Guideline Directed Management of Diabetes Comorbidities

April 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)*

Health lifestyle behaviors; Diabetes Self-Management Education and Support (DSMES); Social Determinants of Health (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3-6 MONTHS)

Goal: Cardiorenal risk reduction in high-risk patients with Type-2 diabetes (in addition to comprehensive CV risk management)*

+ASCVD†
Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk
While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+HF
Current or prior symptoms of HF with documented HFrEF or HFpEF

+CKD
eGFR<60 mL/min per 1.73 m^2 OR albuminuria (ACR ≥3.0 mg/mmol [30mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD

+ASCVD/Indicators of High Risk

GLP-1 RA# with proven CVD benefit **Either / OR** SGLT2i§ with proven CVD benefit

If A1C above target

- For patients on a GLP-1 RA, consider incorporating SGLT2i with proven CVD benefit and vice versa
- TZD^

+HF

SGLT2i § with proven HF benefit in this population

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY
SGLT2i§ with primary evidence of reducing CKD progression
Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73m^2; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1RA or vice versa

If additional cardiorenal risk reduction or glycemic lowering needed

Goal: Achievement and maintenance of glycemic and weight management goals

Glycemic management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals
Prioritize avoidance of hypoglycemia in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

Efficacy for glucose lowering

Very high: Dulaglutide (high dose), Semaglutide, Tirzepatide
Insulin Combination Oral, Combination injectable (GLP-1 RA/Insulin)

High: GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate: DPP-4i

Achievement and maintenance of weight management goals:

Set individualized weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/physical activity	Intensive evidence-based structured weight management program	Consider medication for weight loss	Consider metabolic surgery

When choosing glucose-lowering therapies:
Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very high: Semaglutide, Tirzepatide

High: Dulaglutide, Liraglutide

Intermediate: GLP-1 RA (not listed above), SGLT2i

Neutral: DPP-4i, Metformin

If A1c above target

Identify barriers to goals:

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

* 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, HHF, 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

MANAGEMENT OF T2D

Antihyperglycemic therapy

2022 DCRM Multispecialty Practice Recommendations for the management of diabetes, cardiorenal, and metabolic diseases

Lifestyle Therapy

Reduce ASCVD and Kidney Risks Based on Comorbidities

CAD	HFrEF HFpEF	CKD	Stoke/TIA
LA GLP1-RA	SGLT2i	SGLT2i	LA GLP1-RA
SGLT2i		LA GLP1-RA	Pio
Pio			

Recommended Hierarchy

Preferred

- GLP1-RA
- SGLT2i
- Metformin
- TZD
- DPP4i
- Insulin
- SU

Less used

- Glinide
- Colesevelam
- AGI
- Bromocriptine QR
- Pramlintide

Manage Hyperglycemia to Individualized Goal

Younger, healthier, at lower CV risk

A1C: 6.0% 6.5% 7.0% 7.5%

Older, complex, more frail, at higher CV risk

Most patients

- Use initial combination therapy for patients with A1C >1-2% above goal
- Assess glucose control with A1C (3 months), CGM or SMBG (daily, Weekly, or Monthly), glycated albumin or fructosamine (3 weeks)
- Add agents with complementary MOA to maintain glucose control at goal[a]
- Choose agents according to recommended hierarchy, based on patient's individualized risks and benefits, preferences, and access to therapies
- Insulin is necessary for patients with diabetes symptoms

Proven benefits in CVOTs Hypoglycemia and/or HF risk

[a]do not combine GLP1-RA and DPP4i. Use caution when combining insulin + SU or insulin + TZD
LA GLP1-RA, dulaglutide, liraglutide or semaglutide
A1C, glycated hemoglobin; AGI, alpha glucosidase inhibitors; CAD,Coronary artery disease; CGM, continuous glucose monitoring; CKD, Chronic Kidney Disease; CV, cardiovascular; DPP4i, dipeptidyl peptidase 4 inhibitors; LA GLP-1 RA, long-acting glucagon-like peptide 1 receptor agonist ; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MOA, mode of action; Pio, pioglitazone; SGLT2i, sodium-glucose co transporter 2 inhibitor; self-monitoring of blood glucose (SMBG); SU, sulfonylurea; TIA, transient ischemic attack; T2D, type 2 diabetes; TZD, thiazolidinedione
Handelsman Y et al. J Diabetes Complications. 2022;36(2):108101

