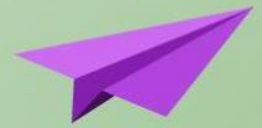


Beyond glycemic management: Assessing and managing comorbidities and complications

Amy Butts PA-C, DFAAPA, BC-ADM, CDCES

WVU Medicine Wheeling Hospital

Wellsburg, WV



Disclosures:

- Speaker Bureau- Abbott, Novo Nordisk, Xeris
- Advisory Board- Corcept, Xeris

Learning Objectives:

Discuss

- Cardiovascular disease and risk management

Review

- diagnosing, staging, and treatment of chronic kidney disease

Learn

- the recommendations of screening and treating retinopathy and neuropathy



Cardiovascular Disease and Risk Management



Defining ASCVD

Leading cause of morbidity and mortality for individuals with diabetes

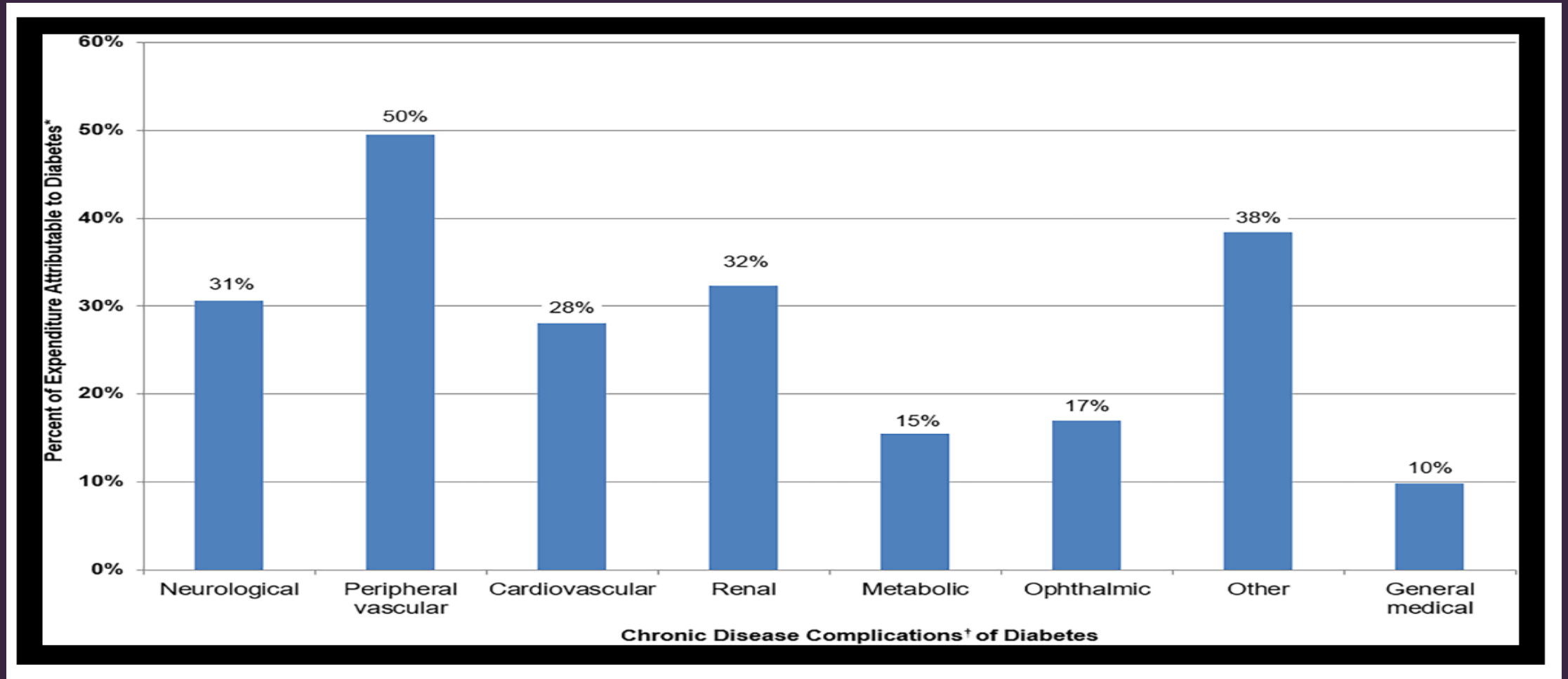
\$39.4 billion in cardiovascular-related spending per year associated with diabetes

Coronary Artery
Disease

Cerebrovascular
Disease

Peripheral Artery
Disease

Percent of medical expenditures attributable to diabetes by chronic complication



Emily D. Parker, Janice Lin, Troy Mahoney, Nwanneamaka Ume, Grace Yang, Robert A. Gabbay, Nuha A. ElSayed, Raveendhara R. Bannuru; Economic Costs of Diabetes in the U.S. in 2022. *Diabetes Care* 2 January 2024; 47 (1): 26–43. <https://doi.org/10.2337/doi23-0085>

Years of life gained by
multifactorial intervention in
patients with type 2 diabetes
mellitus and microalbuminuria:
21 years follow-up on the Steno-
2 randomized trial

1

160 patients with T2DM & Microalbuminuria assigned either conventional or intensified therapy both behavioral and pharmacological for 7.8 years

2

Conclusions/interpretation
: At 21.2 years of follow-up of 7.8 years of the intensive group had a median of 7.9 years of gain of life.

3

The hazard for all microvascular complications was decreased in the intensive-therapy group in the range 0.52 to 0.67, except for peripheral neuropathy

Congestive Heart Failure

Two-fold higher in people with diabetes

Hypertension is precursor

Can include:

- HFpEF
- HFmEF
- HFrEF

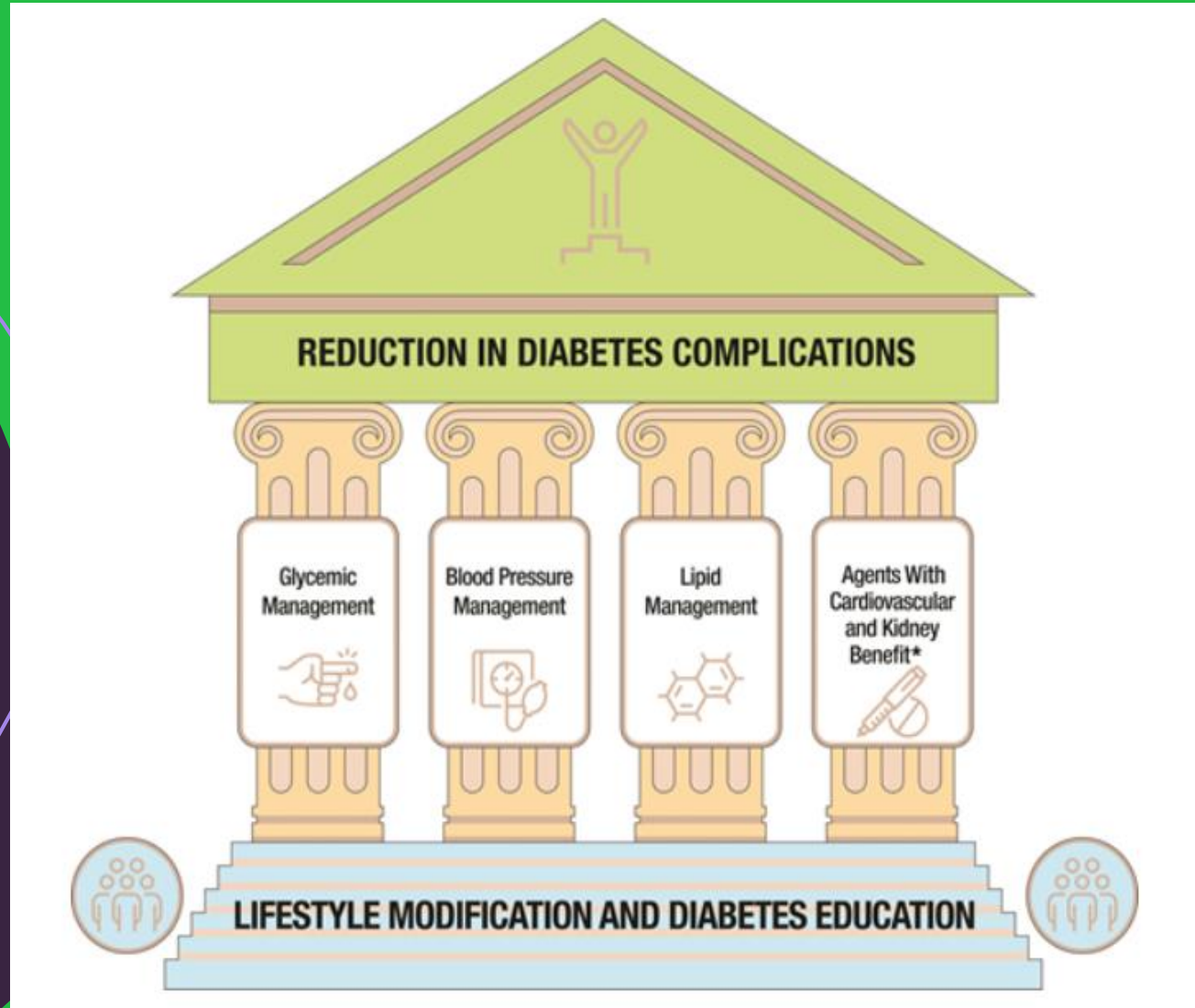


Prevention and Management of ASCVD & Heart Failure

- Assess annually:
 - Duration of Diabetes
 - Obesity/Overweight
 - Hypertension
 - Dyslipidemia
 - Smoking
 - Family Hx Premature Coronary Disease
 - CKD
 - Presence of albuminuria

Multifactorial approach to reduction in risk of diabetes complications

American Diabetes Association Professional Practice Committee; 10. Cardiovascular Disease and Risk Management: *Standards of Care in Diabetes—2024*. *Diabetes Care* 1 January 2024; 47 (Supplement_1): S179–S218. <https://doi.org/10.2337/dc24-S010>



