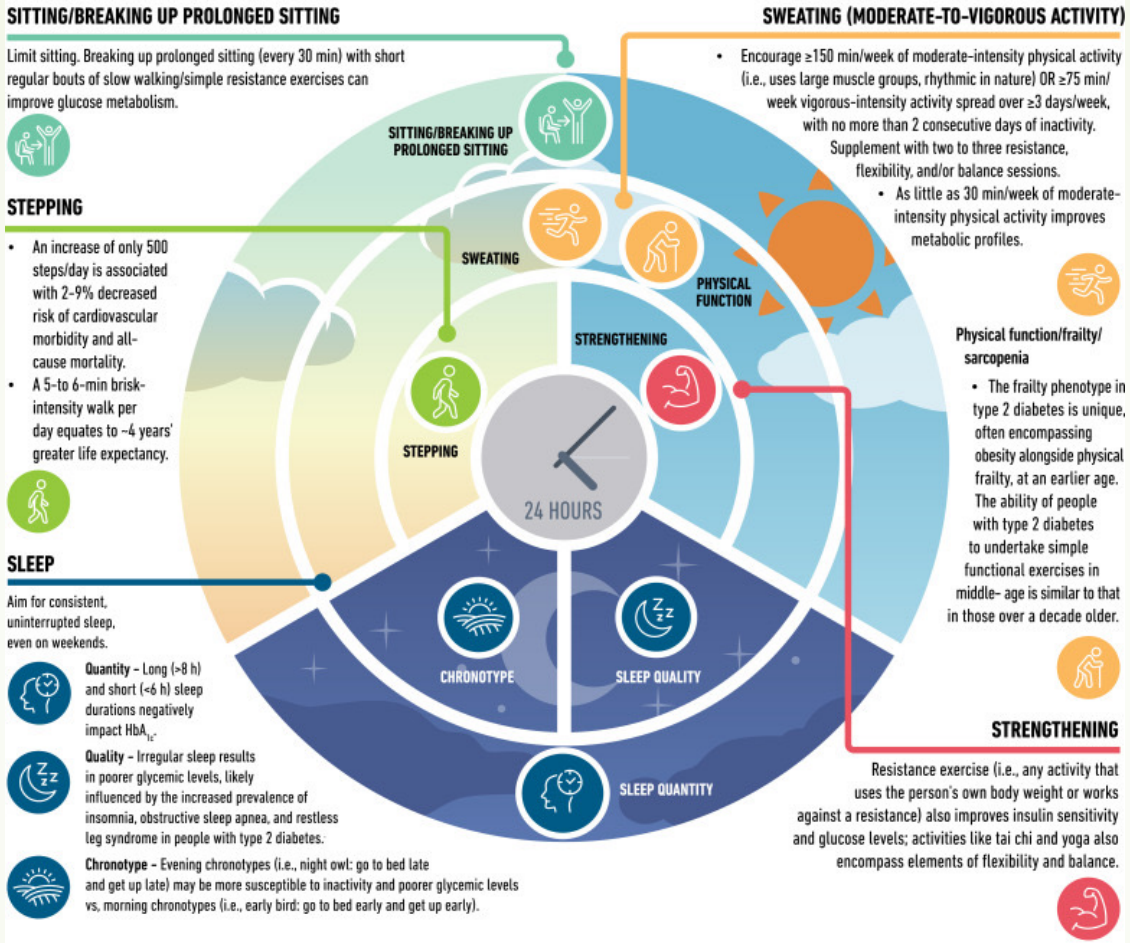
- A lower target may be reasonable, particularly when using pharmacological agents that are not associated with hypoglycemic risk.

- Higher targets can be appropriate in cases of limited life expectancy, advanced complications, or poor tolerability or if other factors such as frailty are present.