T2D AND ITS COMPLICATIONS

Diabetes-related complications affect multiple organs[1]

Microvascular complications

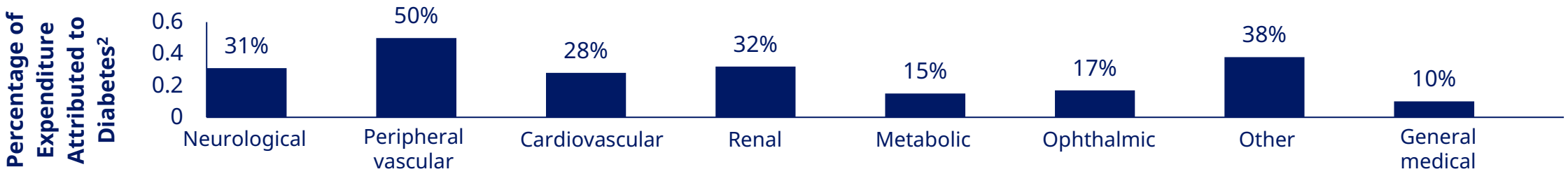
- Retinopathy
- Chronic kidney disease
- Neuropathy

Macrovascular complications

- Coronary artery disease
- Heart failure
- Peripheral arterial disease
- Stroke

Non-classic complications

- Cognitive impairment
- Depression
- NAFLD/NASH



NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

1. American Diabetes Association (ADA). Diabetes Care 2022 Jan; 45(Supplement 1); 2. Parker ED et al. Diabetes Care 2 January 2024; 47 (1): 26–43

T2D AND ITS COMPLICATIONS

Microvascular and Macrovascular complications of T2D

Microvascular complications
Damage to **small blood vessels** caused by severe and prolonged hyperglycemia

Macrovascular complications
Damage to **larger vessels** including coronary arteries and vessels in the brain and limbs

Diabetic retinopathy

~35%

of patients with T2D have retinopathy and the risk increases over time[1]

Chronic kidney disease

~7%

of patients with T2D already have **microalbuminuria** at the time of diagnosis[2]

Diabetic neuropathy

45%

incidence of neuropathy for patients with T2D[3]

Coronary artery disease

>25%

of asymptomatic patients with diabetes have CAD [4]

Heart failure

2-5x

T2D increases the risk of HF up to 2-fold in men and 5-fold in women compared with age-matched controls[5]

Peripheral arterial disease

2-4x

increase in risk of developing PAD for diabetic patients[6]