ASCVD Risk Calculator

- American College of Cardiology
- Estimate 10-year risk of a first ASCVD event
- tools.acc.org/ASCVD-Risk-Estimator-Plus



Hypertension

- **Screening and Diagnosis**
- **Recommendations**
- **10.1** Blood pressure should be measured at every routine clinical visit. When possible, individuals found to have elevated blood pressure (systolic blood pressure 120–129 mmHg and diastolic <80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. **A** Hypertension is defined as a systolic blood pressure ≥ 130 mmHg or a diastolic blood pressure ≥ 80 mmHg based on an average of two or more measurements obtained on two or more occasions. **A** Individuals with blood pressure $\geq 180/110$ mmHg and cardiovascular disease could be diagnosed with hypertension at a single visit. **E**

Hypertension

- **Treatment Goals**
- **Recommendations**
- **10.3** For people with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and individual preferences. **B**
- **10.4** The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained. **A**



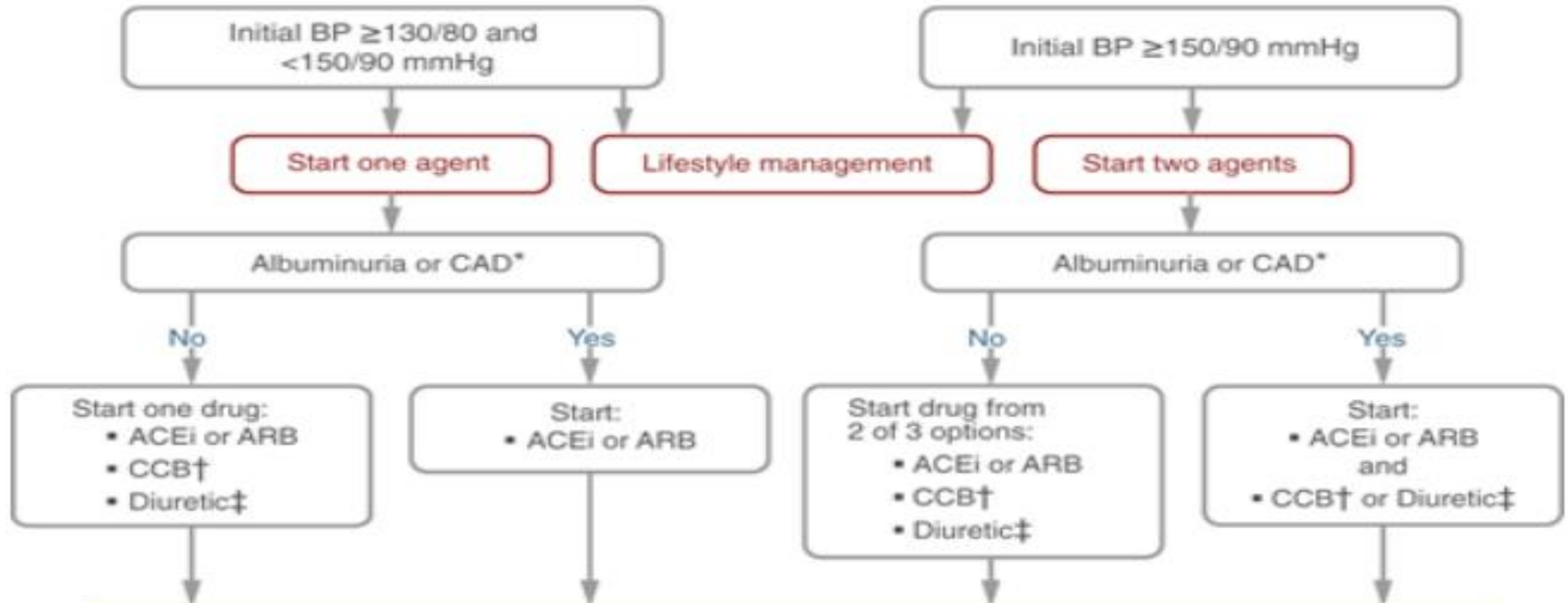
Hypertension Treatment Strategies

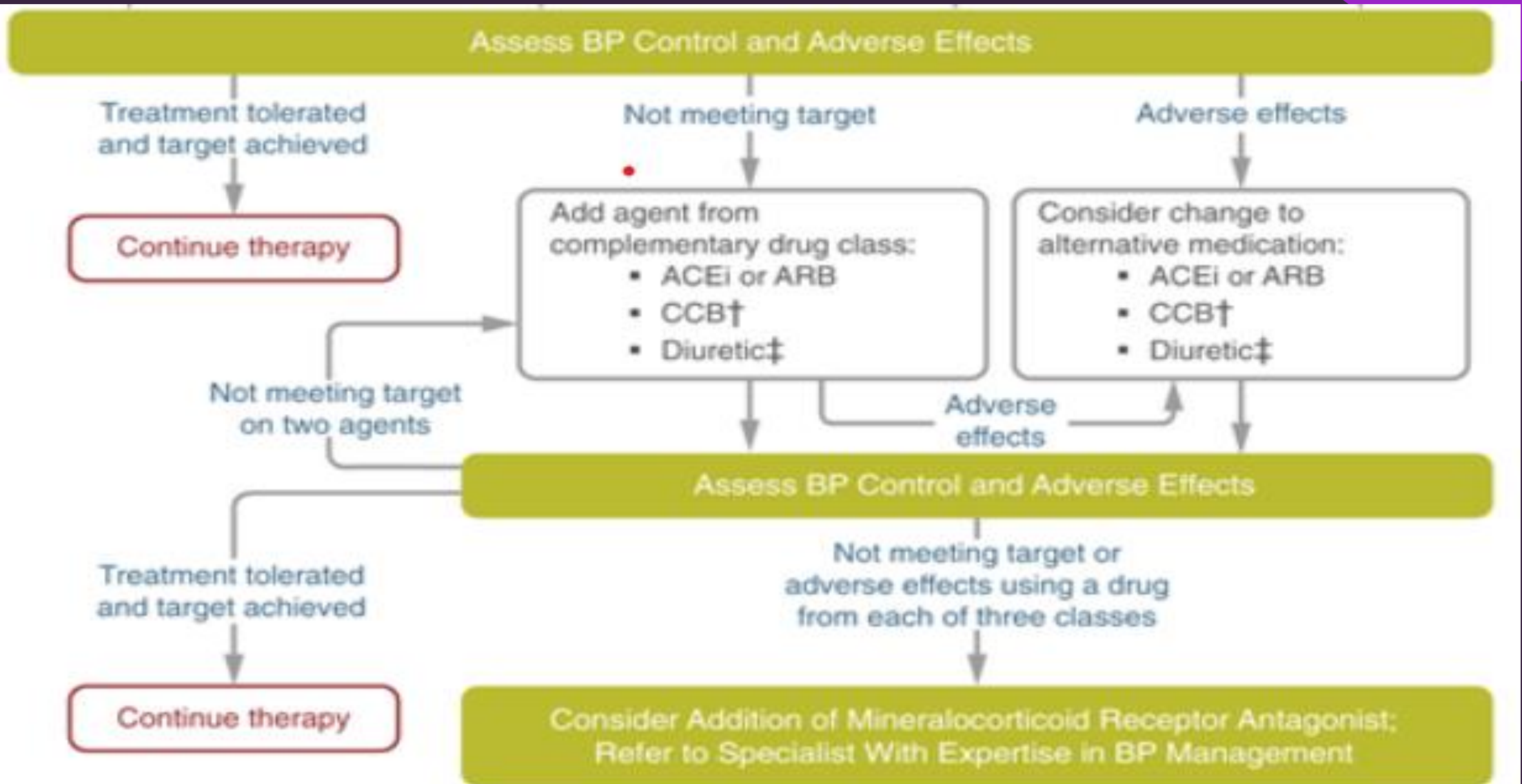
- Lifestyle Management
 - Weight loss if indicated
 - 150 minutes of moderate-intensity aerobic activity/week
 - Sodium intake < 2300 mg/day
 - Alcohol intake- 2 servings/day for men and 1 serving/day women

Pharmacologic Interventions

- **Recommendations**
- **10.7** Individuals with confirmed office-based blood pressure $\geq 130/80$ mmHg qualify for initiation and titration of pharmacologic therapy to achieve the recommended blood pressure goal of $<130/80$ mmHg. **A**
- **10.8** Individuals with confirmed office-based blood pressure $\geq 150/90$ mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single-pill combination of drugs demonstrated to reduce cardiovascular events in people with diabetes. **A**
- **10.9** Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in people with diabetes. **A** ACE inhibitors or angiotensin receptor blockers (ARBs) are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. **A**
- **10.10** Multiple-drug therapy is generally required to achieve blood pressure targets. However, combinations of ACE inhibitors and ARBs and combinations of ACE inhibitors or ARBs (including ARBs/neprilysin inhibitors) with direct renin inhibitors should not be used. **A**
- **10.11** An ACE inhibitor or ARB, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in people with diabetes and urinary albumin-to-creatinine ratio ≥ 300 mg/g creatinine **A** or 30–299 mg/g creatinine. **B** If one class is not tolerated, the other should be substituted. **B**
- **10.12** For adults treated with an ACE inhibitor, ARB, mineralocorticoid receptor antagonist (MRA), or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored within 7–14 days after initiation of therapy and at least annually. **B**

Recommendations for the Treatment of Confirmed Hypertension in Nonpregnant People With Diabetes





Resistant Hypertension

- **Recommendation**
- **10.13** Individuals with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for MRA therapy. **A**

Examples: Spironolactone and Eplerenone

Increase risk for hyperkalemia



Lipid Management



Lifestyle Intervention

- **Recommendations**
- **10.14** Lifestyle modification focusing on weight loss (if indicated); application of a Mediterranean or DASH eating pattern; reduction of saturated fat and *trans* fat; increase of dietary n-3 fatty acids, viscous fiber, and plant stanol/sterol intake; and increased physical activity should be recommended to improve the lipid profile and reduce the risk of developing atherosclerotic cardiovascular disease (ASCVD) in people with diabetes. **A**
- **10.15** Intensify lifestyle therapy and optimize glycemic control for people with diabetes with elevated triglyceride levels (≥ 150 mg/dL [≥ 1.7 mmol/L]) and/or low HDL cholesterol (< 40 mg/dL [< 1.0 mmol/L] for men and < 50 mg/dL [< 1.3 mmol/L] for women). **C**

