

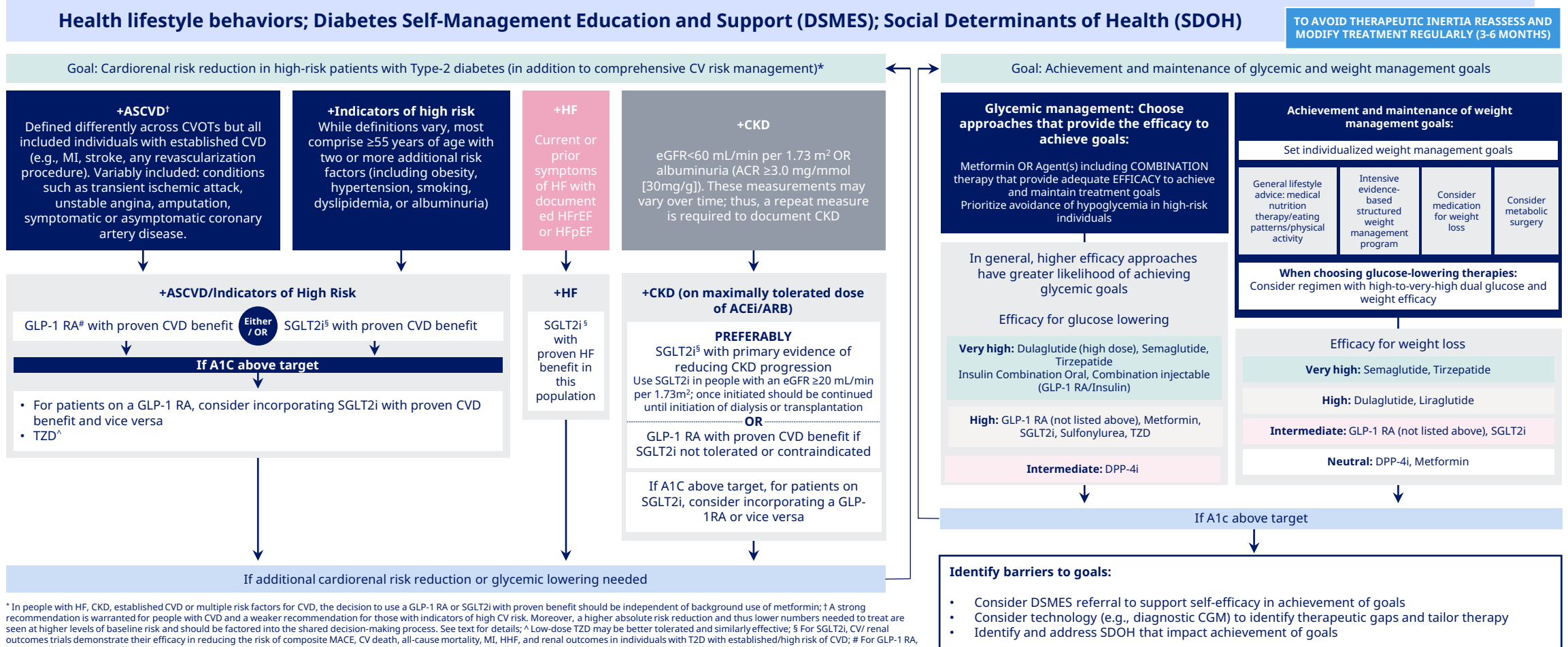
Guideline Directed Management of Diabetes Comorbidities



August 2024

ADA STANDARDS OF MEDICAL CARE IN DIABETES – 2024

2024 ADA: Use of Glucose-lowering medications in the management of T2D (Figure 9.3; S166)



* 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; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HFrEF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD

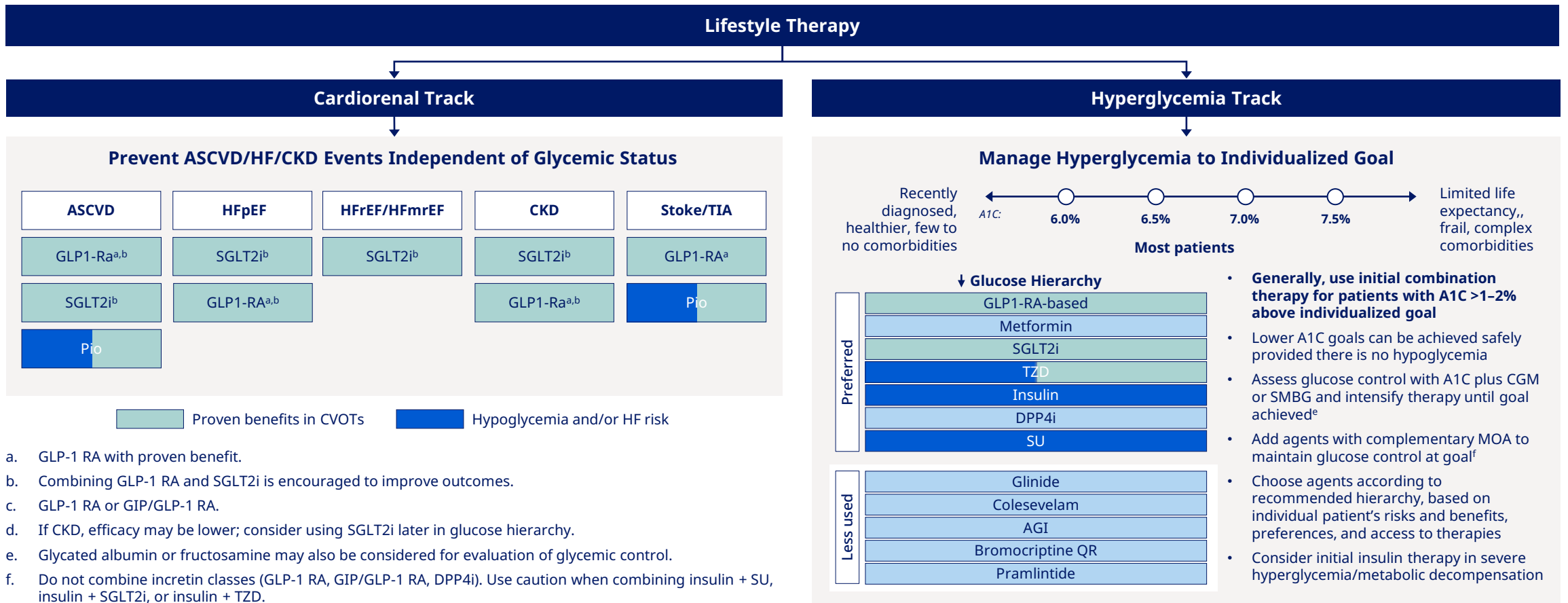
A1C, glycated hemoglobin; ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TZD, thiazolidinedione.