Stroke

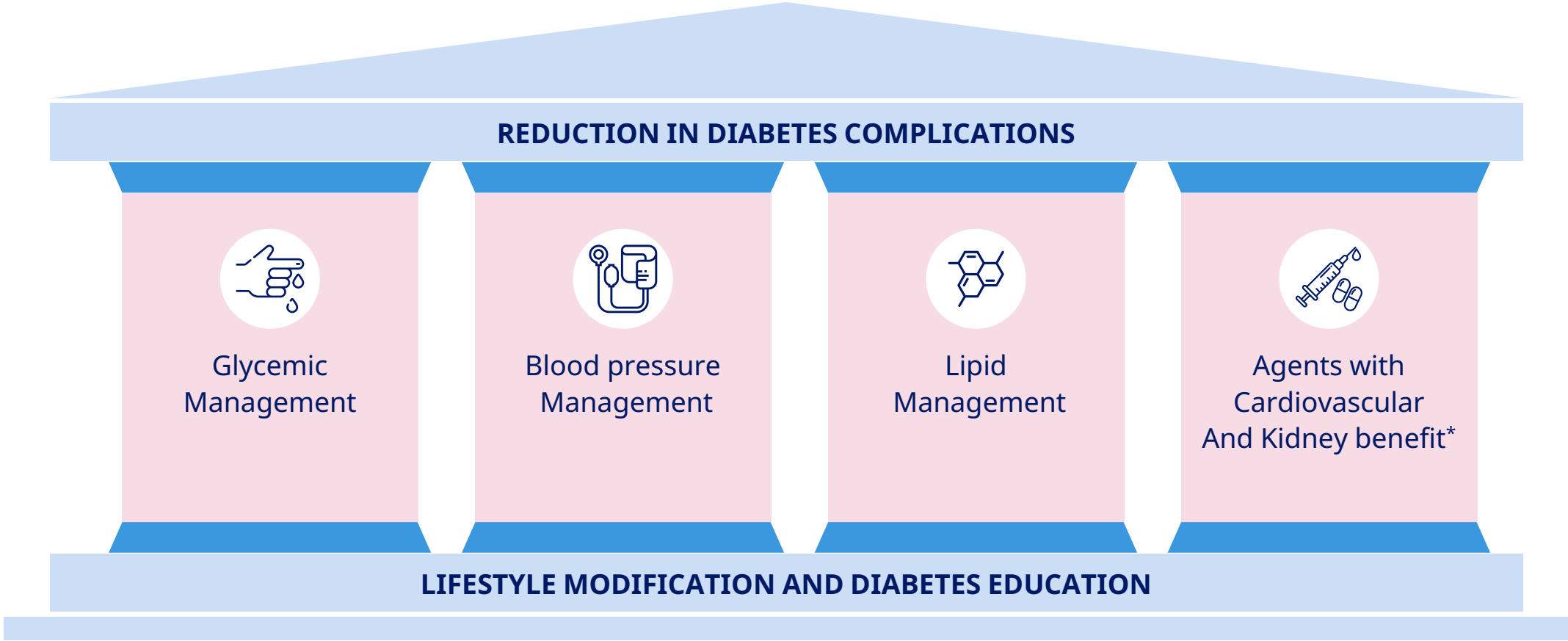
2x

Higher risk of stroke in patients with T2D[7]

PAD, peripheral arterial disease; T2D, type 2 diabetes

1. Yau JWY et al. Diabetes Care 2012;35:556–564; 2. Gross JL et al. Diabetes Care 2005;28:164–176; 3. Russel KW, Zilliox LA. Continuum (Minneap Minn) 2014;20:1226–1240 ; 4. Tavares CAF et al. Archives Endocrinol Metab 2016;60:143–151; 5. Kenny HC, Abel ED. Circ Res. 2019 Jan 4;124(1):121-141; 6. Beckman J-A, Creager M-A. Circ Res 2016;118:1771–1785; 7. Laakso M, Kuusisto J. International Congress Series 2007;1303:65–69