Ongoing Therapy and Monitoring with Lipid Panel

- **Recommendations**
- **10.16** In adults with prediabetes or diabetes not taking statins or other lipid-lowering therapy, it is reasonable to obtain a lipid profile at the time of diagnosis, at an initial medical evaluation, annually thereafter, or more frequently if indicated. **E**
- **10.17** Obtain a lipid profile at initiation of statins or other lipid-lowering therapy, 4–12 weeks after initiation or a change in dose, and annually thereafter, as it may help to monitor the response to therapy and inform medication taking. **A**

Statin Treatment

- **Primary Prevention**
- **Recommendations**
- **10.18** For people with diabetes aged 40–75 years without ASCVD, use moderate-intensity statin therapy in addition to lifestyle therapy. **A**
- **10.19** For people with diabetes aged 20–39 years with additional ASCVD risk factors, it may be reasonable to initiate statin therapy in addition to lifestyle therapy. **C**
- **10.20** For people with diabetes aged 40–75 years at higher cardiovascular risk, including those with one or more ASCVD risk factors, it is recommended to use high-intensity statin therapy to reduce LDL cholesterol by $\geq 50\%$ of baseline and to target an LDL cholesterol goal of < 70 mg/dL (< 1.8 mmol/L). **A**
- **10.21** For people with diabetes aged 40–75 years at higher cardiovascular risk, especially those with multiple ASCVD risk factors and an LDL cholesterol ≥ 70 mg/dL (≥ 1.8 mmol/L), it may be reasonable to add ezetimibe or a PCSK9 inhibitor to maximum tolerated statin therapy. **B**
- **10.22** In adults with diabetes aged > 75 years already on statin therapy, it is reasonable to continue statin treatment. **B**
- **10.23** In adults with diabetes aged > 75 years, it may be reasonable to initiate moderate-intensity statin therapy after discussion of potential benefits and risks. **C**
- **10.24** In people with diabetes intolerant to statin therapy, treatment with bempedoic acid is recommended to reduce cardiovascular event rates as an alternative cholesterol-lowering plan. **A**
- **10.25** Statin therapy is contraindicated in pregnancy. **B**

Statin Treatment

- **Secondary Prevention**
- **Recommendations**
- **10.26** For people of all ages with diabetes and ASCVD, high-intensity statin therapy should be added to lifestyle therapy. **A**
- **10.27** For people with diabetes and ASCVD, treatment with high-intensity statin therapy is recommended to target an LDL cholesterol reduction of $\geq 50\%$ from baseline and an LDL cholesterol goal of < 55 mg/dL (< 1.4 mmol/L). Addition of ezetimibe or a PCSK9 inhibitor with proven benefit in this population is recommended if this goal is not achieved on maximum tolerated statin therapy. **B**
- **10.28a** For individuals who do not tolerate the intended statin intensity, the maximum tolerated statin dose should be used. **E**
- **10.28b** For people with diabetes and ASCVD intolerant to statin therapy, PCSK9 inhibitor therapy with monoclonal antibody treatment, **A** bempedoic acid therapy, **A** or PCSK9 inhibitor therapy with inclisiran siRNA **E** should be considered as an alternative cholesterol-lowering therapy.

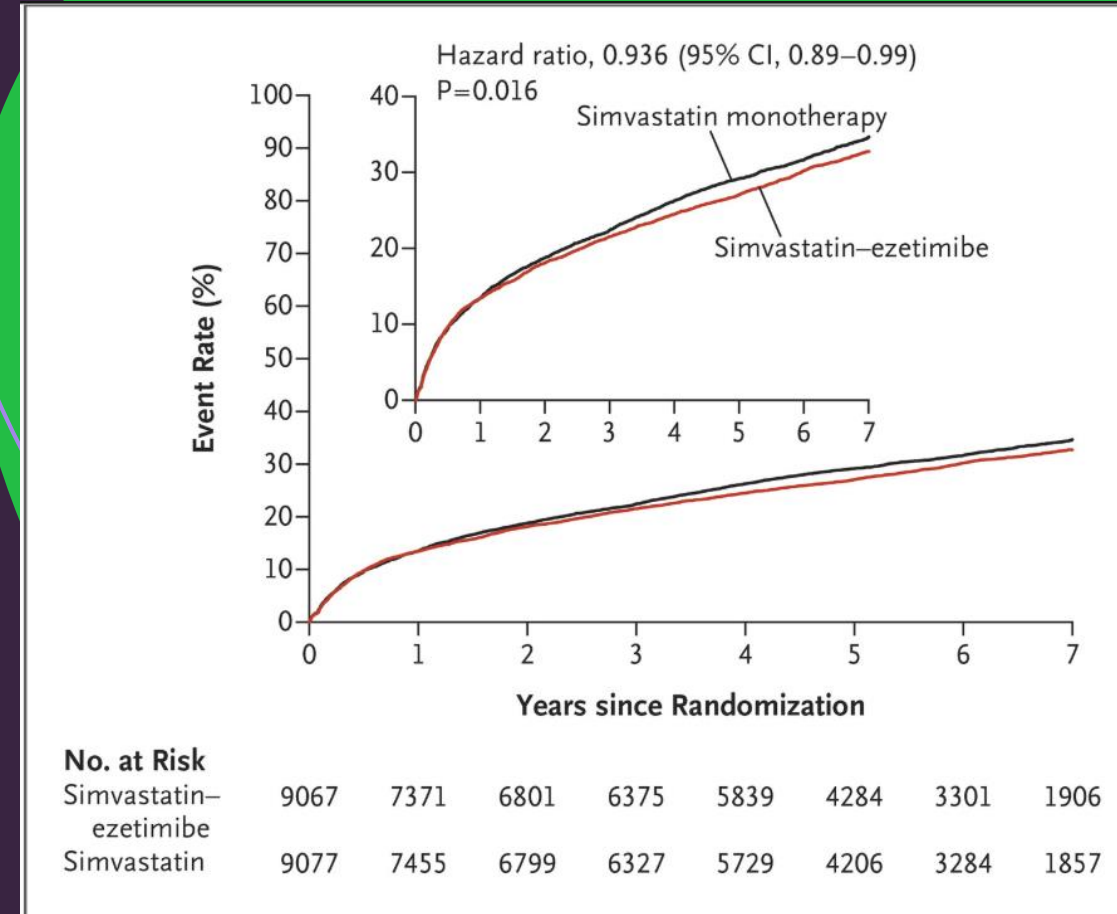
High-intensity & Moderate-intensity therapy

High-intensity statin therapy (lowers LDL \geq 50%)	Moderate-intensity statin therapy (lowers LDL by 30-49%)
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg
	Simvastatin 20-40 mg
	Pravastatin 40-80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 1-4 mg

Once-daily dosing. XL, extended release

IMPROVE-IT

- ≥ 50 years of age
- Recent Acute Coronary Syndrome
- Randomized to simvastatin or simvastatin/ezetimibe
- Treated for an average 6 years
- Ezetimibe- 6.4% relative benefit and 2% absolute reduction in MACE



Statins & PCSK9 Inhibitors

- Evolocumab & Alirocumab + maximum tolerated doses of statin therapy
- High Risk for ASCVD
- Average reduction LDL 36 to 59%
- Approved for adjunctive therapy for ASCVD or familial hypercholesterolemia
- No primary prevention trials

Intolerance to Statins

- Switch to a different high-intensity statin if indicated
- Switching to moderate-intensity or low-intensity statin
- Lowering the statin dose
- Using nondaily dosing of statins
- Consider non statin options

PCSK9 Inhibitors

- Statin intolerant trials
 - ODYSSEY ALTERNATIVE- Alirocumab (54.8% reduction) vs Ezetimibe (20.1% reduction)
 - GAUS 1, 2, 3 Trials- Evolocumab/Ezetimibe (41 to 63%) vs Placebo/Ezetimibe (15 to 18%)
 - Difficult to get covered unless established ASCVD due to lack of primary prevention trials
 - Must have documented failure of statin therapy

Bempedoic Acid

- Indicated as an adjunct to diet and maximum tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established ASCVD who require additional lowering of LDL cholesterol
- Lowers LDL by 23% compared to placebo
- Use if can not tolerate statin or if other medications ineffective

Treatment of Other Lipoprotein Fractions or Targets

- **Recommendations**
- **10.29** For individuals with fasting triglyceride levels ≥ 500 mg/dL (≥ 5.7 mmol/L), evaluate for secondary causes of hypertriglyceridemia and consider medical therapy to reduce the risk of pancreatitis. **C**
- **10.30** In adults with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175–499 mg/dL [2.0–5.6 mmol/L]), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, and hypothyroidism), and medications that raise triglycerides. **C**
- **10.31** In individuals with ASCVD or other cardiovascular risk factors on a statin with controlled LDL cholesterol but elevated triglycerides (135–499 mg/dL [1.5–5.6 mmol/L]), the addition of icosapent ethyl can be considered to reduce cardiovascular risk. **A**

Other Combination Therapy

- **Recommendations**
- **10.32** Statin plus fibrate combination therapy has not been shown to improve ASCVD outcomes and is generally not recommended. **A**
- **10.33** Statin plus niacin combination therapy has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. **A**

