MICIS

Maine Independent Clinical Information Service

Maine Medical Association

Department of Health and Human Services
Maine People Living Safe, Healthy and Productive Lives

Diabetes Update Focusing on GLP-1s + SGLT-2s

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Disclosures

- MICIS does not accept any money from pharmaceutical companies nor ineligible companies
- None of the individuals in control of content for this activity have relevant financial relationships to disclose
- I have no conflicts of interest
- Off-label use of GLP-1s is pointed out
- *This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Maine Medical Education Trust and the Maine Independent Clinical Information Service (MICIS). The Maine Medical Education Trust is accredited by the Maine Medical Association Committee on Continuing Medical Education and Accreditation to provide continuing medical education for physicians.*

Learning Objectives

At the end of this presentation, learners should be able to:

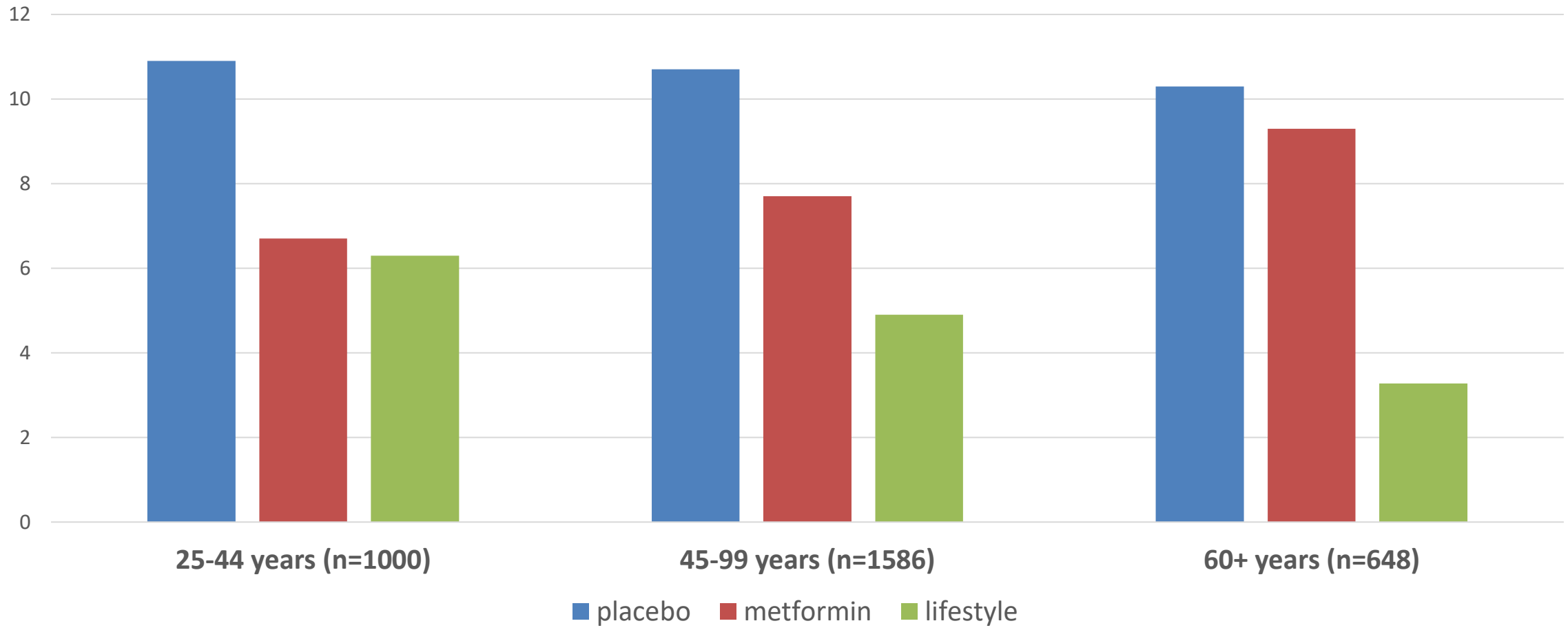
- Analyze strategies for diabetes prevention
- Investigate the pharmacology of the diabetes drug classes: GLP-1s and SGLT-2s
- Formulate a framework for comprehensive diabetes care