Weight Reduction as a Targeted Intervention

- Weight reduction has mostly been seen as a strategy to improve HbA_{1c} and reduce the risk for weight-related complications.
- However, it was recently suggested that weight loss of 5–15% should be a primary target of management for many people living with type 2 diabetes
- A higher magnitude of weight loss confers better outcomes.
- Weight loss of 5–10% confers metabolic improvement; weight loss of 10–15% or more can have a disease-modifying effect and lead to remission of diabetes, defined as normal blood glucose levels for 3 months or more in the absence of pharmacological therapy
- Weight loss may exert benefits that extend beyond glycemic management to improve risk factors for cardiometabolic disease and quality of life.

IMPORTANCE OF 24-HOUR PHYSICAL BEHAVIORS FOR TYPE 2 DIABETES



	Glucose/insulin	Blood pressure	HbA_{1c}	Lipids	Physical function	Depression	Quality of life
SITTING/BREAKING UP PROLONGED SITTING	↓	↓	↓	↓	↑	↓	↑
STEPPING	↓	↓	↓	↓	↑	↓	↑
SWEATING (MODERATE-TO-VIGOROUS ACTIVITY)	↓	↓	↓	↓	↑	↓	↑
STRENGTHENING	↓	↓	↓	↓	↑	↓	↑
ADEQUATE SLEEP DURATION	↓	↓	↓	↓	?	↓	↑
GOOD SLEEP QUALITY	↓	↓	↓	↓	?	↓	↑
CHRONOTYPE/CONSISTENT TIMING	↓	?	↓	?	?	↓	?

IMPACT OF PHYSICAL BEHAVIORS ON CARDIOMETABOLIC HEALTH IN PEOPLE WITH TYPE 2 DIABETES

↑ **Higher levels/improvement** (physical function, quality of life); ↓ **Lower levels/improvement** (glucose/insulin, blood pressure, HbA_{1c}, lipids, depression); ? no data available;
↑ Green arrows = strong evidence; ↑ Yellow arrows = medium strength evidence; ↑ Red arrows = limited evidence.

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Metformin

- high efficacy in lowering HbA_{1c}
- minimal hypoglycemia risk when used as monotherapy
- weight neutrality with the potential for modest weight loss
- good safety profile
- low cost
- traditionally been recommended as first-line glucose-lowering therapy for the management of type 2 diabetes

SGLT2i

- The SGLT2i are oral medications that reduce plasma glucose by enhancing urinary excretion of glucose.

- have intermediate-to-high glycemic efficacy, with lower glycemic efficacy at lower estimated glomerular filtration rate (eGFR).

- Cardiorenal outcome trials have demonstrated their efficacy in reducing the risk of composite major adverse cardiovascular events (MACE), cardiovascular death, myocardial infarction, hospitalization for heart failure (HHF), and all-cause mortality and improving renal outcomes in individuals with type 2 diabetes with an established/high risk of CVD

GLP-1 RA

- GLP-1 RA augment glucose-dependent insulin secretion and glucagon suppression, decelerate gastric emptying, curb post-meal glycemic increments, and reduce appetite, energy intake, and body weight

- Specific GLP-1 RA have also been approved for reducing risk of MACE in adults with type 2 diabetes with established CVD (Dulaglutide, Liraglutide, and subcutaneous Semaglutide) or multiple cardiovascular risk factors (dulaglutide) and for chronic weight management

Glucose-Dependent Insulinotropic Polypeptide and GLP-1 RA

- In May 2022, the U.S. Food and Drug Administration (FDA) approved Tirzepatide, a GIP and GLP-1 RA, for once-weekly subcutaneous administration to improve glucose control in adults with type 2 diabetes as an addition to healthy eating and exercise.