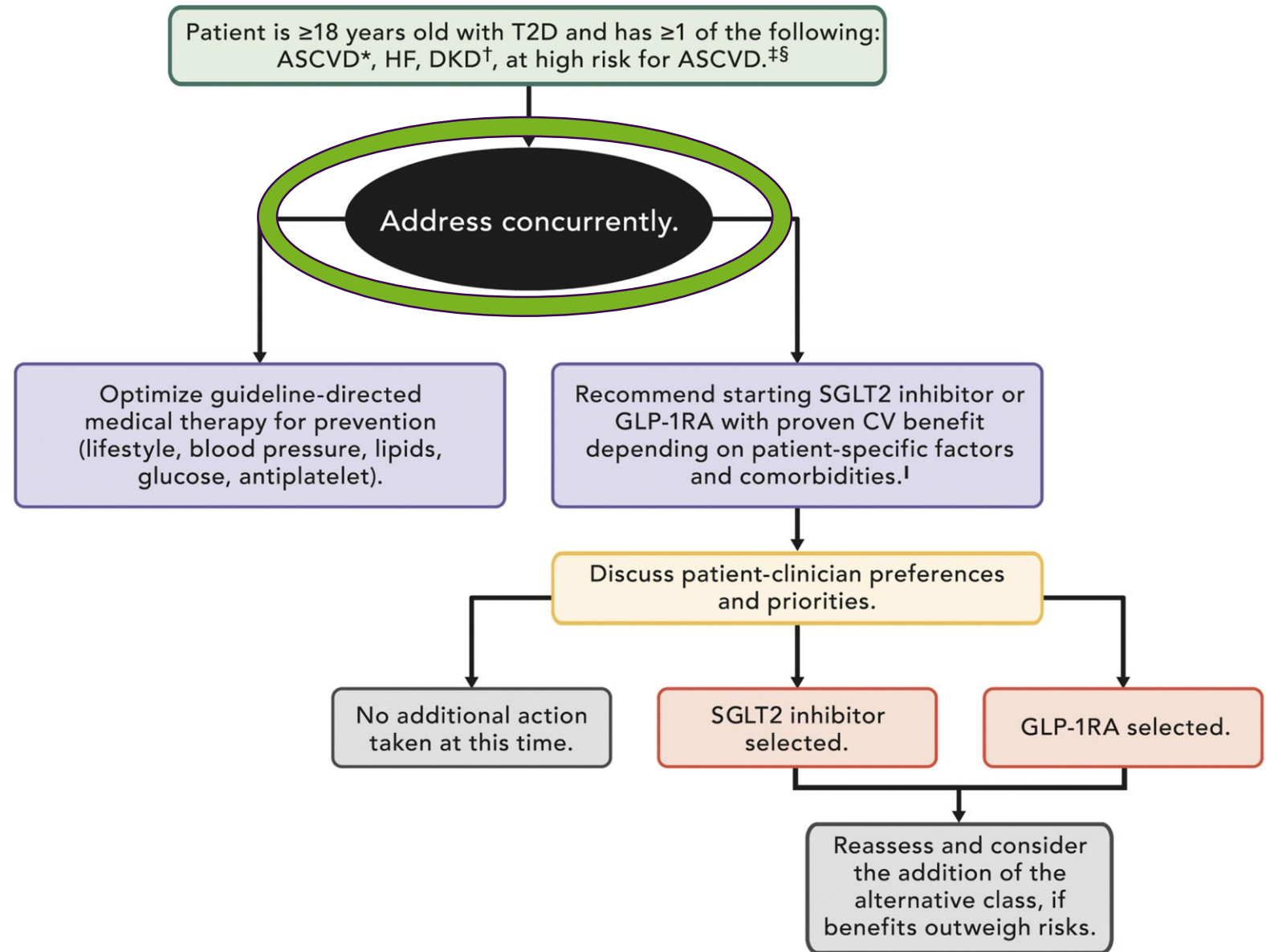
Antiplatelet agents

- **Recommendations**
- **10.34** Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of ASCVD. **A**
- **10.35a** For individuals with ASCVD and documented aspirin allergy, clopidogrel (75 mg/day) should be used. **B**
- **10.35b** The length of treatment with dual antiplatelet therapy using low-dose aspirin and a P2Y12 inhibitor in individuals with diabetes after an acute coronary syndrome or acute ischemic stroke/transient ischemic attack should be determined by an interprofessional team approach that includes a cardiovascular or neurological specialist, respectively. **E**
- **10.36** Combination therapy with aspirin plus low-dose rivaroxaban should be considered for individuals with stable coronary and/or peripheral artery disease (PAD) and low bleeding risk to prevent major adverse limb and cardiovascular events. **A**
- **10.37** Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a comprehensive discussion with the individual on the benefits versus the comparable increased risk of bleeding. **A**

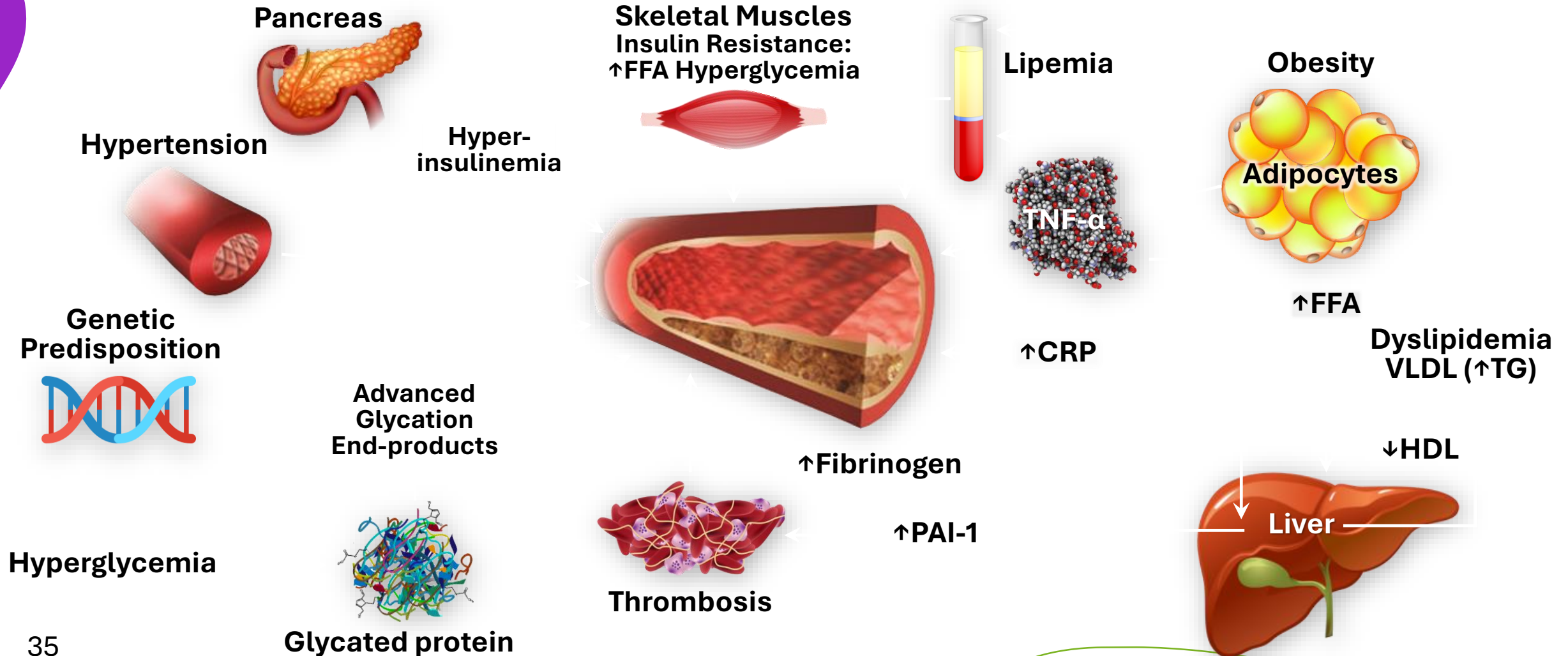
Cardiovascular Disease Screening

- **Recommendations**
- **10.38a** In asymptomatic individuals, routine screening for coronary artery disease is not recommended, as it does not improve outcomes as long as ASCVD risk factors are treated. **A**
- **10.38b** Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms; signs or symptoms of associated vascular disease, including carotid bruits, transient ischemic attack, stroke, claudication, or PAD; or electrocardiogram abnormalities (e.g., Q waves). **E**
- **10.39a** Adults with diabetes are at increased risk for the development of asymptomatic cardiac structural or functional abnormalities (stage B heart failure) or symptomatic (stage C) heart failure. Consider screening adults with diabetes by measuring a natriuretic peptide (B-type natriuretic peptide [BNP] or N-terminal pro-BNP [NT-proBNP]) to facilitate prevention of stage C heart failure. **B**
- **10.39b** In asymptomatic individuals with diabetes and abnormal natriuretic peptide levels, echocardiography is recommended to identify stage B heart failure. **A**
- **10.40** In asymptomatic individuals with diabetes and age ≥ 50 years, microvascular disease in any location, or foot complications or any end-organ damage from diabetes, screening for PAD with ankle-brachial index testing is recommended to guide treatment for cardiovascular disease prevention and limb preservation. **A** In individuals with diabetes duration ≥ 10 years, screening for PAD should be considered. **B**