Adapted from Davies et al. (84).

American Diabetes Association (ADA). Diabetes Care 2024;47(Supplement_1):S158-S178

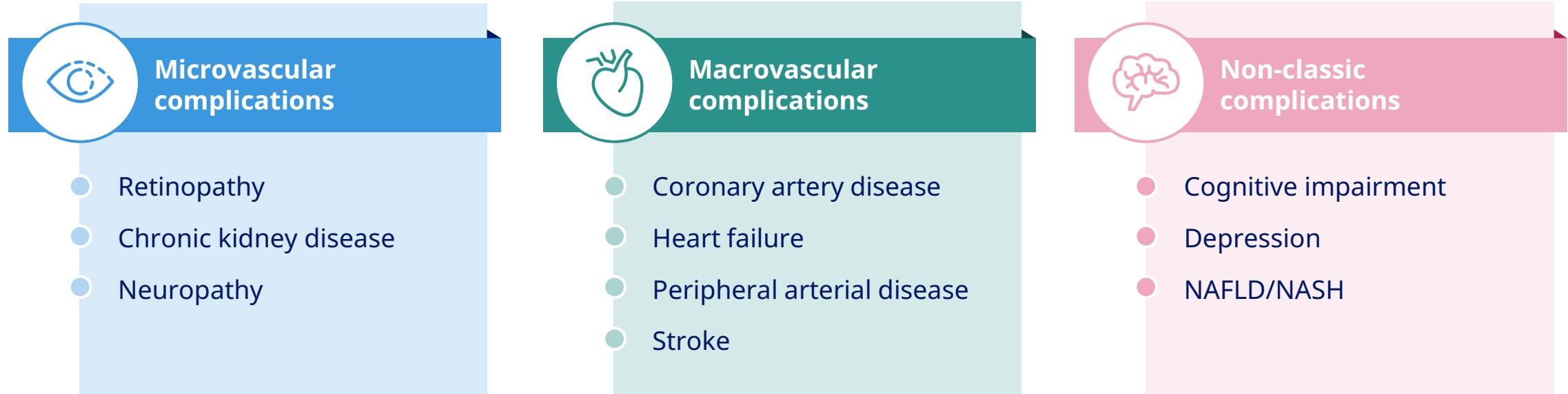
DCRM 2.0 MULTISPECIALTY PRACTICE RECOMMENDATIONS

Antihyperglycemic therapy in Type 2 Diabetes



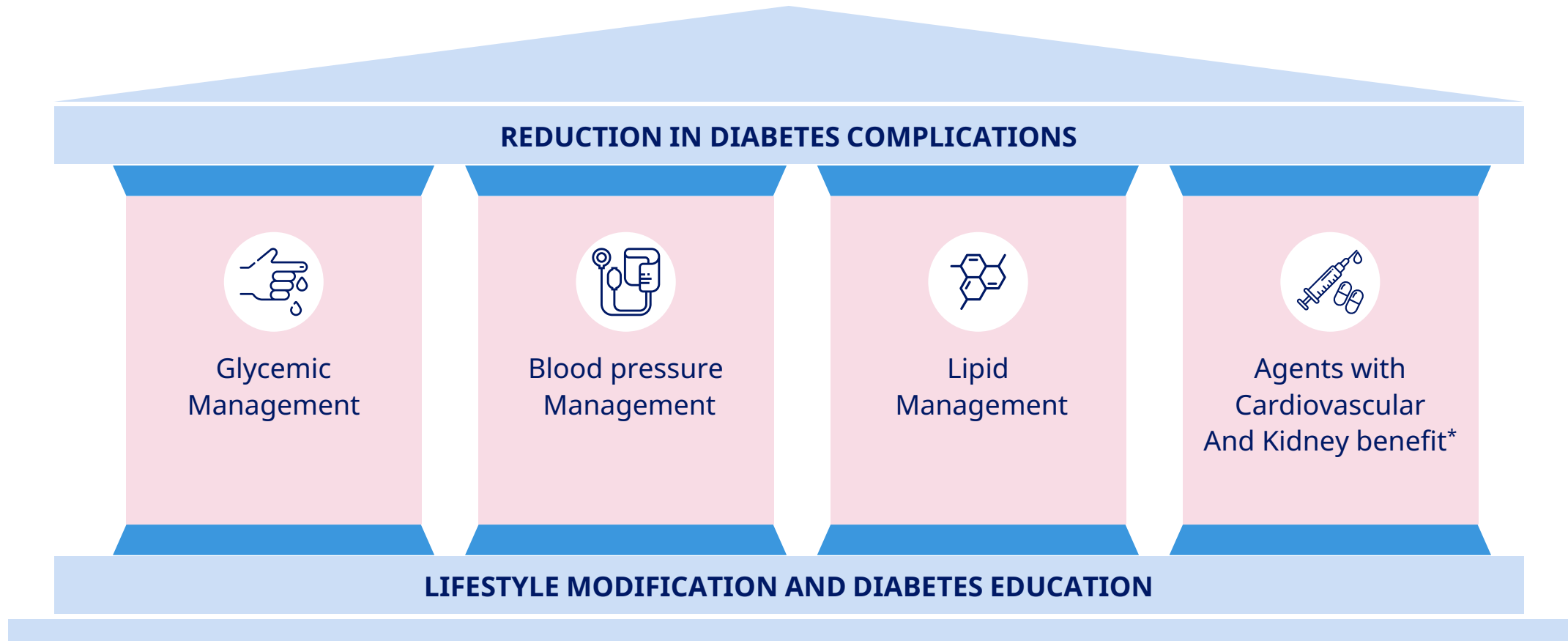
ADA STANDARDS OF MEDICAL CARE IN DIABETES – 2024: T2D AND ITS COMPLICATIONS

Diabetes-related complications affect multiple organs



ADA STANDARDS OF MEDICAL CARE IN DIABETES – 2024

2024 ADA: Multifactorial approach to reduction in risk of diabetes complications (Figure 10.1; S180)



*Risk reduction interventions to be applied as individually appropriate
American Diabetes Association (ADA). Diabetes Care 2024;47(Supplement_1):S179–S218

AHA/ACC TREATMENT GUIDELINES

Recommendations for prevention and treatment of ASCVD

	Primary prevention	Secondary prevention
Treatment goals ^{1,2,5}	Lifestyle/smoking interventions SBP <130 mmHg DBP <80 mmHg) + LDL-C: No specific guidance [†]	Lifestyle/smoking interventions SBP <130 mmHg DBP <80 mmHg) + LDL-C: ≥50% reduction from baseline ≥1.8 mmol/L (≥ 70 mg/dL) [†]
	Intensify treatment based on CV risk and other patient factors	Intensify treatment based on CV risk and other patient factors Use SGLT2 inhibitor or GLP-1 RA with proven CV benefit in patients with CCD and T2D and SGLT2 inhibitor in patients with CCD and HF