- Based on meta-analysis findings, Tirzepatide was superior to its comparators, including other long-acting GLP-1 RA, in reducing glucose and body weight, but was associated with increased odds for gastrointestinal adverse events, in particular nausea

- Current short-term data from RCTs suggest that Tirzepatide does not increase the risk of MACE versus comparators; however, robust data on its long-term cardiovascular profile will be available after completion of the SURPASS-CVOT trial

Dipeptidyl Peptidase 4 Inhibitors

- Oral medications that inhibit the enzymatic inactivation of endogenous incretin hormones, resulting in glucose-dependent insulin release and a decrease in glucagon secretion.
- Modest glucose-lowering efficacy and a neutral effect on weight and are well tolerated with minimal risk of hypoglycemia.
- CVOTs have demonstrated the cardiovascular safety without cardiovascular risk reduction of four DPP-4i (saxagliptin, alogliptin, sitagliptin, and linagliptin)
- While generally well tolerated, an increased risk of HHF was found with saxagliptin, which is reflected in its label, and there have been rare reports of arthralgia and hypersensitivity reactions with the DPP-4i class

Sulfonylureas

- high glucose-lowering efficacy, but with a lack of durable effect, and the advantages of being inexpensive and accessible
- glucose-independent stimulation of insulin secretion, they are associated with an increased risk for hypoglycemia
- also associated with weight gain

Thiazolidinediones

- oral medications that increase insulin sensitivity and are of high glucose-lowering efficacy
- high durability of glycemic response, most likely through a potent effect on preserving β-cell function
- Beneficial effects on nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) have been seen with pioglitazone
- possible side effects of fluid retention and congestive HF , weight gain , and bone fracture
- Side effects can be mitigated by using lower doses and combining TZD therapy with other medications (SGLT2i and GLP-1 RA) that promote weight loss and sodium excretion

Insulin

- primary advantage of insulin therapy is that it lowers glucose in a dose-dependent manner and thus can address almost any level of blood glucose.
- However, its efficacy and safety are largely dependent on the education and support provided to facilitate self-management
- Careful consideration should be given to the pharmacokinetic and pharmacodynamic profiles of the available insulins as well as the matching of the dose and timing to an individual's physiological requirements.
- mimicking physiological insulin release patterns

Insulin

- Challenges of insulin therapy include weight gain, the need for education and titration for optimal efficacy, risk of hypoglycemia, the need for regular glucose monitoring, and cost. The approval of biosimilar insulins may improve accessibility at lower treatment costs.

- Comprehensive education on self-monitoring of blood glucose, diet, injection technique, self-titration of insulin, and prevention and adequate treatment of hypoglycemia are of utmost importance when initiating and intensifying insulin therapy

- Novel formulations and devices, including prefilled syringes, auto-injectors, and intranasal insufflators, are now available to administer glucagon in the setting of severe hypoglycemia and should be considered for those at risk