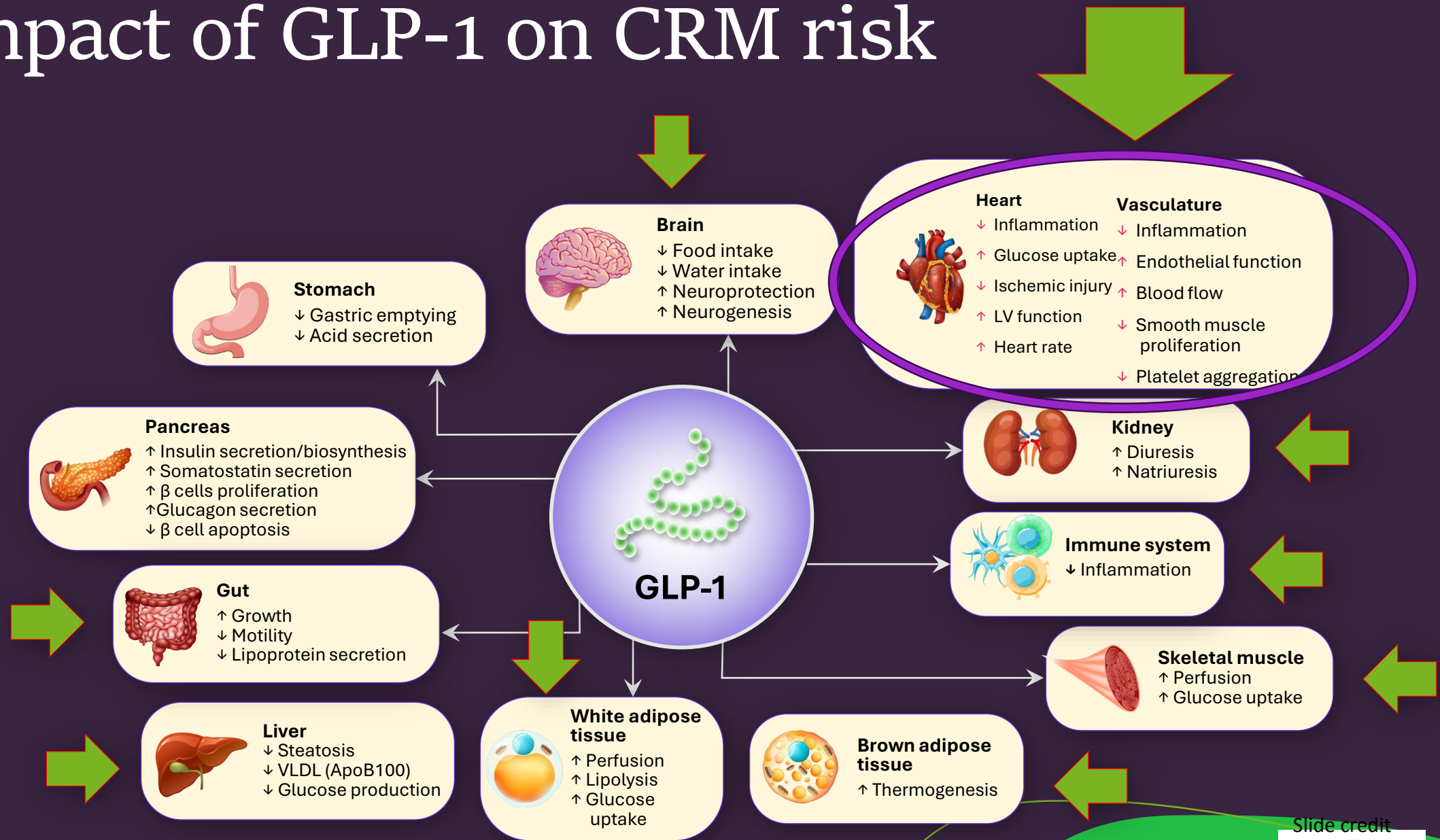
From: **10. Cardiovascular
Disease and Risk
Management: Standards of
Care in Diabetes—2024**



T2D and ASCVD



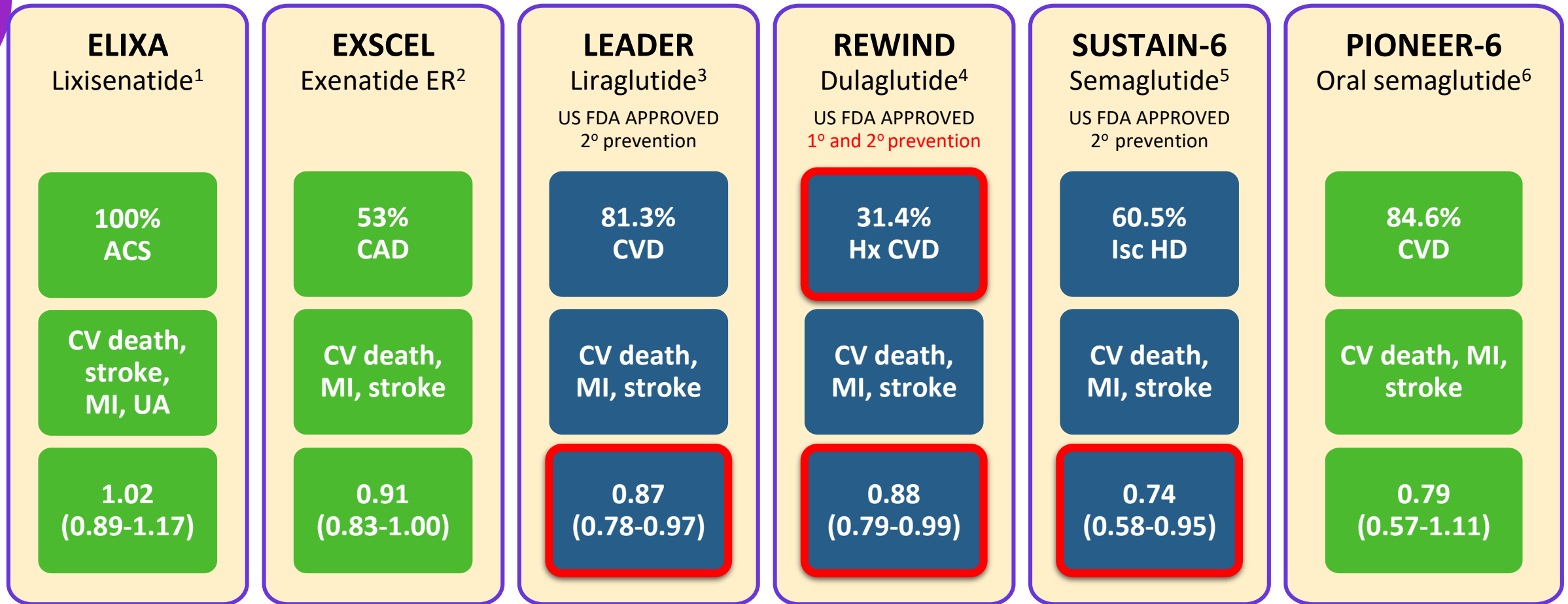
Impact of GLP-1 on CRM risk



Slide credit



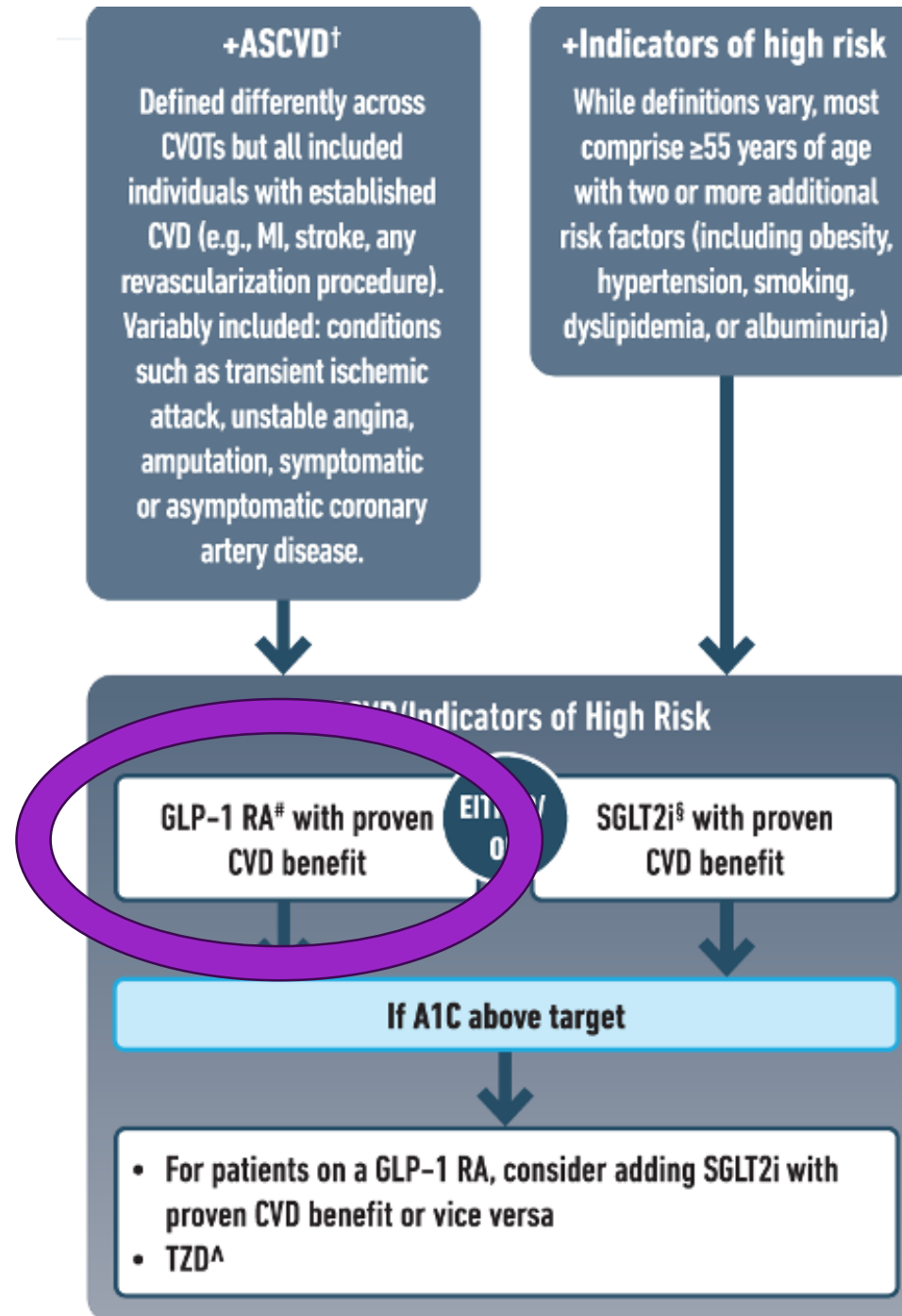
CV Outcomes Trials for GLP-1 RAs: Primary Endpoints—Some Reduce MACE



1. Pfeffer MA et al. *N Engl J Med*. 2015;373(23):2247-2257. 2. Holman RR et al. *N Engl J Med*. 2017;377(13):1228-1239. 3. Marso SP et al. *N Engl J Med*. 2016;375(4):311-322.
4. Gerstein HC et al. *Lancet*. 2019. 5. Marso SP et al. *N Engl J Med*. 2016;375(19):1834-1844. 6. Husain M et al. *N Engl J Med*. 2019.