Prediabetes

- Identify those at risk
- Screen
- Encourage diet changes & exercise

Progression to diabetes in patients with prediabetes

(per 100 person years)



Lifestyle Management Recommendations

- Meal Planning
  - Discuss food + housing insecurity, financial limitations
  - Refer to Diabetes Educator or Dietician or local Diabetes Prevention Program (Bangor YMCA)
- Exercise
  - Combination of aerobic & resistance training
  - Stand up & move every 30 minutes
  - Any activity is better than none

Diagnosis

Prediabetes:
A1C 5.7-6.4

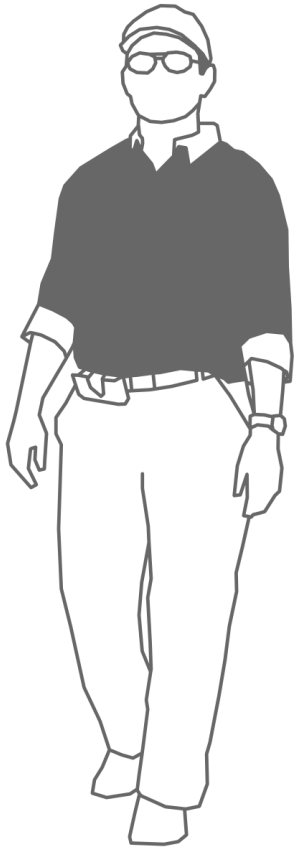
Diabetes: FPG>126 or

A1C>6.5 or

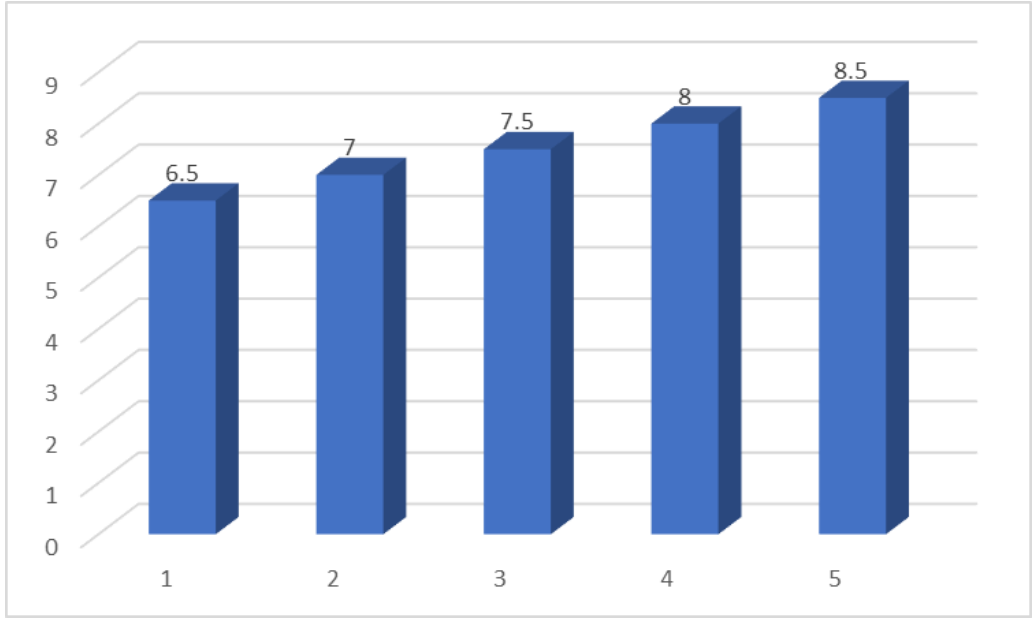
Random PG>200 + classic sx

Case Study: Angus

- 45 year old recently diagnosed with type II diabetes
- Works as a local delivery truck driver and lives in Crabapple Cove, Maine
- What are some initial strategies to employ and what are our goals?



