Treatment of Hyperglycemia in Type 2 Diabetes

- Upon diagnosis, **set a patient-specific A1C target**. **Implement comprehensive lifestyle modifications** with MNT, physical activity, weight loss if obese, smoking cessation, and psychologic support upon diagnosis and reinforce them at every visit.
- **Initiate metformin as first-line therapy in patients without contraindications or tolerability issues**. Start with a low dose and titrate to the maximum effective dose over time to improve tolerability.
- If the initial A1C is close to goal (eg, ≤7.5%) **consider initial treatment with lifestyle modifications alone** if the patient is motivated.

- Consider **starting two medications** (metformin plus a second agent) if the initial A1C is >**1.5% higher than the target A1C.**

- **Consider early introduction of basal insulin in patients with** very high A1C levels (>10%), symptoms of hyperglycemia, or evidence of catabolism (eg, weight loss).

- **See patients at least every 3 months if they are not meeting their goals and at least every 6 months if they are meeting goals.** At those times, check an A1C level, assess medication adherence, and reinforce lifestyle recommendations. **Add additional therapy if glucose targets have not been met.**

- For patients maximized on metformin therapy but with A1C levels above the target, add a **second-line antihyperglycemic agent**. The ADA Standards of Care identify six drug classes to consider:
- (1) DPP-4 inhibitors, (2) GLP1-RAs, (3) SGLT-2 inhibitors, (4) sulfonylureas, (5) TZDs, and (6) basal insulin.
- Patient-specific factors to consider in medication selection include the individualized A1C target and **presence of comorbidities** (eg, ASCVD, HF, CKD, obesity).

- **Established ASCVD or CKD**: SGLT-2 inhibitor (eg, empagliflozin) or GLP1-RA (eg, liraglutide) with proven CV benefit.
- **Established ASCVD and HF:** SGLT-2 inhibitor with proven benefit in reducing HF progression. Avoid TZDs in patients with HF.
- **CKD (with or without ASCVD):** SGLT-2 inhibitor with proven benefit in reducing CKD progression.
- **Need to minimize weight gain or promote weight loss in patients without ASCVD or CKD:** GLP1-RA or SGLT-2 inhibitor. If these agents cannot be used, use a weight-neutral medication such as a DPP-4 inhibitor. Avoid sulfonylureas, insulin, and TZDs due to weight gain.
- **Compelling need to minimize hypoglycemia**: DPP-4 inhibitor, GLP1-RA, SGLT-2 inhibitor, or TZD could be added to metformin.

- If the A1C target is not achieved after 3 months of dual therapy or if the patient did not tolerate the selected drug(s), **then triple therapy is warranted**, adding a drug from another class.
- Insulin is recommended for extreme (A1C >10%) or symptomatic hyperglycemia. Otherwise, **GLP-1 RAs are preferred over basal insulin** because they have equal or superior A1C lowering efficacy and lead to weight loss instead of weight gain with a low risk of hypoglycemia.

- **Basal insulin can be initiated** if additional glucose lowering is needed after the GLP-1 RA dose has been maximized.
- **If the A1C target is not reached by maximally titrating basal insulin**, PPG levels are likely elevated and **a GLP1-RA or SGLT-2 inhibitor should be considered** if the patient is not already taking one.
- **Prandial insulin is also an option**. Titrate the dose over time to achieve target PPG levels <180 mg/dL. **A second or third injection can be added** to the other meals if needed

Treatment of Hyperglycemia in Type 1 Diabetes

- **Intensive insulin regimens** can be given with either **multiple daily injections** (MDI) or use of **continuous subcutaneous insulin infusion** (CSII) via an **insulin pump.**
- A common MDI approach is one injection of long-acting insulin (eg, insulin glargine) for the basal component and three injections of rapid acting insulin (eg, insulin lispro) for the prandial component.
- **Insulin pump therapy or CSII infuses rapid-acting insulin to cover both the basal and prandial insulin needs** . The pump infuses a basal rate constantly throughout the day and allows **the patient to give bolus doses using a bolus dose calculator** based on current glucose levels, carbohydrate intake, and insulin on board.

What is an insulin pump_.mp4

- **The total daily insulin dose is divided to give 50% as basal insulin and 50% as prandial insulin (distributed across meals).** The insulin doses would then be adjusted based on SMBG data. Ideally, patients should learn to count carbohydrates so they can match their prandial insulin doses to their carbohydrate intake.

- **Pramlintide is indicated as adjunctive treatment** in patients with type 1 DM who are not achieving glycemic targets despite optimization of mealtime insulin.