Lifestyle/smoking interventions ^{1,2,5}	 Physical activity  Diet & alcohol consumption	 Body weight/composition  Smoking Cessation
Lipid-lowering agents ^{1,2,5}	Initiate/intensify statin	② Add ezetimibe ③ Add PCSK9i Bempedoic acid or inclisiran may be added in place of PCSK9i
Anti-hypertensive agents ^{3,5}	① First-line agents include beta-blockers, thiazide diuretics, calcium channel blockers, and ACE inhibitors or ARBs	② Intensification: Combination therapy and/or MRA to optimize BP control
Anti-thrombotic agents ^{1,4,5}	Low-dose aspirin (75–100 mg daily) in select adults (40–70 years); not routinely administered in adults >70 years	Aspirin in patients with CAD → DAPT to intensify* in patients ≤1 y post-ACS or stable IHD >1 y post-PCI Initiate proton pump inhibitor [‡]

[†] Specific recommendations are depending on risk factors; [‡] Both for patients with clinical ASCVD and very high-risk ASCVD with multiple risk factors; * Intensification of antithrombotic therapy should always account for individual patient bleeding risk;

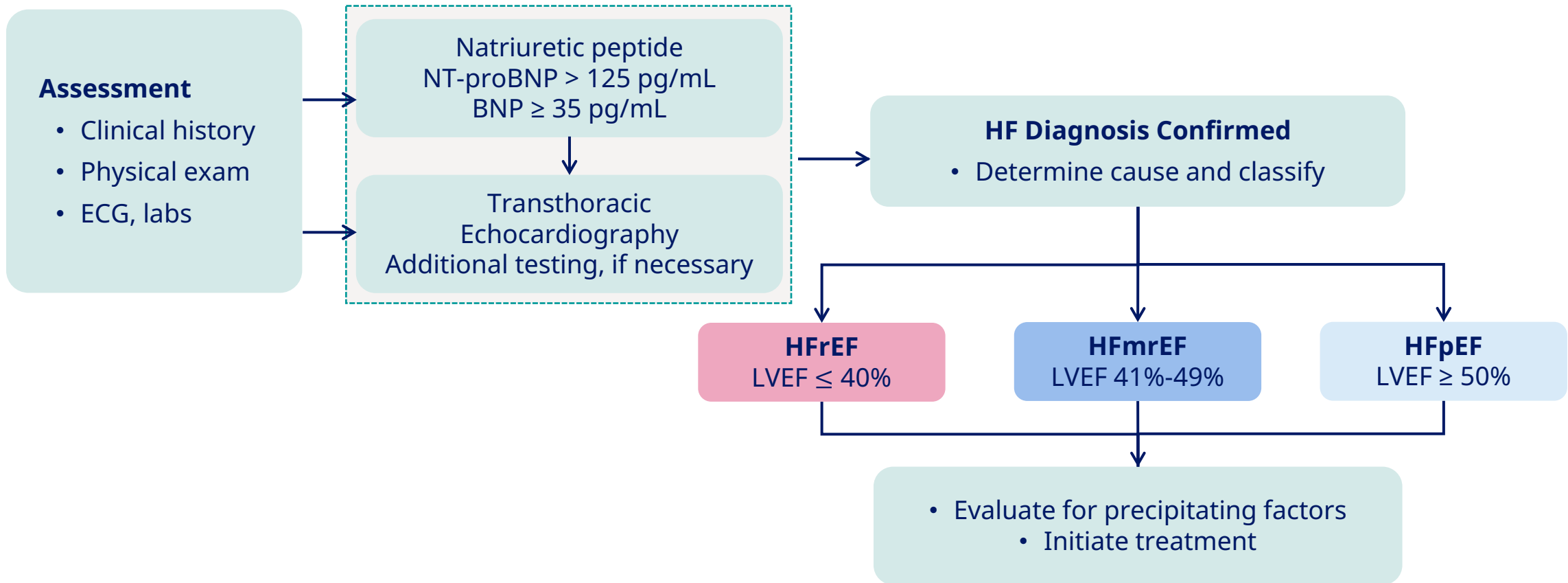
[‡] In patients with history/ currently increased risk of gastrointestinal bleeding.