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

TREATMENT GUIDELINES

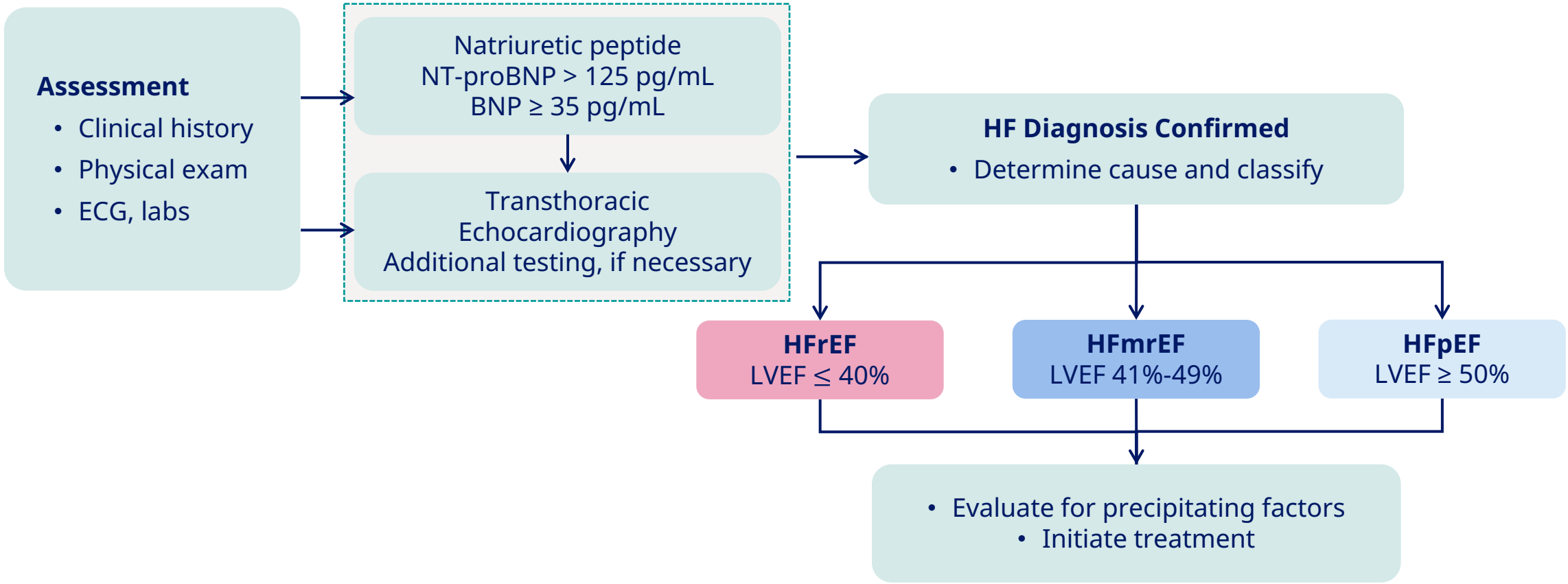
Recommendations for prevention and treatment of ASCVD

	Primary prevention	Secondary prevention
Treatment goals[1,2,5]	Lifestyle/smoking interventions SBP <130 mmHg DBP <80 mmHg) + LDL-C: No specific guidance‡ Intensify treatment based on CV risk and other patient factors	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 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