- **Pramlintide may improve glycemic control and minimize weight gain caused by insulin**, but its use is limited by adverse effects such as nausea and vomiting, modest glucose improvements, increased injections and cost, and increased risk of hypoglycemia.

Common insulin regimens

- (A) Multiple-component insulin regimen consisting of **one injection of long-acting** insulin (detemir, glargine degludec) to provide basal glycemic coverage and **three injections of rapid-acting insulin** (aspart, lispro, glulisine) to provide glycemic coverage for each meal.
- (B) Insulin regimen consisting of **two injections of intermediate-acting insulin** (NPH) and rapid-acting insulin (aspart, lispro, glulisine), or short-acting regular insulin. Only one formulation of short-acting insulin is used.
- (C) **Insulin administration by insulin infusion device**. The basal insulin rate is decreased during the evening and increased slightly prior to the patient awakening in the morning. Rapid-acting insulin (aspart, lispro, or glulisine) is used in the insulin pump.

Hypoglycemia

- **Hypoglycemia is a common complication** of some diabetes medications and is associated with falls, injury, motor vehicle accidents, decreased quality of life, and increased risk of developing dementia, CV events, arrhythmias, and death.
- The severity of hypoglycemia is classified as follows:
- **Level 1** (hypoglycemia alert value; ≤70 mg/dL: May not cause symptoms but should be treated with a fast-acting carbohydrate and may need medication dose adjustment
- **Level 2** (clinically significant hypoglycemia; <54 mg/dL: Serious, clinically important hypoglycemia
- **Level 3** (severe hypoglycemia): Associated with cognitive impairment requiring external assistance for recovery and can be life threatening.

- **Initial autonomic symptoms include** tachycardia, palpitations, sweating, tremors, and hunger. **Neuroglycopenic symptoms** often occur with BG <60 mg/dL and can include cognitive impairment, confusion, behavioral changes, anger, irritability, blurred vision, headaches, seizures, and loss of consciousness.
- **hypoglycemia unawareness** increased risk for the serious sequelae associated with severe hypoglycemia.
- **SMBG and CGM can be useful in preventing hypoglycemia**. Patients must be educated to understand situations that increase risk of hypoglycemia (eg, delaying meals, during or after exercising, or fasting).
- **Treatment of hypoglycemia** requires ingestion of carbohydrates, preferably glucose. Patients should carry a source of fast-acting glucose with them at all times and use the **“rule of 15” f**or proper treatment:

- First use SMBG to confirm BG <70 mg/dL and then **ingest 15 g** of fast-acting carbohydrates such as 1/2 cup (4 oz or 125 mL) of milk, juice, or soda; 1 tablespoon of honey; hard candy; jelly beans; or glucose tablets.
- **Repeat SMBG in 15 minutes**; if the BG is <70 mg/dL, **repeat the process.**
- **Once the BG is normalized**, **eat a snack or meal that includes complex carbohydrates** and protein to prevent further hypoglycemic episodes.
- If the patient is **unconscious**, **give IV glucose or glucagon injection**.
- **1 mg (1 unit) IM/SC/IV** if no IV for dextrose
- Repeat q15min once or twice; give dextrose as soon as it is available and if no response

- **A glucagon kit should be prescribed and readily available to all patients on insulin who have a history of or high risk for severe hypoglycemia**. It can take 10–15 minutes before glucose levels start to rise, and patients often **vomit.**