ACC/AHA, American college of Cardiology/ American heart association; ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; DBP, diastolic blood pressure; CAD, coronary artery disease; CCD, chronic coronary disease; CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; IHD, ischemic heart disease; LDL-C, low-density lipoprotein cholesterol; MRA, mineralocorticoid receptor antagonists; PCI, percutaneous coronary intervention; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes

1. Arnett DK et al. Circulation 2019;140:e596–e646; 2. Grundy SM et al. Circulation. 2019;139:e1046–e1081; 3. Whelton PK et al. Hypertension 2018;71:e13–e115; 4. Levine GN et al. J Am Coll Cardiol 2016;68:1082–1115; 5. Virani SS et al. J Am Coll Cardiol. 2023;S0735-1097(23)05281-6

2022 AHA/ACC/HFSA GUIDELINE

Diagnostic Algorithm for HF and EF-Based Classification



DCRM 2.0 MULTISPECIALTY PRACTICE RECOMMENDATIONS

Heart Failure Prevention and Management

Initial and Longitudinal Clinical Assessment
Serially assess for signs or symptoms of congestion/volume overload or inadequate perfusion

Prevention of Heart Failure

General Recommendations	
All	• Lifestyle intervention (low-salt diet, smoking cessation, physical activity, maintaining healthy weight) • BP control; target SBP <130 mm Hg • ASCVD interventions as indicated
T2D	Natriuretic peptide screening followed by team-based care, including cardiology referral, can be useful in preventing HF
High HF risk	
Medication Recommendations	
T2D + high CV risk or established CVD	SGLT2i
CKD with or without T2D	SGLT2i
T2D + CKD	Nonsteroidal MRA

- a. ARNI preferred over ACE or ARB.
- b. Steroidal MRA.
- c. Select agent with proven benefits; recommended to improve symptoms and physical limitations
- d. If T2D + CKD, consider nonsteroidal MRA.

Strongly recommended

Reasonable to use

May be considered

Treatment of Heart Failure

Heart failure defined as:

- Signs and/or symptoms of HF caused by structural/functional cardiac abnormality
- plus-
- Elevated natriuretic peptides or objective evidence of congestion (e.g. echocardiograph evidence, right heart catheterization)

HFrEF
(EF ≤40%)

Diuretic (if congested) + quadruple therapy

ARNI (or ACEi/ARB) + β-blocker + SGLTi + MRA^b

Follow HF guidelines for device and Class II therapy recommendations

HFmrEF
(EF=41-49%)

Diuretic (if congested) + SGLTi + Consider additional therapies

GLP-1 RA^c (if BMI ≥30 kg/m² and EF ≥45%) + ARNI or ACEi or ARB^a + β-blocker + MRA^{b,d}

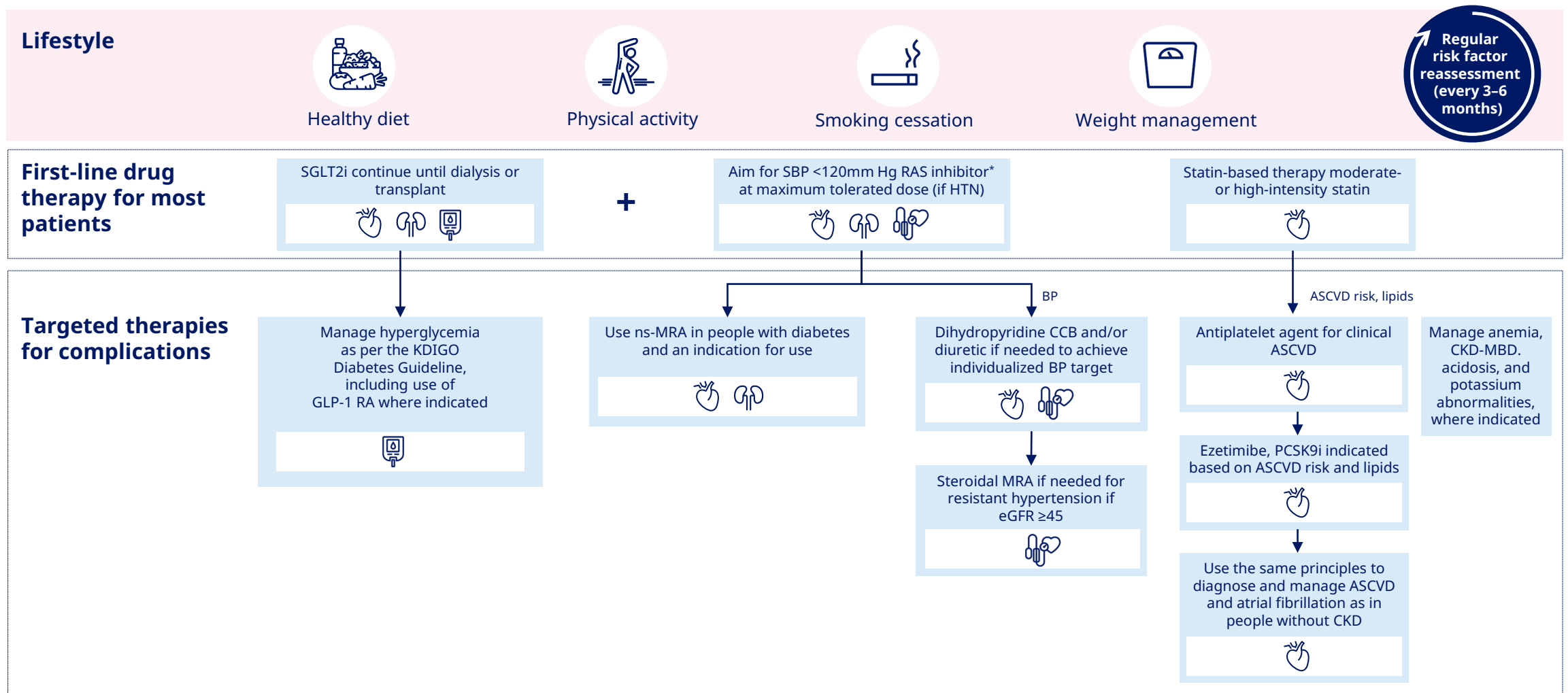
HFpEF
(EF ≥50%)