From: **9. Pharmacologic
Approaches to Glycemic
Treatment: Standards of Care in
Diabetes—2024**

**Liraglutide
Dulaglutide
Semaglutide SQ**



SGLT2i Mediates HF Risk

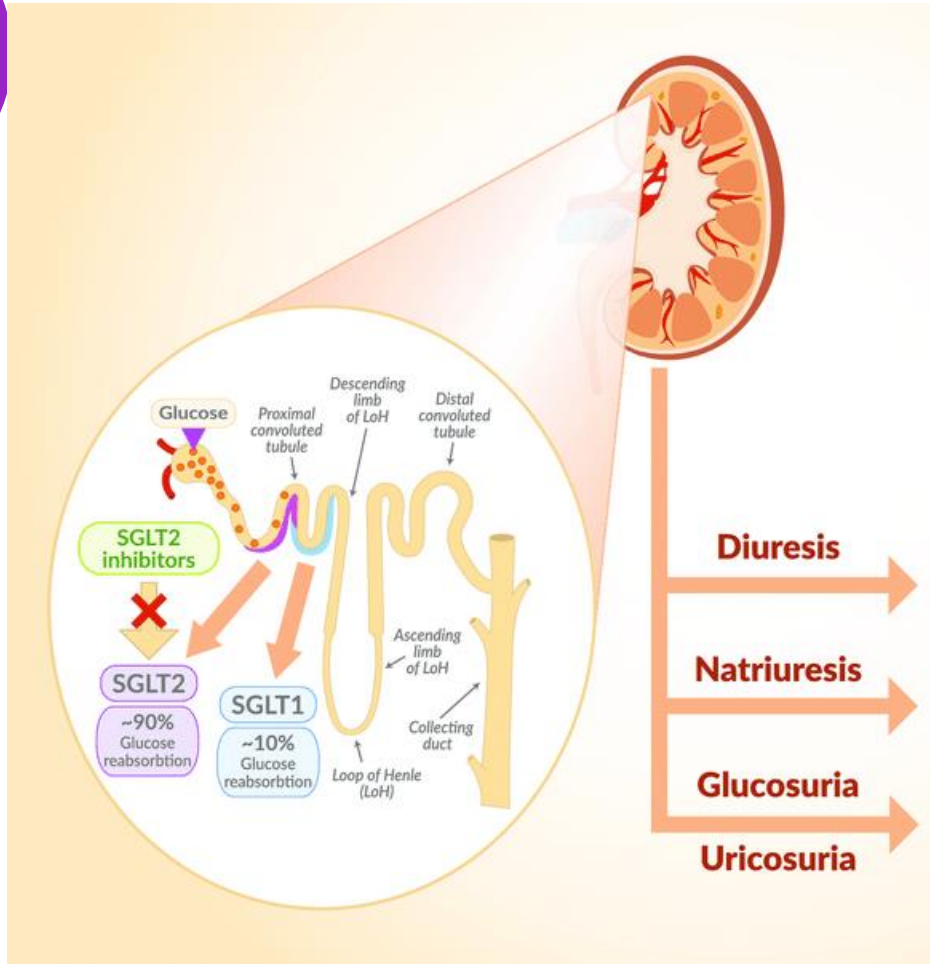


Figure 1: Creative Commons license CC-BY-4.0
Wei J & Du J. (2021) *Heart Fail Rev*, 2(3). DOI:
10.1007/s10741-020-10041-1



Figure 2: Creative Commons license CC-BY-4.0
Wei J & Du J. (2023) *CVIA*, 8(1). DOI:
10.15212/CVIA.2023.0028

Summary: SGLT2 Inhibitors and Heart Failure

EMPA-REG OUTCOME (empagliflozin)



HHF



35%
reduction

CANVAS/CANVAS-R (canagliflozin)



HHF



33%
reduction

DECLARE-TIMI 58 (dapagliflozin)



HHF



27%
reduction

VERTIS CV (ertugliflozin)



HHF



30%
reduction

EMPEROR-Reduced (empagliflozin)

*Patients with HFrEF,
with or without T2D*



HHF



31%
reduction

EMPEROR-Preserved (empagliflozin)

*Patients with HFpEF,
with or without T2D*



HHF



29%
reduction

CREDENCE (canagliflozin)

*Patients with
T2D and CKD*



HHF



39%
reduction

DAPA-HF (dapagliflozin)

*Patients with HFrEF,
with or without T2D*



HHF



30%
reduction

AMPLITUDE-O (efpeglenatide)



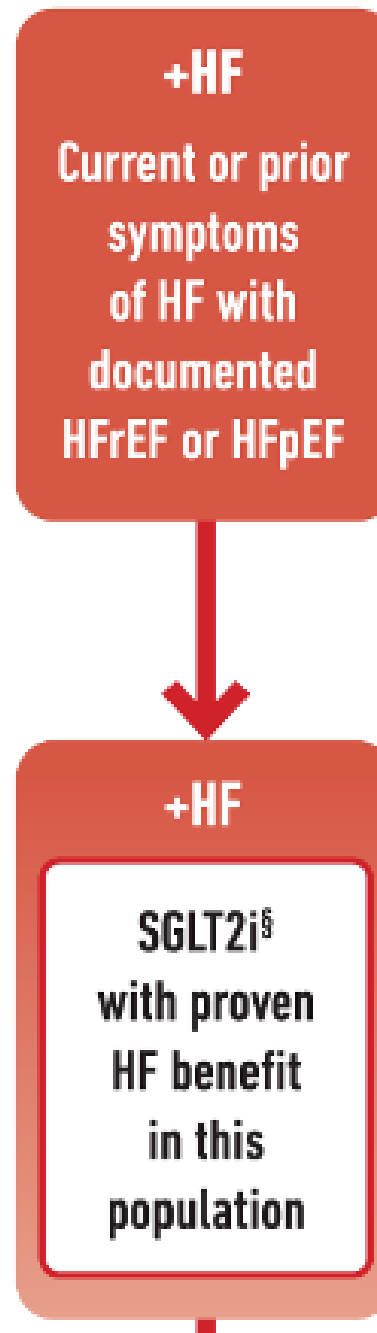
HF



39%
reduction

From: **9. Pharmacologic
Approaches to Glycemic
Treatment: Standards of Care in
Diabetes—2024**

ALL SGLT2i for HF



Diabetes Care.
2023;47(Supplement_1):S158-S178.
doi:10.2337/dc24-S009



Chronic Kidney Disease and Risk Management



Screening

- **Screening**
- **Recommendations**
- **11.1a** At least annually, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio [UACR]) and estimated glomerular filtration rate [eGFR] should be assessed in people with type 1 diabetes with duration of ≥ 5 years and in all people with type 2 diabetes regardless of treatment. **B**
- **11.1b** In people with established chronic kidney disease (CKD), urinary albumin (e.g., spot UACR) and eGFR should be monitored 1–4 times per year depending on the stage of the kidney disease (**Fig. 11.1**). **B**

Diabetes Care. 2023;47(Supplement_1):S219-S230. doi:10.2337/dc24-S011

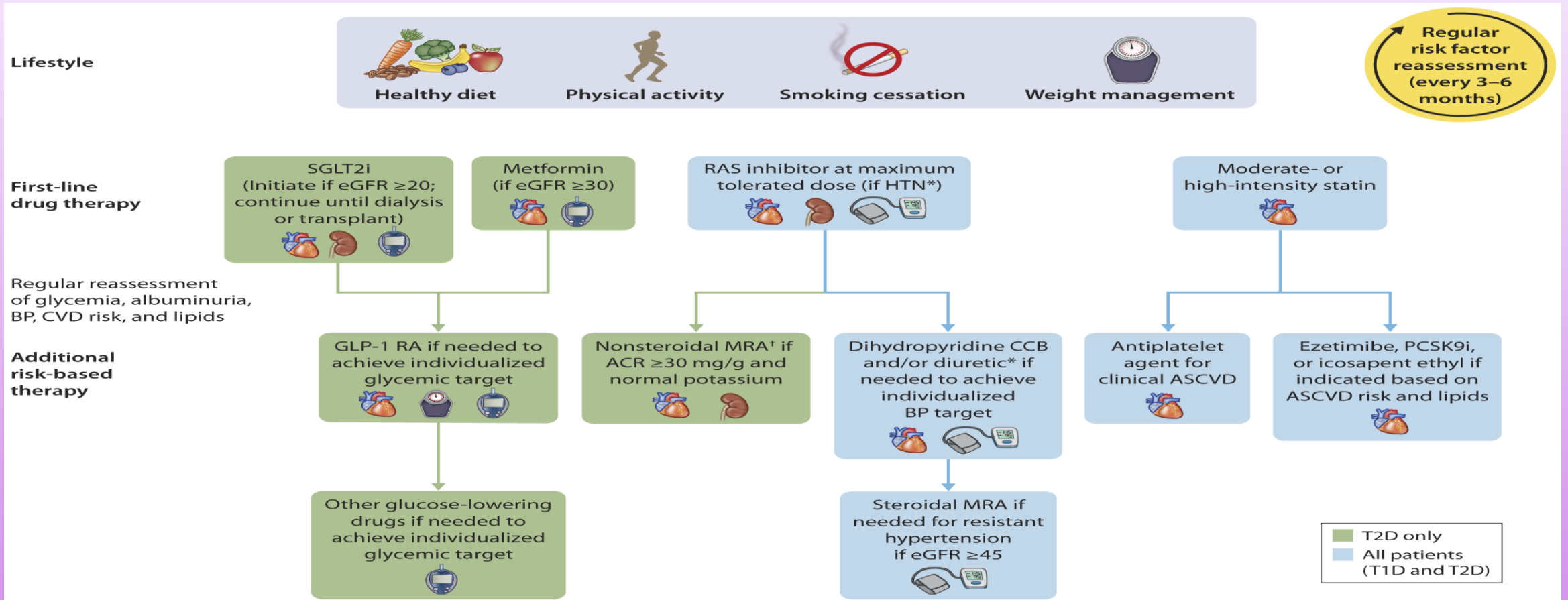
CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m²) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+
				<div>Low risk (if no other markers of kidney disease, no CKD)</div> <div>Moderately increased risk</div>	<div>High risk</div> <div>Very high risk</div>	