Combination GLP-1–Insulin Therapy

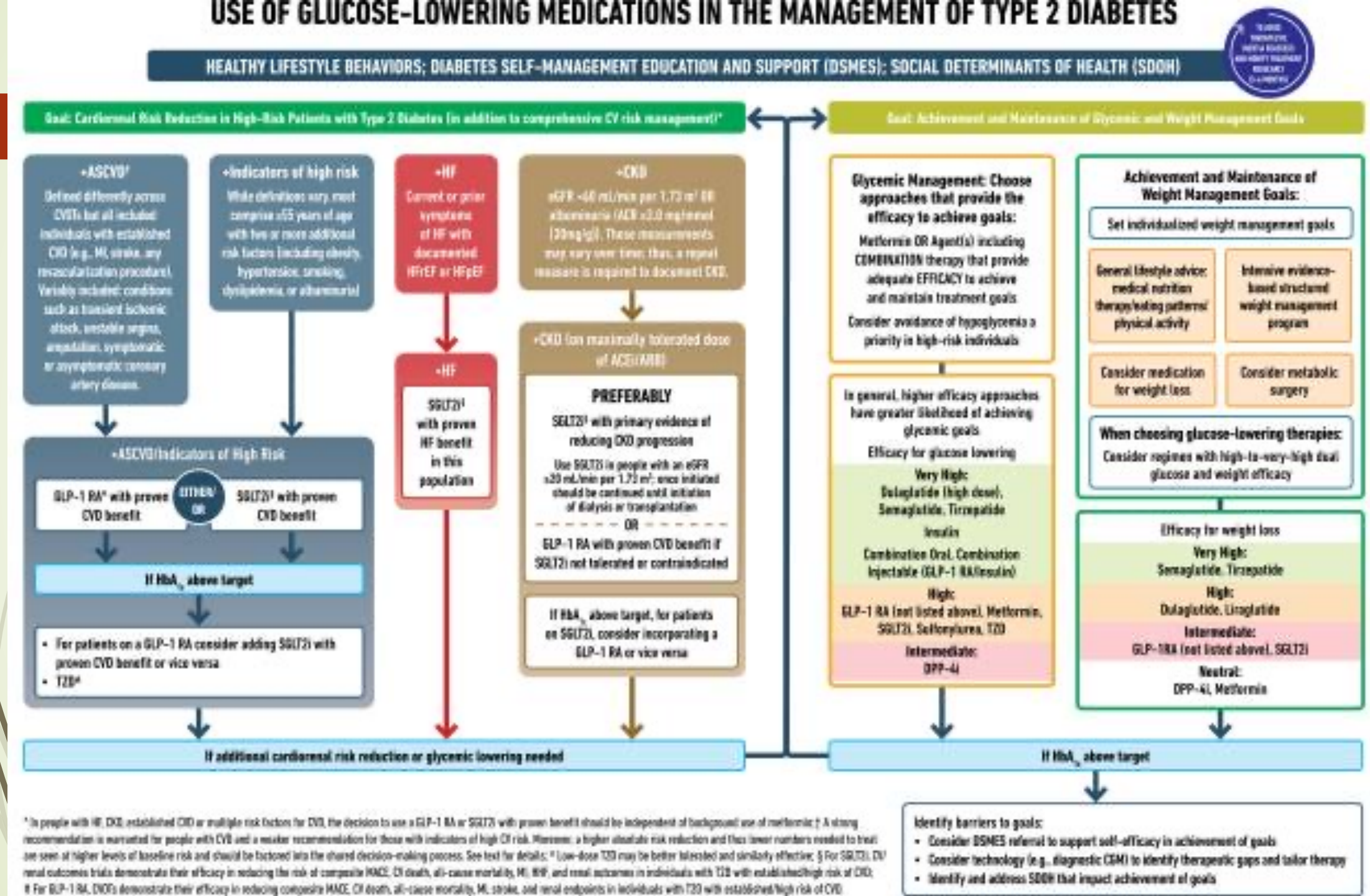
- Two fixed-ratio combinations of GLP-1 RA with basal insulin analogs are available:
  - insulin degludec plus liraglutide (IDegLira)
  - insulin glargine plus lixisenatide (iGlarLixi).
- Combination of basal insulin with GLP-1 RA results in greater glycemic lowering efficacy than the mono-components, with less weight gain and lower rates of hypoglycemia than with intensified insulin regimens, and better gastrointestinal tolerability than with GLP-1 RA alone

Less Commonly Used Glucose-Lowering Medications

- α-Glucosidase inhibitors improve glycemic control by reducing postprandial glycemic excursions and glycemic variability and may provide specific benefits in cultures and settings with high carbohydrate consumption or reactive hypoglycemia

- Other glucose-lowering medications (i.e., meglitinides, colesevelam, quick-release bromocriptine, and pramlintide) are not commonly used in the U.S., and most are not licensed in Europe

- The overall goal of the management of type 2 diabetes is to maintain quality of life and avoid complications.
- The management approach must be holistic and multifactorial and account for the lifelong nature of type 2 diabetes
- Holistic person-centered approach to T2DM management (Personalized Approach to Treatment Based on Individual Characteristics and Comorbidities)