Diuretic (if congested) + SGLTi + Consider additional therapies

GLP-1 RA^c (if BMI ≥30 kg/m²) + ARNI or ARB^a (EF up to 55-60%) + MRA^{b,d} (EF up to 55-60%)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; CVD, CV disease; EF, ejection fraction; GLP-1 RA, glucagon-like receptor agonist; HFmrEF, HF with mildly reduced EF; HFpEF, HF with preserved EF; HFrEF, HF with reduced EF; MRA, mineralocorticoid receptor agonist; SBP, systolic blood pressure; SGLT2i, sodium glucose cotransporter 2 inhibitor; T2D, type 2 diabetes. Handelsman Y et al. Metabolism. 2024 Jun 4;155931. doi: 10.1016/j.metabol.2024.155931

Holistic approach to chronic kidney disease (CKD) treatment and risk modification



*Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker should be first-line therapy for blood pressure (BP) control when albuminuria is present; otherwise dihydropyridine calcium channel blocker (CCB) or diuretic can also be considered. All 3 classes are often needed to attain BP targets..

ASCVD, atherosclerotic cardiovascular disease; CKD-MBD, chronic kidney disease-mineral and bone disorder; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HTN hypertension; KDIGO, Kidney Disease: Improving Global Outcomes; MRA, mineralocorticoid receptor antagonist; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin-angiotensin system; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter-2 inhibitor

Kidney Int. 2024 Apr;105(4S):S117-S314. doi: 10.1016/j.kint.2023.10.018.

CKD Prevention and Management

Prevention

Risk Assessment

CKD associated with:

▲ Mortality

▲ ASCVD (increased risk if UACR ≥30 mg/g / ≥3 mg/mmol)

▲ HF

▲ ESKD

▲ Hypertension

▲ Arrhythmia

▲ Hypoglycemia

Lifestyle Therapy *Plus* Goal-Directed Pharmacotherapy

• BP control (<130/80 mm Hg)

• Glucose control (A1C <7.0% / <53 mmol/mol)

• Lipid control (max dose statin ± other lipid-lowering agents)

• Albuminuria reduction (RASi + SGLT2i)

Management

Screening and Diagnosis

Assess:

Diagnose CKD if:

• UACR

-and-

• eGFR

• Persistent UACR ≥30 mg/g / ≥3 kg/mmol

-and/or-

• Persistent eGFR <60 mL/min/1.73 m²

CKD with diabetes

Max tolerated RASi^a

+

SGLT2i

+

Nonsteroidal MRA

+

GLP-1 RA

CKD without diabetes

Max tolerated RASi^a

+

SGLT2i

^a Avoid down-titration or cessation if hyperkalemic

A1C, hemoglobin A1C (HbA1c); ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; GLP-1 RA, glucagon-like peptide 1 receptor agonist with proven benefit; MRA, mineralocorticoid receptor agonist; RASi, renin angiotensin system inhibitor; SGLT2i, sodium glucose cotransporter 2 inhibitor; UACR, urine albumin-creatinine ratio. Handelsman Y et al. Metabolism. 2024 Jun 4;155931. doi: 10.1016/j.metabol.2024.155931