Diagnostic Algorithm for HF and EF-Based Classification

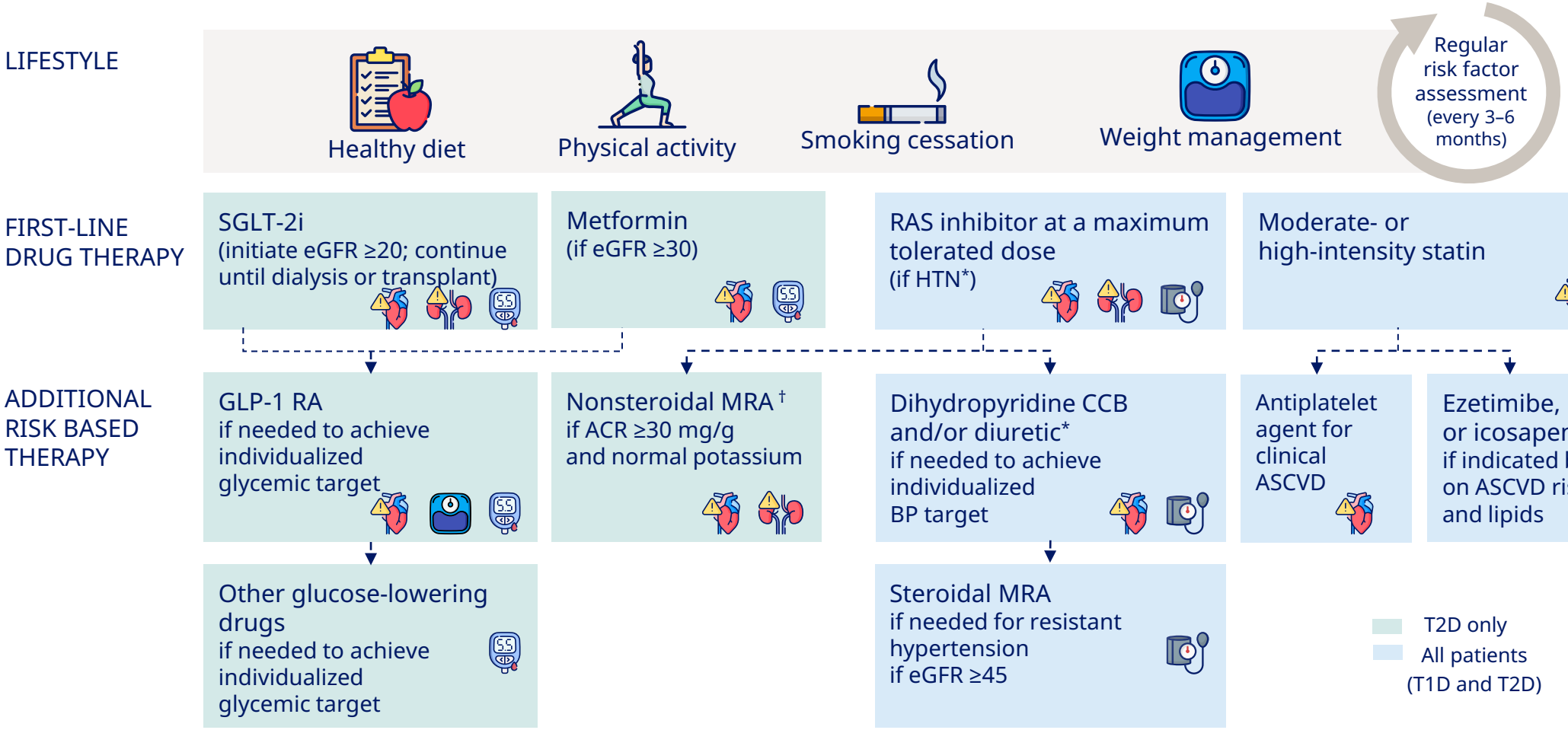


BNP indicates B-type natriuretic peptide; ECG, electrocardiogram; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricle; LVEF, left ventricular ejection fraction; and NT-proBNP, N-terminal pro-B type natriuretic peptide.

Heidenreich, P. A. et al. (2022). 2022 AHA/ACC/HFSA Guideline for Heart Failure. Circulation.

ADA STANDARDS OF MEDICAL CARE IN DIABETES – 2024

Holistic approach for improving outcomes in patients with diabetes and CKD *(Fig. 11.2; S225)*



**ACEi or ARB (at maximal tolerated doses) should be first-line therapy HTN when albuminuria is present. Otherwise, CCB or diuretic can also be considered; all 3 classes are often needed to attain BP targets. eGFR is presented in units of mL/min/1.73m²*
†Finerenone is currently the only ns-MRA with proven clinical kidney and cardiovascular benefits.
ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HTN, hypertension; MRA, mineralocorticoid receptor antagonist; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin-angiotensin system; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes
American Diabetes Association (ADA). Diabetes Care 2024;47(Supplement_1):S219–S230; Reprinted from de Boer et al. (1)

TREATMENT GUIDELINES FOR MANAGEMENT OF CKD

Glycemic control in CKD

Factors guiding individualized glycemic target[1,2]

<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 2020[1], 2022[2]

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 goal[1]
<6.5% or <7.0%
Patients with multiple comorbidities or increased hypoglycemia[1]
<7.5% or <8.0%

ADA 2024[3]

- 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 m^2
  - Convenience and cost

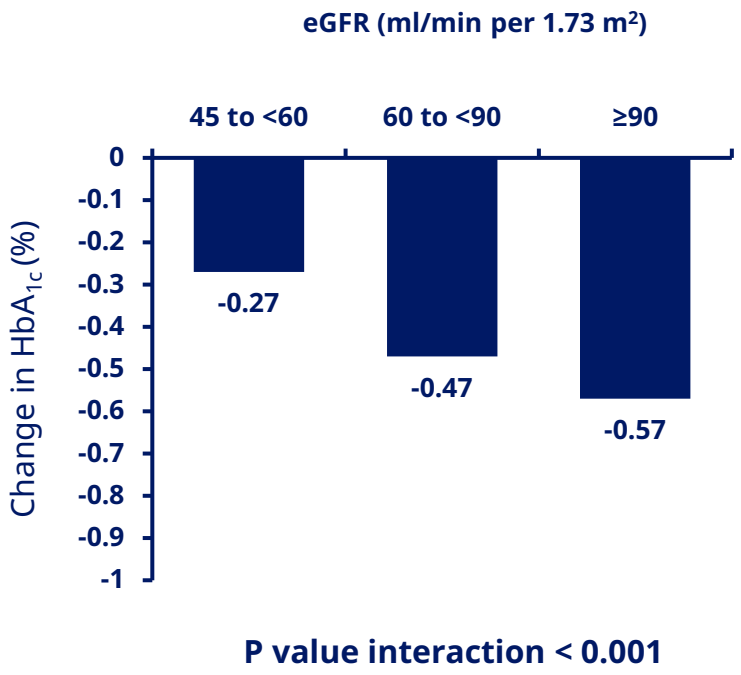
ADA, American diabetes association; CKD, chronic kidney disease; G1, eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; KDIGO, Kidney Disease Improving Global Outcome