How to Use a Glucagon Emergency Kit _ Cincinnati Children's.mp4

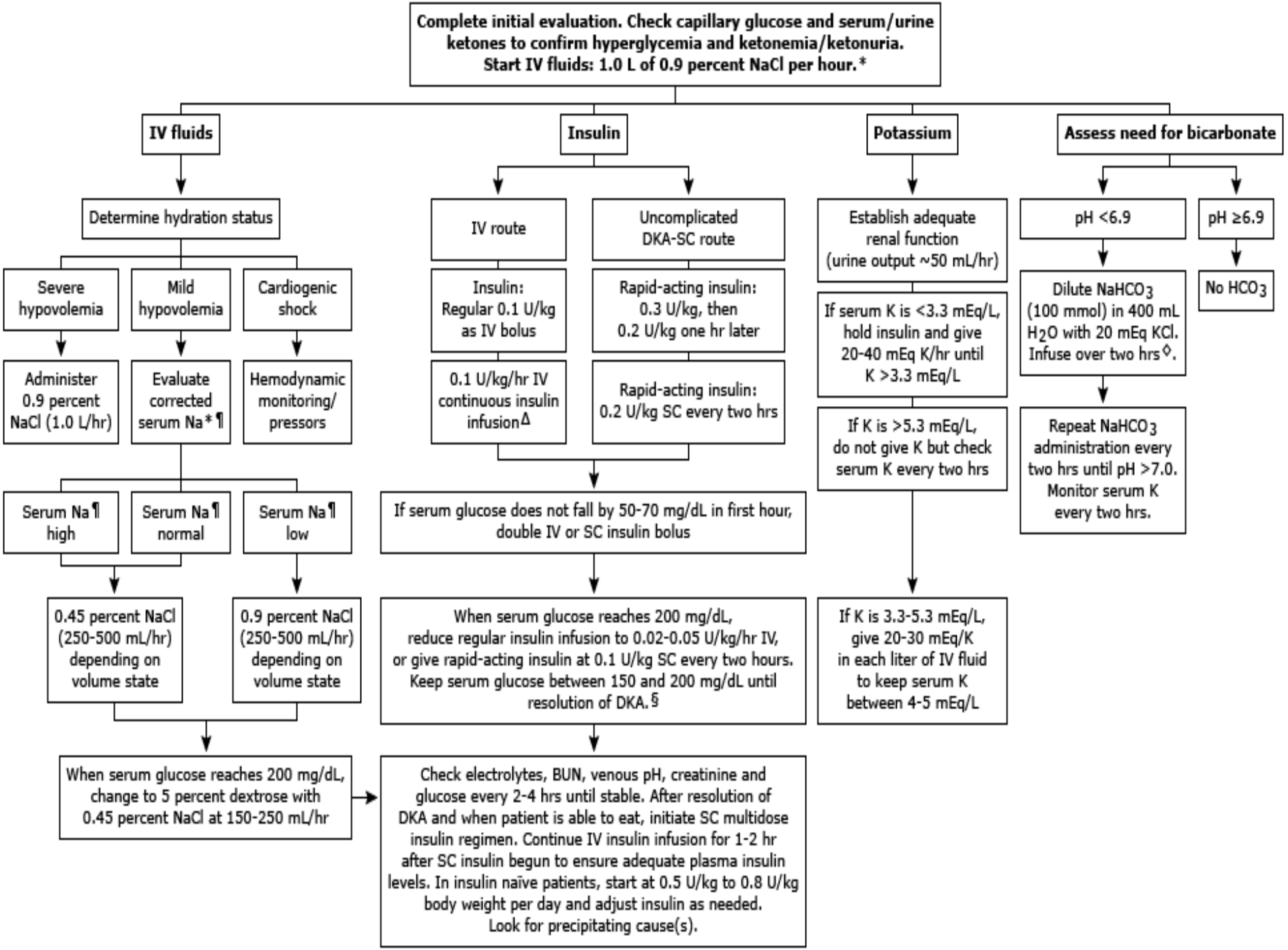
Diabetic Ketoacidosis (DKA)

- **In patients with type 1 DM, DKA is usually precipitated by** omitting insulin, infection, or acute illness with resultant increases in cortisol, catecholamines, glucagon, and growth hormone.
- Patients may be alert, stuporous, or comatose at presentation. Diagnostic laboratory values include **hyperglycemia, anion gap acidosis, and large ketonemia or ketonuria**.

- Patients have **fluid deficits** of several liters and significant sodium and potassium deficits. Treatment requires **restoration of intravascular volume** with normal saline followed by hypotonic saline to replace free water, **potassium supplements**, and **insulin**

- Constant infusion of a fixed insulin dose and administration of IV glucose when the BG level decreases to <250 mg/dL are preferred over titrating the insulin infusion based on the glucose level.
- **Rapid correction of the glucose** (a decrease >75–100 mg/dL/hr) **is not recommended** because it has been associated with cerebral edema, especially in children. Continue the insulin infusion until the urine ketones clear and the anion gap closes

- Give **long-acting insulin 1–3 hours before discontinuing the insulin infusion**. Perform hourly bedside monitoring of glucose and frequent monitoring of potassium (every 2–4 hours).
- **Treatment with bicarbonate** to correct the acidosis **is generally not needed and may be harmful.**
- It is essential to **correct the underlying situation or medical condition** that precipitated DKA. Metabolic improvement is manifested by an increase in serum bicarbonate and pH.