ADA STANDARDS OF MEDICAL CARE IN DIABETES 2024 AND KDIGO: TREATMENT GUIDELINES FOR MANAGEMENT OF CKD

Glycemic control in CKD

<6.5%

HbA_{1c}

<8.0%

CKD G1

Severity of CKD

CKD G5

Absent/minor

Macrovascular complications

Present/severe

Few

Comorbidities

Many

Long

Life expectancy

Short

Present

Hypoglycemia awareness

Impaired

Available

Resources for hypoglycemia management

Scarce

Low

Propensity of treatment to cause hypoglycemia

High

KDIGO 2020¹,
2022²

Patients with diabetes and CKD not treated with dialysis^{1,2}
<6.5% to <8.0%

Patients for whom prevention of complications is the key goal¹
<6.5% or <7.0%

Patients with multiple comorbidities or increased hypoglycemia¹
<7.5% or <8.0%

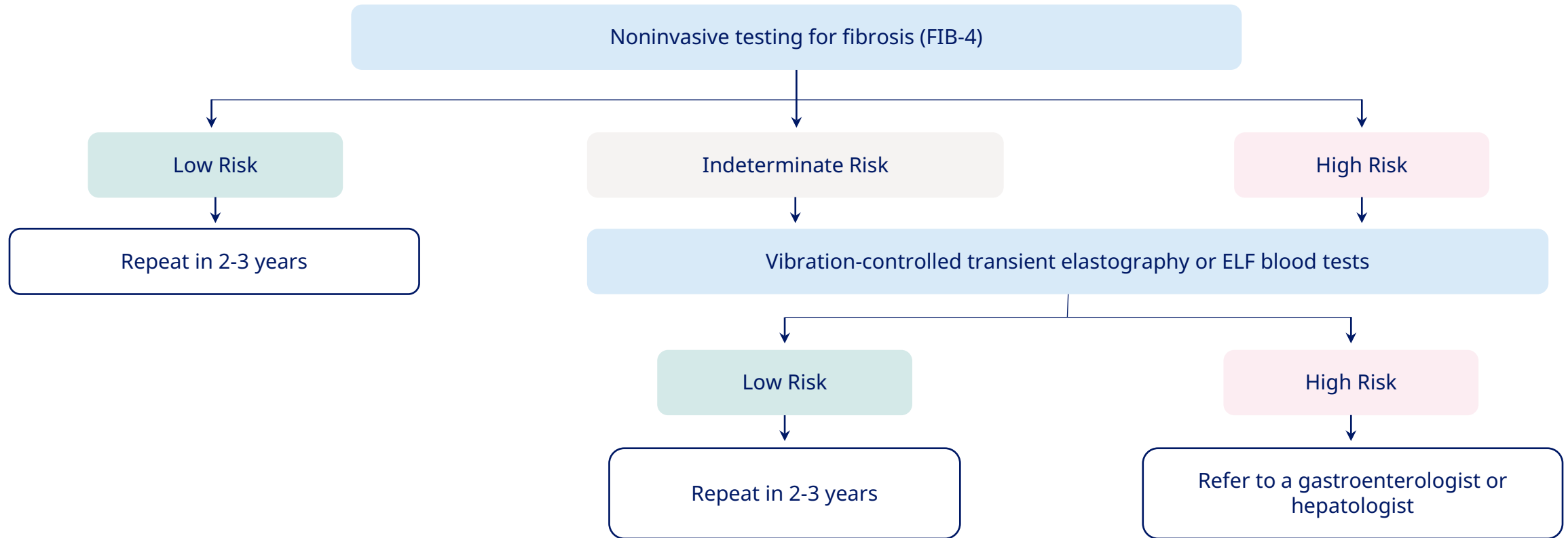
ADA 2024³

- Lowering blood glucose itself helps prevent CKD and its progression
- For people with T2D and established CKD, special considerations for the selection of glucose-lowering medications include
 - Comorbidity and CKD stage
 - Individual patient's risk (cardiovascular and renal in addition to glucose)
 - Drug dosing modification with eGFR <60 mL/min/1.73 m²
 - Convenience and cost

ADA, American diabetes association; CKD, chronic kidney disease; G1, eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; KDIGO, Kidney Disease Improving Global Outcome
1. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. Kidney Int. 2020;98(4S):S1–S115; 2. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2022;102(5S):S1–S127 3. American Diabetes Association (ADA). Diabetes Care 2024;47(Supplement_1)

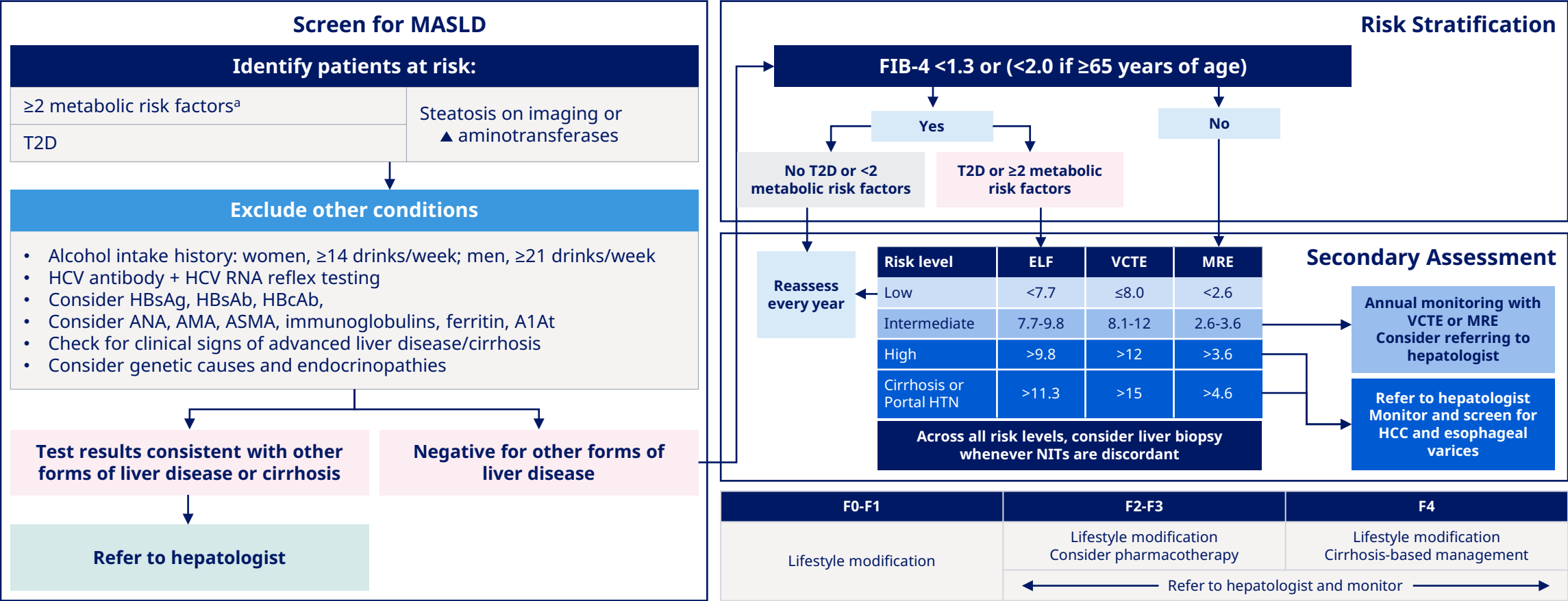
ADA STANDARDS OF MEDICAL CARE IN DIABETES – 2024

2024 ADA: A proposed algorithm for risk stratification in individuals with nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH). (Figure 4.2; S67)



DCRM 2.0 MULTISPECIALTY PRACTICE RECOMMENDATIONS

MASLD/MASH (NAFLD/NASH) Prevention and Management



^a Hyperglycemia, ↑ TG, ↑ BP, ↓ HDL-C, abdominal obesity.