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)

KIDNEY DISEASE AND DIABETES

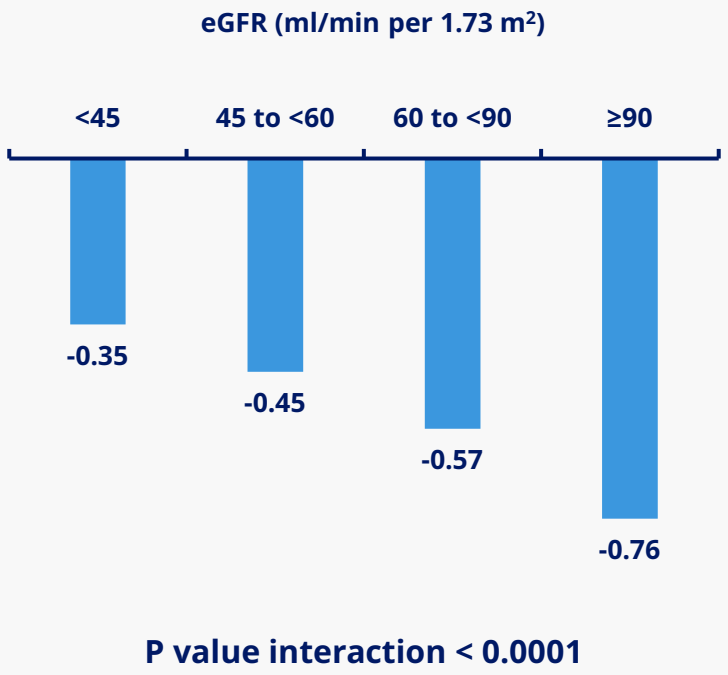
Glycemic efficacy of SGLT2 inhibitors and eGFR

Dapagliflozin vs placebo[1]
Pooled analysis: 11 trials
N = 4,404 (T2D)
Duration: 24 weeks



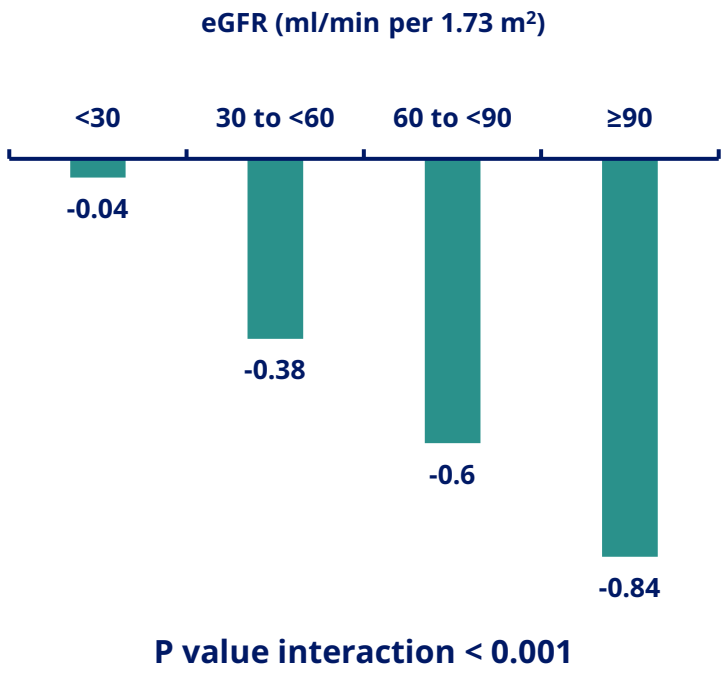
P value interaction < 0.001

Canagliflozin vs placebo[2]
CANVAS Program
N = 10,142 (T2D)
Mean follow-up: 188.2 weeks