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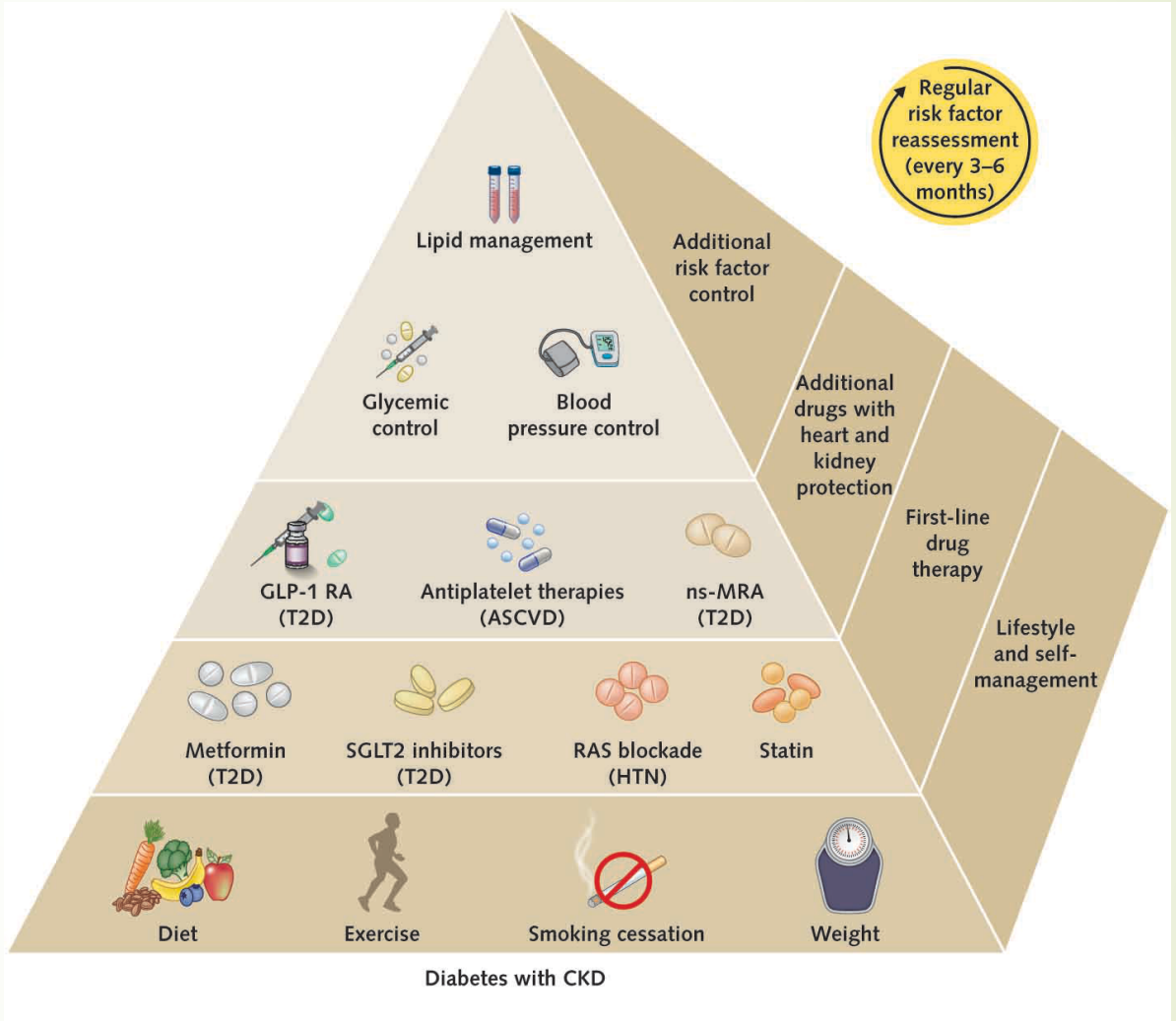
KIDGO 2022- Kidney disease global outcome