- Achieve ≥10% weight reduction with lifestyle, with intensification to pharmacologic or surgical interventions if necessary
- Risk factor reduction: optimal lipid and BP control and appropriate therapy for obesity, diabetes, ASCVD, CKD, HF
- Consider resmetirom if appropriate for subjects with F2–F3 fibrosis
- Consider pioglitazone, SGLT2is, or GLP-1 RAs if indicated for other comorbidities such as T2D
- Consider leptin and pioglitazone for persons with lipodystrophy

A1At, alpha-1 antitrypsin deficiency; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; ASCVD, atherosclerotic cardiovascular disease; ASMA, anti-smooth muscle antibodies; BP, blood pressure; cAb, core antibody; CKD, chronic kidney disease; ELF, enhanced liver fibrosis; F_n, fibrosis stage (0–4); FIB-4, fibrosis 4 calculation; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HB, hepatitis B; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HTN, hypertension; MASLD, metabolic dysfunction–associated steatotic liver disease; MASH, metabolic dysfunction–associated steatohepatitis; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NIT, noninvasive test; sAb, surface antibody; sAg, surface antigen; SGLT2i = sodium glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TG, triglyceride; VCTE, vibration-controlled transient elastography.
Handelsman Y et al. Metabolism. 2024 Jun 4;155931. doi: 10.1016/j.metabol.2024.155931

ADA STANDARDS OF MEDICAL CARE IN DIABETES – 2024

Peripheral Artery Disease (PAD)

ADA recommends screening for asymptomatic PAD using ankle brachial index in people with diabetes at high risk for PAD, including any of the following:



age ≥ 50 years



diabetes with duration ≥ 10 years



comorbid microvascular disease



clinical evidence of foot complications



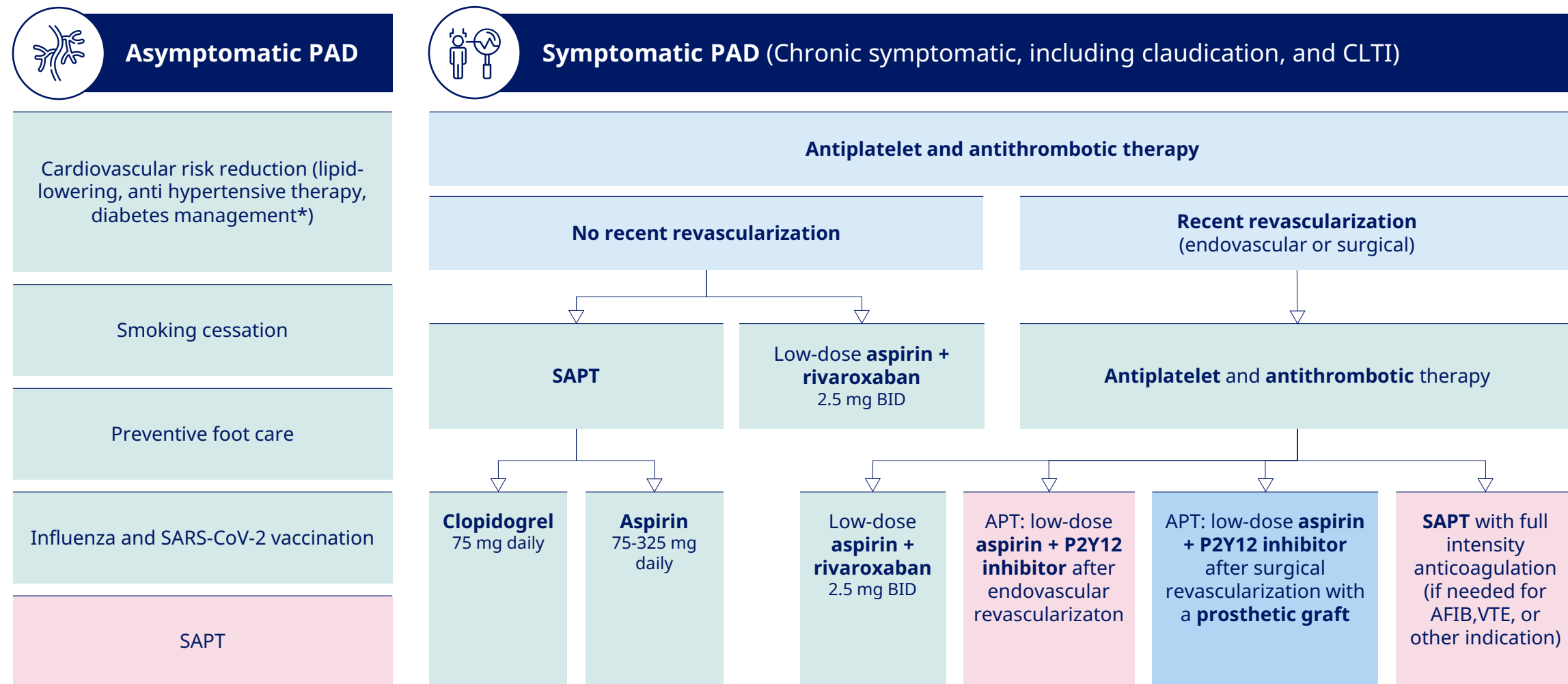
or any end-organ damage from diabetes.

Initial screening for PAD should include:

- Assessment of lower-extremity pulses, capillary refill time
- Rubor on dependency
- Pallor on elevation, and venous filling time
- Individuals with a history of leg fatigue, claudication, and rest pain relieved with dependency or decreased or absent pedal pulses should be referred for ankle-brachial index with toe pressures and for further vascular assessment as appropriate

Medical Therapy and Foot Care for PAD (1/2)

Class1: Strong Class2a: Moderate Class2b: Weak



* In patients with PAD and T2D use of GLP-1RA (liraglutide and semaglutide) and SGLT2i (canagliflozin, dapagliflozin and empagliflozin are effective to reduce the risk of MACE (section 5.5)

Afib, atrial fibrillation; BID, 2 times daily; CLTI, chronic limb-threatening ischemia; DAPT, dual antiplatelet therapy; PAD, peripheral artery disease; SAPT, single antiplatelet therapy; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VTE, venous thromboembolism

Gornik HL, et al. 2024 Circulation. 2024 Jun 11;149(24):e1313-e1410. doi: 10.1161/CIR.0000000000001251.

