Treatment Algorithms and Recommendations for CVD Risk Management, Microvascular Complications and Foot Care and the Pharmacologic Approach to Glycemic Treatment

Treatment Algorithm for Cardiovascular Disease and Risk Management

Purpose of Algorithm

There is no greater cause of morbidity and mortality in patients with diabetes than atherosclerotic cardiovascular disease (ASCVD). Diabetes is a risk factor for ASCVD as are medical conditions that are common among individuals with type 2 diabetes (T2D). Multiple studies have demonstrated that significant benefits result from controlling cardiovascular (CV) risk factors in this patient population.

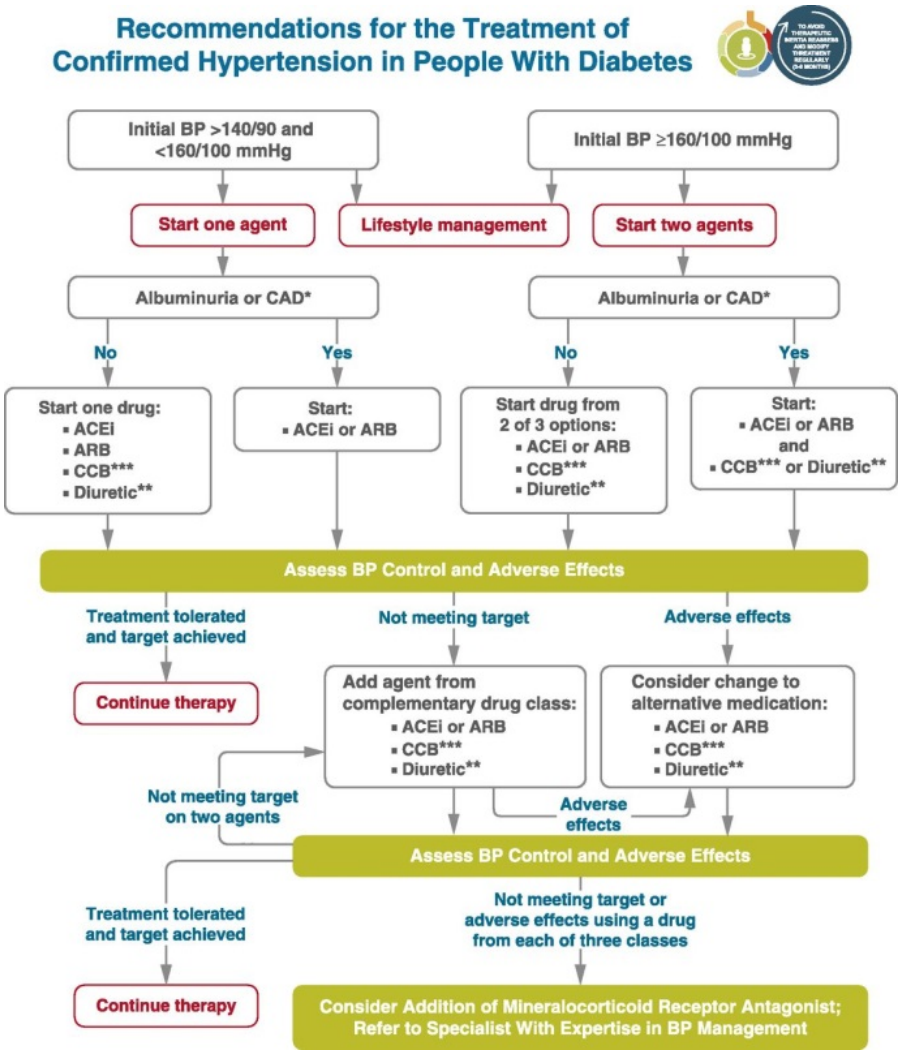

Figure 1: Recommendations for the treatment of confirmed hypertension in people with diabetes. *An ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) is suggested to treat hypertension for patients with coronary artery disease (CAD) or urine albumin-to-creatinine ratio 30–299 mg/g creatinine 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.

Key Recommendations for Patients with T2D

- Sodium-glucose cotransporter 2 inhibitor with a demonstrated CV benefit if ASCVD is established and they have multiple ASCVD risk factors or diabetic kidney disease
- Glucagon-like peptide 1 receptor agonist with demonstrated CV benefit if ASCVD is established or if they have multiple risk factors for ASCVD
- ACE inhibitor or angiotensin receptor blocker if ASCVD is established, especially coronary artery disease (CAD)

Treatment Algorithm for Microvascular Complications and Foot Care

Purpose of Algorithm

Common microvascular complications in patients with T2D include chronic kidney disease (CKD), diabetic retinopathy, neuropathy, foot ulcers and amputation. CKD attributed to diabetes develops in 20-40% of patients, and it can progress to end-stage renal disease. Diabetic retinopathy is the leading cause of blindness in adults living in developed countries. Diabetic neuropathies have a variety of manifestations while foot ulcers and amputations are major causes of morbidity and mortality.