Figure Legend:

Risk of CKD progression, frequency of visits, and referral to nephrology according to GFR and albuminuria. The numbers in the boxes are a guide to the frequency of screening or monitoring (number of times per year). Green reflects no evidence of CKD by estimated GFR or albuminuria, with screening indicated once per year. For monitoring of prevalent CKD, suggested monitoring varies from once per year (yellow) to four times or more per year (i.e., every 1–3 months, [deep red]) according to risks of CKD progression and CKD complications (e.g., cardiovascular disease, anemia, hyperparathyroidism). These are general parameters based only on expert opinion and underlying comorbid conditions, and disease state must be taken into account, as well as the likelihood of impacting a change in management for any individual. CKD, chronic kidney disease; GFR, glomerular filtration rate. Reprinted and adapted from de Boer et al. (1).

Treatment

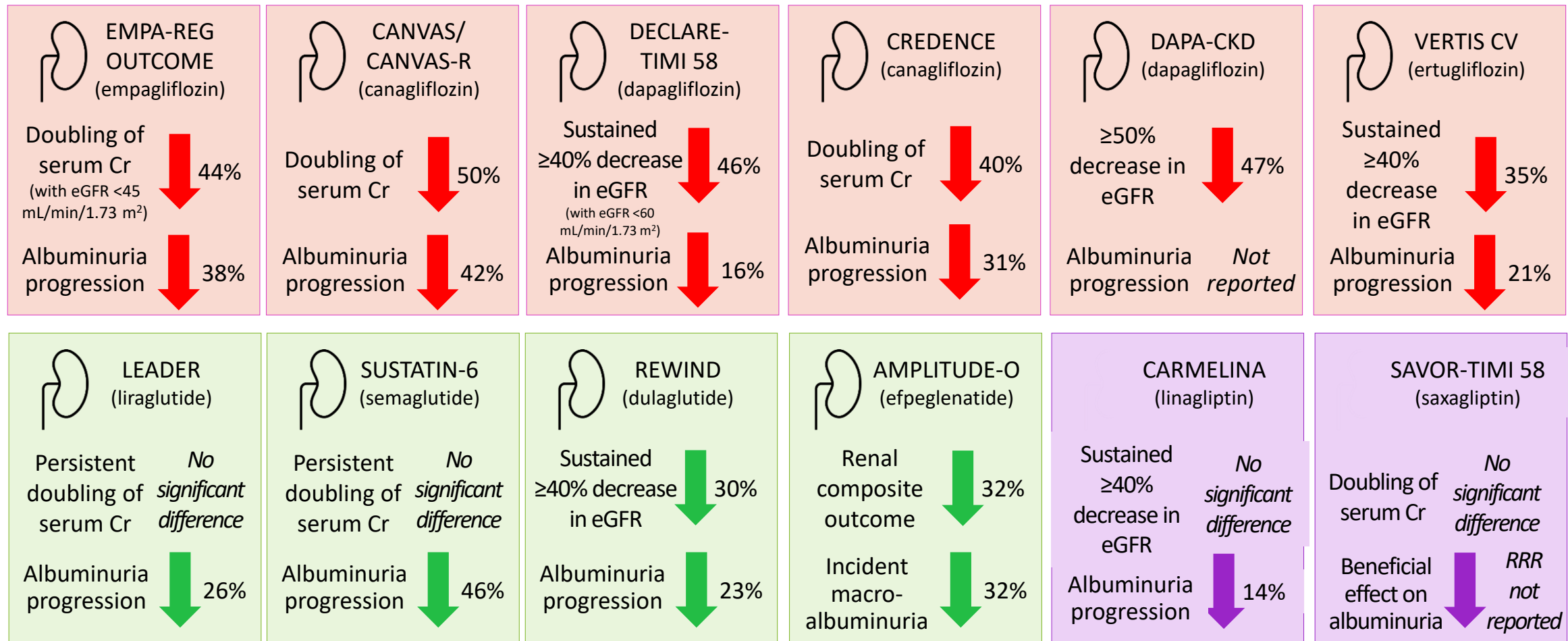
- **11.4a** In nonpregnant people with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker (ARB) is recommended for those with moderately increased albuminuria (UACR 30–299 mg/g creatinine) **B** and is strongly recommended for those with severely increased albuminuria (UACR ≥ 300 mg/g creatinine) and/or eGFR < 60 mL/min/1.73 m² to prevent the progression of kidney disease and reduce cardiovascular events. **A**
- **11.4c** An ACE inhibitor or an ARB is not recommended for the primary prevention of CKD in people with diabetes who have normal blood pressure, normal UACR (< 30 mg/g creatinine), and normal eGFR. **A**
- **11.4d** Do not discontinue renin-angiotensin system blockade for mild to moderate increases in serum creatinine ($\leq 30\%$) in the absence of signs of extracellular fluid volume depletion. **A**
- **11.5a** For people with type 2 diabetes and CKD, use of a sodium–glucose cotransporter 2 (SGLT2) inhibitor is recommended to reduce CKD progression and cardiovascular events in individuals with eGFR ≥ 20 mL/min/1.73 m² and urinary albumin ≥ 200 mg/g creatinine. **A**
- **11.5b** For people with type 2 diabetes and CKD, use of an SGLT2 inhibitor is recommended to reduce CKD progression and cardiovascular events in individuals with eGFR ≥ 20 mL/min/1.73 m² and urinary albumin ranging from normal to 200 mg/g creatinine. **B**
- **11.5c** For cardiovascular risk reduction in people with type 2 diabetes and CKD, consider use of an SGLT2 inhibitor (if eGFR is ≥ 20 mL/min/1.73 m²), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if eGFR is ≥ 25 mL/min/1.73 m²). **A**
- **11.5d** As people with CKD and albuminuria are at increased risk for cardiovascular events and CKD progression, a nonsteroidal mineralocorticoid receptor antagonist that has been shown to be effective in clinical trials is recommended to reduce cardiovascular events and CKD progression (if eGFR is ≥ 25 mL/min/1.73 m²). Potassium levels should be monitored. **A**



Holistic approach for improving outcomes in people with diabetes and CKD. Icons presented indicate the following benefits: BP cuff, BP lowering; glucometer, glucose lowering; heart, cardioprotection; kidney, kidney protection; scale, weight management. eGFR is presented in units of mL/min/1.73 m². *ACEi or ARB (at maximal tolerated doses) should be first-line therapy for hypertension when albuminuria is present. Otherwise, dihydropyridine calcium channel blocker or diuretic can also be considered; all three classes are often needed to attain BP targets.

†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. Reprinted from de Boer et al. (1).

Summary: Newer Glucose-Lowering Drugs and Renal Outcomes





Retinopathy, Neuropathy, & Foot Care



Diabetic Retinopathy

- **Recommendations**
- **12.1** Implement strategies to help people with diabetes reach glycemic goals to reduce the risk or slow the progression of diabetic retinopathy. **A**
- **12.2** Implement strategies to help people with diabetes reach blood pressure and lipid goals to reduce the risk or slow the progression of diabetic retinopathy. **A**

Retinopathy Screening

- **Recommendations**
- **12.3** Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes. **B**
- **12.4** People with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis. **B**
- **12.5** If there is no evidence of retinopathy from one or more annual eye exams and glycemic indicators are within the goal range, then screening every 1–2 years may be considered. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations should be repeated at least annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight-threatening, then examinations will be required more frequently. **B**
- **12.6** Programs that use retinal photography with remote reading or the use of U.S. Food and Drug Administration–approved artificial intelligence algorithms to improve access to diabetic retinopathy screening are appropriate screening strategies for diabetic retinopathy. Such programs need to provide pathways for timely referral for a comprehensive eye examination when indicated. **B**
- **12.7** Counsel individuals of childbearing potential with preexisting type 1 or type 2 diabetes who are planning pregnancy or who are pregnant on the risk of development and/or progression of diabetic retinopathy. **B**
- **12.8** Individuals with preexisting type 1 or type 2 diabetes should receive an eye exam before pregnancy and in the first trimester and should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy. **B**

Retinopathy Treatment

- **Treatment**
- **Recommendations**
- **12.9** Promptly refer individuals with any level of diabetic macular edema, moderate or worse nonproliferative diabetic retinopathy (a precursor of proliferative diabetic retinopathy [PDR]), or any PDR to an ophthalmologist who is knowledgeable and experienced in the management of diabetic retinopathy. **A**
- **12.10** Panretinal laser photocoagulation therapy is indicated to reduce the risk of vision loss in individuals with high-risk PDR and, in some cases, severe nonproliferative diabetic retinopathy. **A**
- **12.11** Intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) are a reasonable alternative to traditional panretinal laser photocoagulation for some individuals with PDR and also reduce the risk of vision loss in these individuals. **A**
- **12.12** Intravitreal injections of anti-VEGF are indicated as first-line treatment for most eyes with diabetic macular edema that involves the foveal center and impairs vision acuity. **A**
- **12.13** Macular focal/grid photocoagulation and intravitreal injections of corticosteroid are reasonable treatments in eyes with persistent diabetic macular edema despite previous anti-VEGF therapy or eyes that are not candidates for this first-line approach. **A**
- **12.14** The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage. **A**

Neuropathy

- **Screening**
- **Recommendations**
- **12.17** All people with diabetes should be assessed for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter. **B**
- **12.18** Assessment for distal symmetric polyneuropathy should include a careful history and assessment of either temperature or pinprick sensation (small-fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function). All people with diabetes should have annual 10-g monofilament testing to identify feet at risk for ulceration and amputation. **B**
- **12.19** Symptoms and signs of autonomic neuropathy should be assessed in people with diabetes starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes, and at least annually thereafter, and with evidence of other microvascular complications, particularly kidney disease and diabetic peripheral neuropathy. Screening can include asking about orthostatic dizziness, syncope, or dry cracked skin in the extremities. Signs of autonomic neuropathy include orthostatic hypotension, a resting tachycardia, or evidence of peripheral dryness or cracking of skin. **E**

DPN – What is it?