Medical Therapy and Foot Care for PAD (2/2)

Class1: Strong Class2a: Moderate Class2b: Weak



Symptomatic PAD (Chronic symptomatic, including claudication, and CLTI)

Cardiovascular risk reduction (lipid-lowering, anti hypertensive therapy, diabetes management)

Smoking cessation

Structured exercise (chronic symptomatic PAD)

Cilostazol (chronic symptomatic PAD)

Preventive foot care (chronic symptomatic PAD)

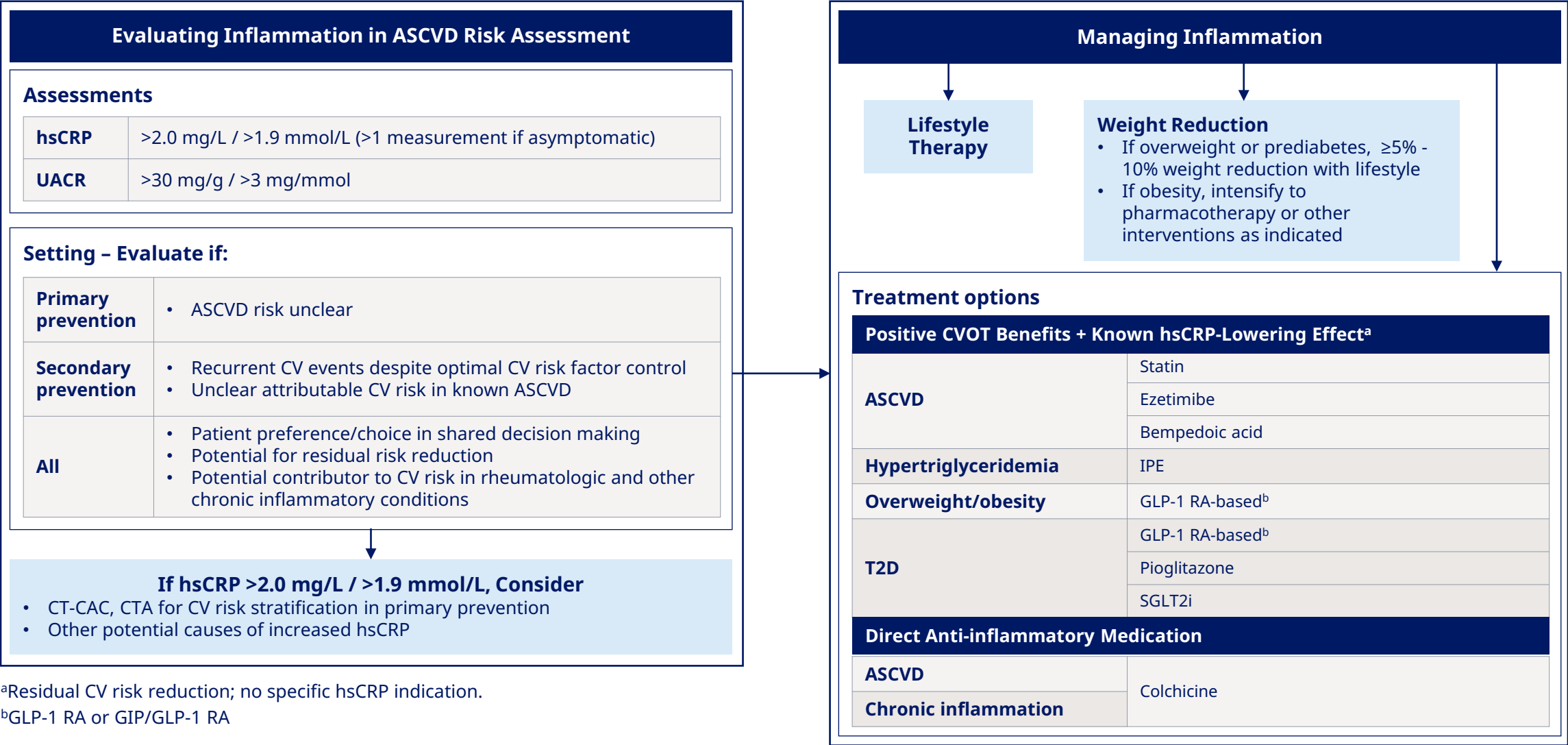
Wound care, pressure offloading, management of infection (CLTI)

Influenza and SARS-CoV-2 vaccination



DCRM 2.0 MULTISPECIALTY PRACTICE RECOMMENDATIONS

Inflammation



^aResidual CV risk reduction; no specific hsCRP indication.

^bGLP-1 RA or GIP/GLP-1 RA

ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CT, computed tomography; CTA, computed tomography angiography; CV, cardiovascular; CVOT, cardiovascular outcome trial; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; hsCRP, high-sensitivity C-reactive protein; IPE, cosapent ethyl; LDL-C, low-density lipoprotein cholesterol; SGLT2i, sodium glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; UACR, urine-albumin creatinine ratio. Handelsman Y et al. Metabolism. 2024 Jun 4;155931. doi: 10.1016/j.metabol.2024.155931

Prediabetes

(HbA1c; hemoglobin A1C) ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; FPG, fasting plasma glucose; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist with proven benefit in indicated population; HF, heart failure; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MRA, mineralocorticoid receptor agonist; PG, plasma glucose; SGLT2i, sodium glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; WHO, World Health Organization.