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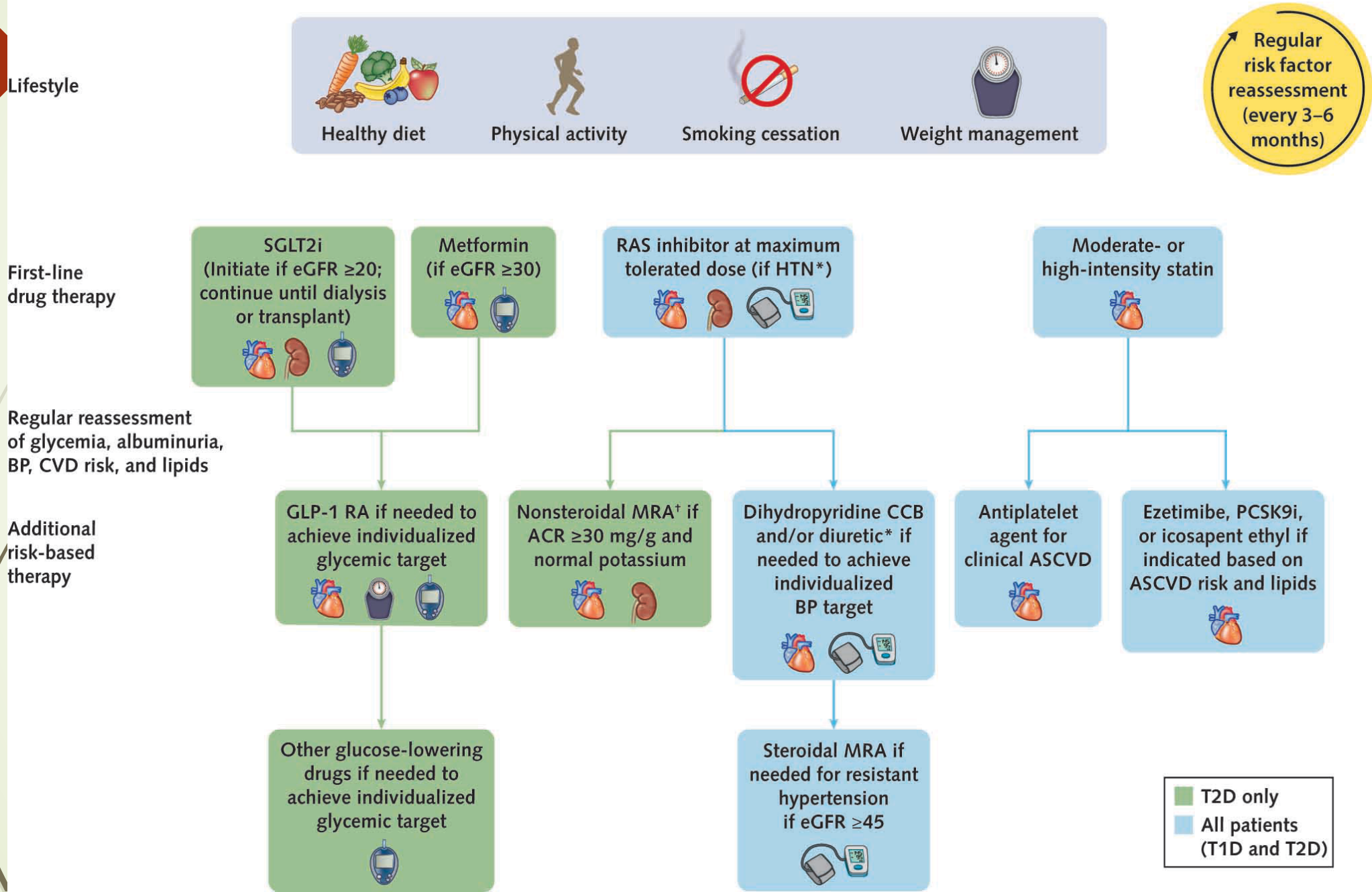