Complete initial evaluation. Check capillary glucose and serum/urine ketones to confirm hyperglycemia and ketonemia/ketonuria.
Start IV fluids: 1.0 L of 0.9 percent NaCl per hour.*
IV fluids
Insulin
Potassium
Assess need for bicarbonate
Determine hydration status
Severe hypovolemia
Mild hypovolemia
Cardiogenic shock
Administer 0.9 percent NaCl (1.0 L/hr)
Evaluate corrected serum Na*¶
Hemodynamic monitoring/ pressors
Serum Na¶ high
Serum Na¶ normal
Serum Na¶ low
0.45 percent NaCl (250-500 mL/hr) depending on volume state
0.9 percent NaCl (250-500 mL/hr) depending on volume state
When serum glucose reaches 200 mg/dL, change to 5 percent dextrose with 0.45 percent NaCl at 150-250 mL/hr
IV route
Uncomplicated DKA-SC route
Insulin: Regular 0.1 U/kg as IV bolus
Rapid-acting insulin: 0.3 U/kg, then 0.2 U/kg one hr later
0.1 U/kg/hr IV continuous insulin infusionΔ
Rapid-acting insulin: 0.2 U/kg SC every two hrs
If serum glucose does not fall by 50-70 mg/dL in first hour, double IV or SC insulin bolus
When serum glucose reaches 200 mg/dL, reduce regular insulin infusion to 0.02-0.05 U/kg/hr IV, or give rapid-acting insulin at 0.1 U/kg SC every two hours. Keep serum glucose between 150 and 200 mg/dL until resolution of DKA.§
Check electrolytes, BUN, venous pH, creatinine and glucose every 2-4 hrs until stable. After resolution of DKA and when patient is able to eat, initiate SC multidose insulin regimen. Continue IV insulin infusion for 1-2 hr after SC insulin begun to ensure adequate plasma insulin levels. In insulin naïve patients, start at 0.5 U/kg to 0.8 U/kg body weight per day and adjust insulin as needed. Look for precipitating cause(s).
Establish adequate renal function (urine output ~50 mL/hr)
If serum K is <3.3 mEq/L, hold insulin and give 20-40 mEq K/hr until K >3.3 mEq/L
If K is >5.3 mEq/L, do not give K but check serum K every two hrs
If K is 3.3-5.3 mEq/L, give 20-30 mEq/K in each liter of IV fluid to keep serum K between 4-5 mEq/L
pH <6.9
pH ≥6.9
Dilute NaHCO3 (100 mmol) in 400 mL H2O with 20 mEq KCl. Infuse over two hrs◊.
No HCO3
Repeat NaHCO3 administration every two hrs until pH >7.0. Monitor serum K every two hrs.

Hyperosmolar Hyperglycemic State (HHS)

- ❖ HHS is a **potentially life-threatening acute complication** of diabetes associated with very high glucose concentrations, typically >400 mg/dL.
- It usually occurs in **older patients with type 2 DM or** in younger patients with prolonged hyperglycemia and dehydration or significant renal insufficiency.
- The **patient presentation is similar to DKA**, but HHS patients usually **have much higher BG, elevated serum osmolality, and little to no ketonuria or ketonemia.**
- HHS typically evolves over several days to weeks, whereas DKA evolves much faster.

- Large ketonemia is not usually seen because residual insulin secretion suppresses lipolysis. Infection or another medical illness is the usual precipitant.
- **Fluid deficits are often greater** and **BG levels higher** (sometimes >1000 mg/dl) in patients with HHS than in patients with DKA.
- **BG should be lowered very gradually** with hypotonic fluids and low-dose insulin infusions (1–2 units/hr)

Macrovascular Complications

- Macrovascular complications (eg, CHD, stroke) **are the leading causes of death in people with diabetes.**
- The ADA recommends **low-dose aspirin therapy** (75–162 mg daily) **in all patients with established ASCVD.** Clopidogrel may be used in patients allergic to aspirin.
- The role of antiplatelet therapy for primary CV prevention is unclear because the benefits may be offset by a higher risk of bleeding; **some practice guidelines recommend aspirin if the 10-year risk of a CV event is >20%.**
- n patients with **established ASCVD**, use of a **GLP1-RA or an SGLT-2 inhibitor should be strongly considered.**
- For all patients whose **BP exceeds 120/80 mm Hg,** the ADA recommends dietary changes, physical activity, and weight loss in overweight or obese patients.

- Drug therapy using agents proven to reduce CV events should be started **for BP >140/90 mm Hg.** A combination of **two medications should be used for BP >160/100 mm Hg**.
- Initiate **high-intensity statin** therapy in all patients with diabetes and preexisting ASCVD regardless of baseline lipid levels. In the absence of ASCVD, prescribe a **moderate-intensity statin t**o all patients with type 1 or type 2 DM over the age of 40.