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73m²) Description and range	G1	Normal to high	≥90	1 If CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 If CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

Figure 2: Risk of chronic kidney disease (CKD) progression, frequency of visits and referral to nephrology according to glomerular filtration rate (GFR) and albuminuria. The GFR and albuminuria grid depicts the risk of progression, morbidity and mortality by color, from best to worst (green, yellow, orange, red, dark red). The numbers in the boxes are a guide to the frequency of visits (number of times per year). Green can reflect CKD with normal eGFR and albumin-to-creatinine ratio only in the presence of other markers of kidney damage, such as imaging showing polycystic kidney disease or kidney biopsy abnormalities, with follow-up measurements annually; yellow requires caution and measurements at least once per year; orange requires measurements twice per year; red requires measurements three times per year; and dark red requires measurements four times per year. These are general parameters only, based on expert opinion and underlying comorbid conditions and disease state as well as the likelihood of impacting a change in management for any individual patient must be taken into account. "Refer" indicates that nephrology services are recommended. *Referring clinicians may wish to discuss with their nephrology service, depending on local arrangements regarding treating or referring.

Key Recommendations for Patients with T2D

- Consider sodium–glucose cotransporter 2 inhibitor in patients with established chronic kidney disease (CKD)
  - If estimated GFR ≥ 30 mL/min/1.73 m^2 and urinary albumin > 300 mg/g creatinine
  - For CV risk reduction when estimated GFR ≥ 30 mL/min/1.73 m^2 and urinary albumin creatinine > 300 mg/g
- Glucagon-like peptide 1 receptor agonist in patients with CKD who have an increased risk for CV events
- Continue reninangiotensin system blockade if
  - Serum creatinine increase is minor (<30%).
  - There is no volume depletion.
- ACE inhibitor or angiotensin receptor blocker in non-pregnant patients with hypertension and
  - Moderately elevated urinary albumin-to-creatinine ratio (30–299 mg/g creatinine)
  - Urinary albumin-to-creatinine ratio ≥ 300mg/g creatinine and/or estimated GFR < 60 mL/min/1.73 m^2 (strong recommendation)

Treatment Algorithm for the Pharmacologic Approach to Glycemic Treatment

Purpose of Algorithm

A patient-centered approach is recommended when selecting pharmacological therapy to manage blood glucose. Key factors to identify include comorbidities, risk for hypoglycemia, impact on body weight, adverse events, cost and preferences of the patient.

	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	HF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30 mL/min/1.73 m²	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin, dapagliflozin‡	High	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin	▪ Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	▪ **FDA Black Box:** Risk of amputation (**canagliflozin**) ▪ Risk of bone fractures (canagliflozin) ▪ DKA risk (all agents, rare in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol ▪ Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide Benefit: See label indication of reducing CVD events	Neutral	High	SQ; oral (semaglutide)	Benefit: liraglutide	▪ Renal dose adjustment required (exenatide, lixisenatide) ▪ Caution when initiating or increasing dose due to potential risk of acute kidney injury	▪ **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) ▪ Gastrointestinal side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ ?Acute pancreatitis risk
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	▪ Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment ▪ No dose adjustment required for linagliptin	▪ Potential risk of acute pancreatitis ▪ Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure [**pioglitazone, rosiglitazone**] ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin Human insulin	Highest	Yes	Gain	Neutral	Neutral	Low	SQ; inhaled	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin Analogs						High	SQ			

Figure 3: SCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVOT, cardiovascular outcomes trial; DPP-4, dipeptidyl peptidase 4; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; HF, heart failure; NASH, nonalcoholic steatohepatitis; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2D, type 2 diabetes. *For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information. †FDA-approved for cardiovascular disease benefit. ‡FDA-approved for heart failure indication. §FDA-approved for chronic kidney disease indication.

Key Recommendations for Patients with T2D

- Metformin is the preferred first drug of choice and should be continued as long as tolerated.
- Combination therapy can be considered as an initial therapy in some patients.
- Consider insulin treatment early in cases of ongoing catabolism, hyperglycemia symptoms, A1C levels >10% [86 mmol/mol] or blood glucose levels ≥300mg/dL [16.7mmol/L]).
- Glucagon-like peptide 1 receptor agonists are preferred over insulin.

References

1. American Diabetes Association. 10. Cardiovascular Disease and Risk Management: *Standards of Medical Care in Diabetes-2021*. Diabetes Care. 2021 Jan;44(Suppl 1):S125-S150. doi: 10.2337/dc21-S010. Erratum in: Diabetes Care. 2021 Jun 16;: PMID: 33298421.
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3. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes-2021*. Diabetes Care. 2021 Jan;44(Suppl 1):S111-S124. doi: 10.2337/dc21-S009. PMID: 33298420.