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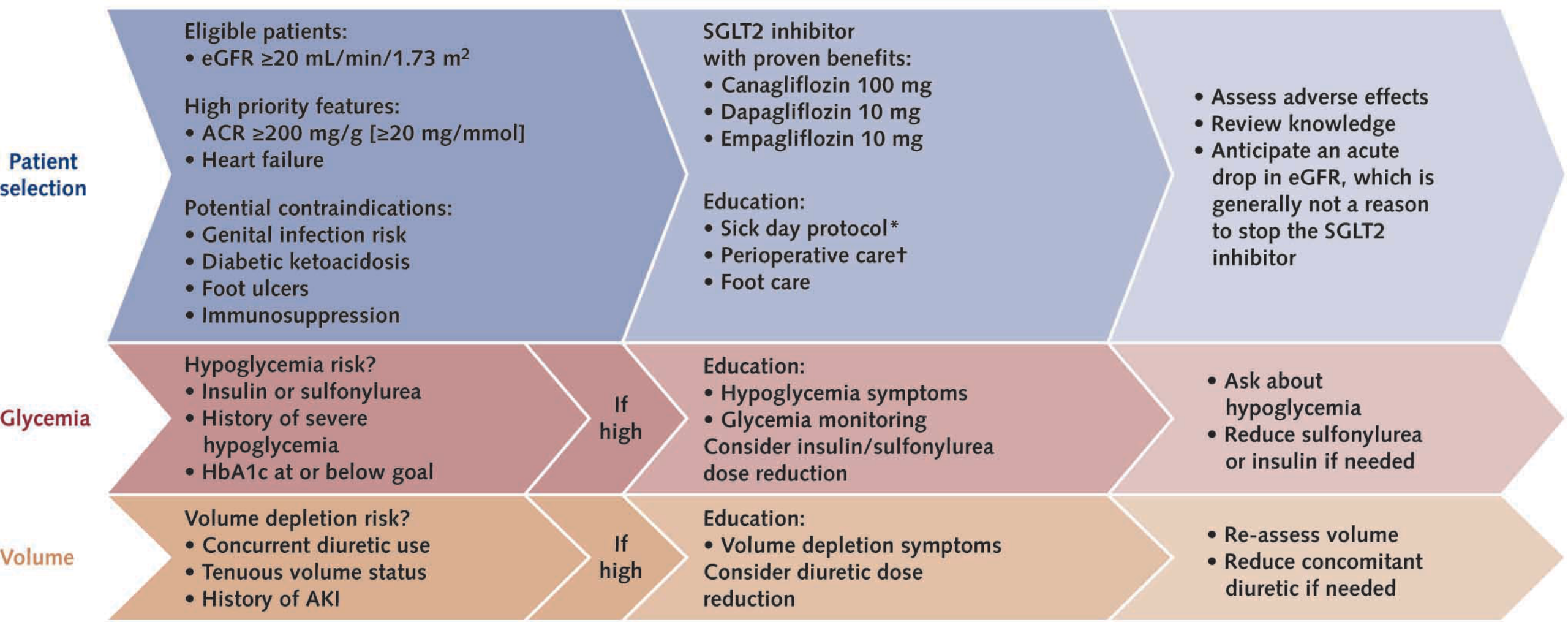
- Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker should be the first-line therapy for HTN when albuminuria is present;
- otherwise, dihydropyridine CCB or diuretic can also be considered
- All 3 classes are often needed to attain BP targets.