P value interaction < 0.0001

Empagliflozin vs placebo[3]
Pooled analysis: 5 trials
N = 2,286 (T2D)
Duration: 24 weeks

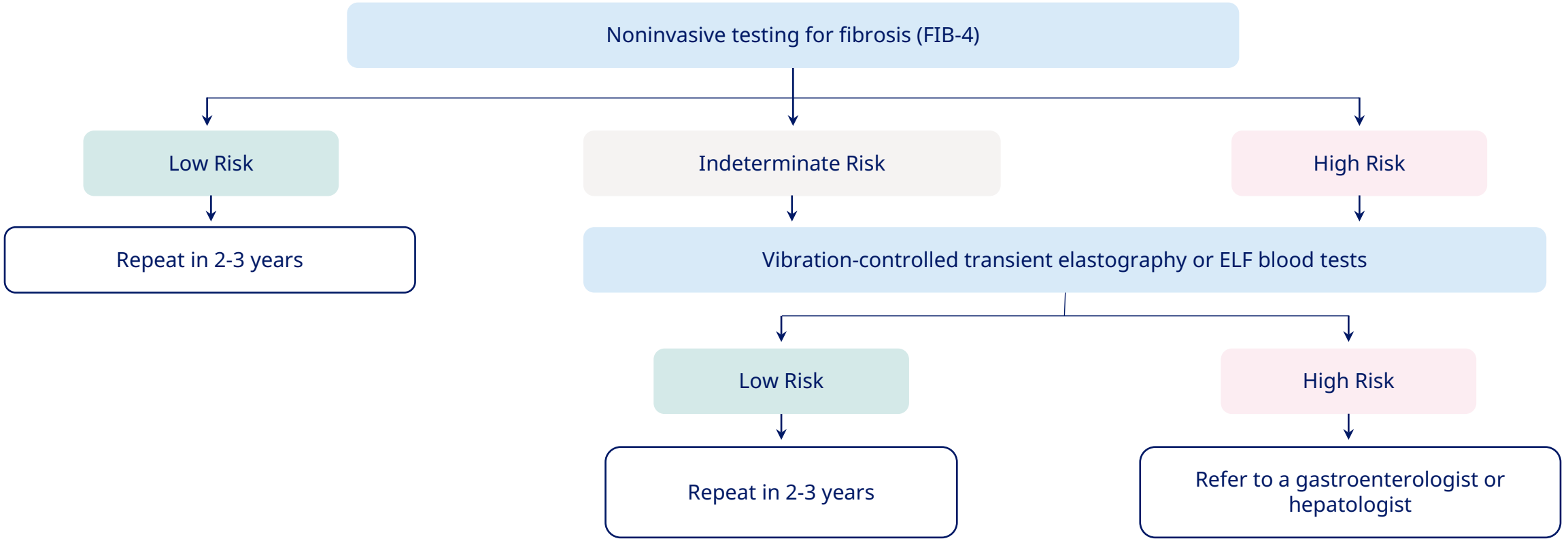


P value interaction < 0.001

eGFR, estimated glomerular filtration rate; SGLT2i, sodium glucose cotransporter 2 inhibitor; T2D, type 2 diabetes
1. Petrykiv S et al. Clin J Am Soc Nephrol. 2017;12(5):751-759; 2. Neuen BL et al. Circulation. 2018;138(15):1537-1550; 3. Cherney DZI et al. Kidney Int. 2018;93(1):231-244

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)*



ELF, enhanced liver fibrosis; FIB-4, fibrosis 4 index Adapted from Kanwal et al (174)
American Diabetes Association (ADA). Diabetes Care 2024;47(Supplement_1):S52–S76

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

PAD, peripheral arterial disease

American Diabetes Association (ADA). Diabetes Care 2024;47(Supplement_1)