Most common (75% of diabetic neuropathies)

Length-dependent “dying-back” of sensory axons

Insidious, slow progression “stocking-glove”

Most often starts in the toes

By mid-calves, fingertips will also be involved

Predictor for foot ulcers, CV and all-cause mortality, and CV morbidity

Major contributor to falls and fracture

DPN – Small Fiber Clinical Manifestations

Abnormal and/or Exaggerated Pain Perception

BURNING, LANCINATING, TINGLING, SHOOTING

Chief Complaint for 25%

Worse at night!

Abnormal Temperature Discrimination

Affects nociception “protective sensation”

Impacts ADL, QoL

DPN - Large Fiber Clinical Manifestations

NUMBNESS, TINGLING WITHOUT PAIN

“wrapped in wool” or “walking with thick socks”

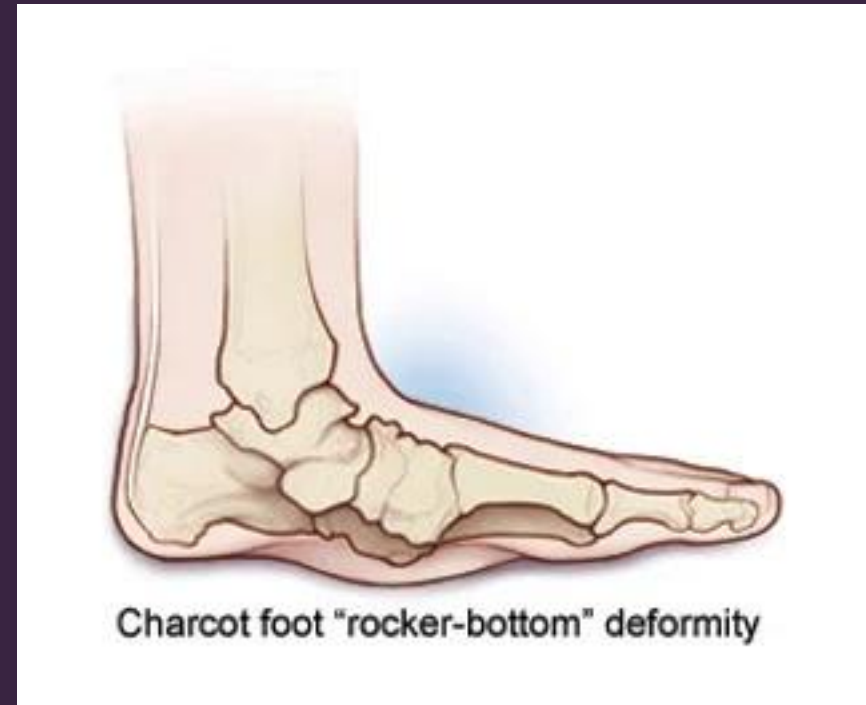
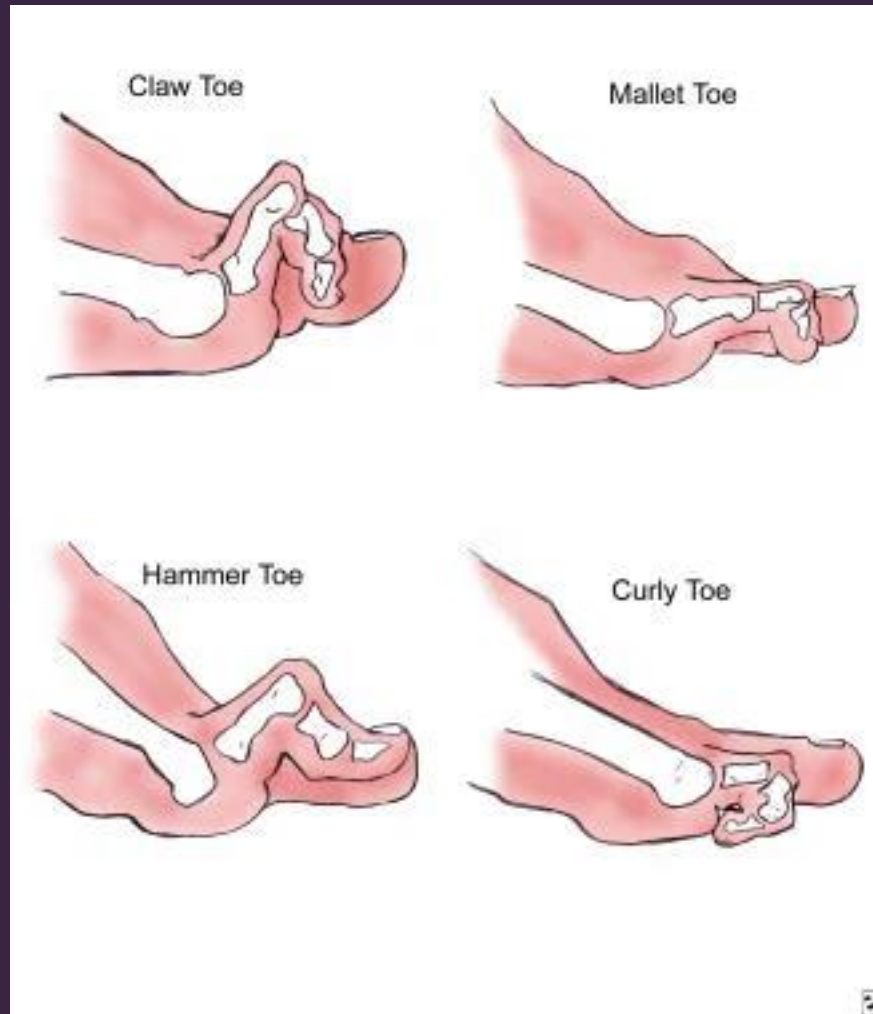
LOSS OF PROTECTIVE SENSATION

High risk for Diabetic Foot Ulcer (DFU)

Wasting small intrinsic muscles, Bone deformities

Poor balance, Abnormal gait

Foot Deformity



Components of a Comprehensive Foot Exam

Vasculature

DP, PT Pulses, capillary refill, temperature

Skeletal

Bony deformities, muscle atrophy

Vast majority of plantar ulcers caused by bony prominence + insensitivity

Skin

integrity: callus, lesion, maceration

Gait/Condition of shoes

Ill-fitting shoes lead contributing factor 36% amputations

Tools of the Trade

Small Fiber

- 1-gm monofilament
- Diminished Prickly Pain (i.e., Wartenberg wheel)



Large Fiber

- 128-Hz Tuning Fork
- 10-gm monofilament



FDA Approved Pharmacotherapies

Duloxetine

60 or 120 mg/d

AE: nausea, somnolence, dizziness

Pregabalin

75 mg twice daily inc. every 3-7 days, max dose 600 mg/d
based on pain relief, 300-600 mg/d

AE: somnolence, dizziness, peripheral edema, weight gain

Caution elderly and $\text{eGFR} < 45 \text{ mL/min/1.73m}^2$

25 mg/d starting dose

Tapentadol & Tramadol – OPIOID, NOT RECOMMENDED

FDA Approved Prescription Medical Food

L-methylfolate calcium, Vitamin B₆, Vitamin B₁₂

Common Off-Label Pharmacotherapies

Amitriptyline; Desipramine; Nortriptyline

10 to 25 mg/d; inc. by 10 mg weekly; 10 to 150 mg/d

AE: dry mouth, urinary retention, drowsiness, confusion, weight gain

Caution elderly, ischemic heart disease

Gabapentin - like pregabalin effectiveness/AE/safety

shorter ½-life, three times daily dosing

most require 1800 mg/d; max dose 3600 mg/d

Venlafaxine – like duloxetine effectiveness but > AE

37.5 mg/d; inc. by 37.5 mg weekly

150 to 225 mg/d

Lidocaine 5% patch

Capsaicin patch/cream

At Home Foot Care

Never barefoot

Daily foot checks

Dry thoroughly between toes

Moisturize

When to seek medical attention

- Nails cutting into skin

- Callus

- Areas Redness/warmth

Orthostatic Hypotension

- Nonpharmacologic Measures
 - Adequate salt intake
 - Avoid meds that cause hypotension
 - Compressive garments over the legs and abdomen
- Pharmacologic Measures
 - Midodrine and droxidopa are FDA approved
- Treatment of BP medication at bedtime with shorter-acting drugs such as guanfacine, clonidine, isradipine, atenolol, or metoprolol tartrate

Gastroparesis

- Low fiber, low fat eating plan
- Small frequent meals
- Liquid calories
- D/C drugs that slow GI motility
 - Opioids, Anticholinergics, TCAs, GLP-1 RAs, Pramlintide
- FDA approved treatment- Metoclopramide
 - Due to side effects not recommended by FDA to use > 12 weeks

Erectile Dysfunction

- PDE 5 inhibitors
 - Sildenafil, Vardenafil, Tadalafil
- Intracorporeal or intraurethral prostaglandins
- Vacuum Devices
- Penile Prostheses
- Treat hypogonadism if present

Summary

- A multifactorial approach of addressing glycemic management, lipid management, and hypertension is necessary to reduce diabetes complications
- Regular screenings for chronic kidney disease and staging is important to implement appropriate therapies to slow progression
- Retinopathy & neuropathy are microvascular complications that require screening, monitoring, and possible treatment