- Finerenone is currently the only nonsteroidal MRA with proven clinical kidney and cardiovascular benefits (eGFR >25, normal serum potassium and albuminuria >30mg/g despite a maximum tolerated dose of RAS inhibitor

Practical provider guide to initiating SGLT2 inhibitors in patients with type 2 diabetes and CKD



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- **Sick day protocol (for illness or excessive exercise or alcohol intake)**:
  - Temporarily withhold SGLT2 inhibitors; keep drinking and eating (if possible); check blood glucose and blood ketone levels more often; and seek medical help early, especially if patient has nausea and vomiting

- **Periprocedural/perioperative care**:
  - Inform patients about risk for diabetic ketoacidosis, especially in patients with long disease duration during acute illnesses due to relative insulin insufficiency and increased stress hormones
  - withhold SGLT2 inhibitors the day of day-stay procedures and limit fasting to minimum required
  - withhold SGLT2 inhibitors at least 2 d in advance and on the day of a procedure requiring ≥1 d in the hospital and/or bowel preparation (which may require increasing doses of other glucose-lowering drugs during that time)
  - restart SGLT2 inhibitor therapy after procedure only when patient is eating and drinking normally.

Consensus Recommendations

- All people with type 2 diabetes should be offered access to ongoing DSMES programs.
- Providers and health care systems should prioritize the delivery of person-centered care.
- Optimizing medication adherence should be specifically considered when selecting glucose-lowering medications.
- MNT focused on identifying healthy dietary habits that are feasible and sustainable is recommended in support of reaching metabolic and weight goals.
- Physical activity improves glycemic control and should be an essential component of type 2 diabetes management.
- Adults with type 2 diabetes should engage in physical activity regularly (>150 min/week of moderate- to vigorous-intensity aerobic activity) and be encouraged to reduce sedentary time and break up sitting time with frequent activity breaks.
- Aerobic activity should be supplemented with two to three resistance, flexibility, and/or balance training sessions/week. Balance training sessions are particularly encouraged for older individuals or those with limited mobility/poor physical function.

- Metabolic surgery should be considered as a treatment option in adults with type 2 diabetes who are appropriate surgical candidates with a BMI ≥40.0 kg/m^2 (BMI ≥37.5 kg/m^2 in people of Asian ancestry) or a BMI of 35.0–39.9 kg/m^2 (32.5–37.4 kg/m^2 in people of Asian ancestry) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods.

- In people with established CVD, a GLP-1 RA with proven benefit should be used to reduce MACE, or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes.

- In people with CKD and an eGFR ≥20 ml/min per 1.73 m^2 and a UACR >3.0 mg/mmol (>30 mg/g), an SGLT2i with proven benefit should be initiated to reduce MACE and HF and improve kidney outcomes. Indications and eGFR thresholds may vary by region. If such treatment is not tolerated or is contraindicated, a GLP-1 RA with proven cardiovascular outcome benefit could be considered to reduce MACE and should be continued until kidney replacement therapy is indicated.

- In people with HF, SGLT2i should be used because they improve HF and kidney outcomes
- In individuals without established CVD but with multiple cardiovascular risk factors (such as age ≥55 years, obesity, hypertension, smoking, dyslipidemia, or albuminuria), a GLP-1 RA with proven benefit could be used to reduce MACE, or an SGLT2i with proven benefit could be used to reduce MACE and HF and improve kidney outcomes.
- In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin.
- SGLT2i and GLP-1 RA reduce MACE, which is likely to be independent of baseline HbA_{1c}. In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or an SGLT2i with proven benefit should be independent of baseline HbA_{1c}.
- In general, selection of medications to improve cardiovascular and kidney outcomes should not differ for older people.
- In younger people with diabetes (<40 years), consider early combination therapy.
- In women with reproductive potential, counseling regarding contraception and taking care to avoid exposure to medications that may adversely affect a fetus are important.

Managing other co-morbidities and complications

- HTN
- HLD
- Cardiovascular disease
- CKD
- Neuropathy, falls, and lower extremity problems
- Eye complications
- Dental complications
- Obesity (Bariatric surgery)
- OSA
- NAFLD
- Pain management
- Mental health
- Smoking cessation