- In patients <40 years of age, a **moderate intensity statin** may be appropriate for patients with multiple CV risk factors.
- A **fibrate** (eg, fenofibrate), **omega-3 fatty acid**, or **niacin** can be added for patients with marked **hypertriglyceridemia**.
- **Peripheral arterial disease** can lead to claudication, nonhealing foot ulcers, and limb amputation.
- Smoking cessation, statin therapy, good glycemic control, and antiplatelet therapy are important strategies.
- **Cilostazol** may be useful in select patients to reduce symptoms.
- **Revascularization** surgery can be considered in some situations.

Microvascular Complications

Nephropathy:

- **Albuminuria is a marker of renal damage**
- Screening **with type 1 DM** should begin with puberty **and after 5-years'** disease duration.
- **BP control is important for preventing and slowing progression of nephropathy**. ACE inhibitors and ARBs can slow the progression of renal disease in patients with diabetes.
- **Diuretics** are often necessary due to volume expanded states and are recommended **second-line therapy**.
- The ADA recommends a **BP goal <140/90 mm Hg in patients with nephropathy** but a **lower target** (eg, <130/80 mm Hg) **if it can be achieved without undue burden or side effects**. **Three or more antihypertensives are often needed to reach goal BP.**

Retinopathy:

- Patients with diabetes should have **routine dilated eye examinations to fully evaluate the retina.**
- **Early background retinopathy may reverse with improved glycemic control and optimal BP control**.
- **Laser photocoagulation** has markedly improved sight preservation.
- **Intravitreal antivascular endothelial growth factor (VEGF) therapy** is also highly effective for sight preservation.
- **Bevacizumab** (used off-label) and **ranibizumab** are **anti-VEGF monoclonal antibodies**, and **aflibercept** is a VEGF **decoy receptor**

Neuropathy:

- **Peripheral neuropathy** is the most common complication in patients with type 2 DM.
- **Paresthesias, numbness**, or **pain** are **the predominant symptoms**. The feet are involved (diabetic foot)far more often than the hands.
- **Improved glycemic control is the primary treatment and may alleviate some symptoms.** Pharmacologic therapy is symptomatic and includes low-**dose tricyclic antidepressants** (nortriptyline or desipramine), **duloxetine**, **gabapentin**, **pregabalin**, **venlafaxine**, **topical capsaicin**, and **tramadol**.
- **Gastroparesis** can be severe and debilitating. Improved glycemic control, discontinuation of medications that slow gastric motility, and use of **metoclopramide** or **low-dose erythromycin** may be helpful.

- **Diabetic diarrhea** is often **nocturnal** and frequently responds to a 10- to 14-day course of an antibiotic such as **doxycycline** or **metronidazole**. **Octreotide** may be useful in unresponsive cases.
- **Orthostatic hypotension** may require mineralocorticoids (eg, **fludrocortisone**) or adrenergic agonists (**midodrine**).
- **Erectile dysfunction** is common, and initial therapy should include a trial of an oral phosphodiesterase-5 inhibitor (eg, **sildenafil**, **vardenafil**, or **tadalafil**).

Evaluation of therapeutic outcomes

- **Measure A1C every 3–6 months to follow long-term glycemic control for the previous 2–3 months**.
- **SMBG provides an opportunity to adjust** medications, food intake, or physical activity and enables patients to detect hypoglycemia.
- For patients with type 1 DM, **SMBG is typically performed 4–6 times per day**—prior to food intake and physical activity and at bedtime.
- The optimal **frequency of SMBG in patients with type 2 DM on oral agents is controversial**.
- **At each visit**, ask patients with type 1 DM **about the frequency and severity of hypoglycemia**.

- -Screen for **eye exams** in type 2 DM and an initial exam in the first 5 years in type 1 DM, then yearly.
- Assess **BP at each visit**.
- **Examine the feet at each visit**. Screen for pedal sensory loss annually.
- **Screen for albuminuria**. At least once a year, assess urinary albumin (urine albumin-to-creatinine ratio) and eGFR in all patients with type 2 DM and in patients with type 1 DM for at least 5 years.
- **Check fasting lipid panel annually** if the patient is on lipid-lowering therapy.
- Administer an **annual influenza vaccine** and assess for administration of the **pneumococcal vaccine and hepatitis B vaccine** series along with management of other CV risk factors (eg, smoking).