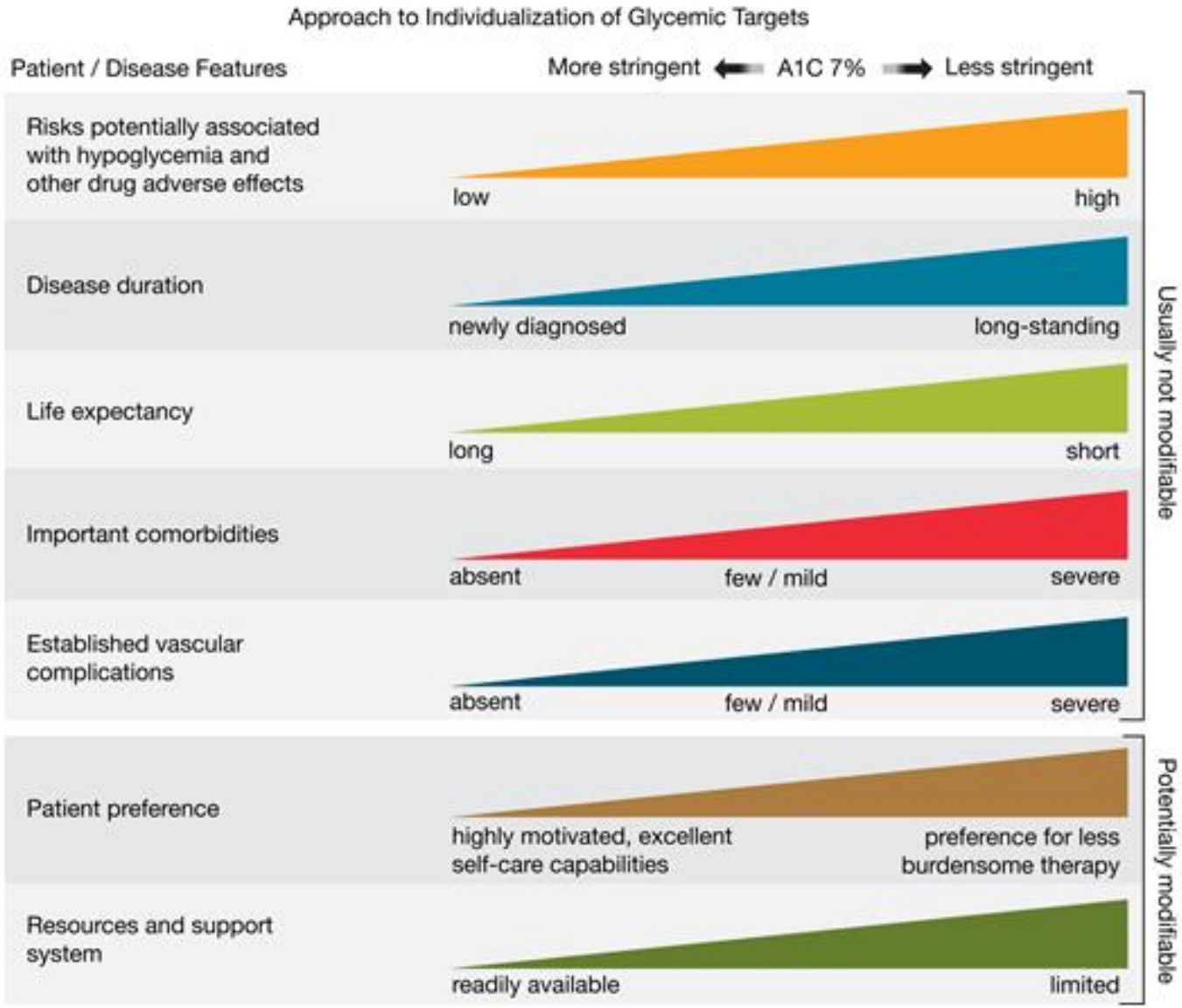
Individualize A1C Goals



- <6.5 tight control (young, recent dx)
- <7 usual control (most patients)
- <8 relaxed control (older, comorbidities, decreased function)
- <8.5 loose control (frail, end-stage)

*consider that A1C has a margin of error 0.5% on either side of value

Individualizing Control



Individualizing Control

- Lower risk of hypoglycemia/side effects
- Newer diagnosis
- Long life expectancy
- Absent major co-morbidities
- Absent vascular complications
- Patient motivation & ability for self-care
- High support level/access to resources

→ Higher risk of hypoglycemia/side effects

→ Long-standing disease duration

→ Short life expectancy

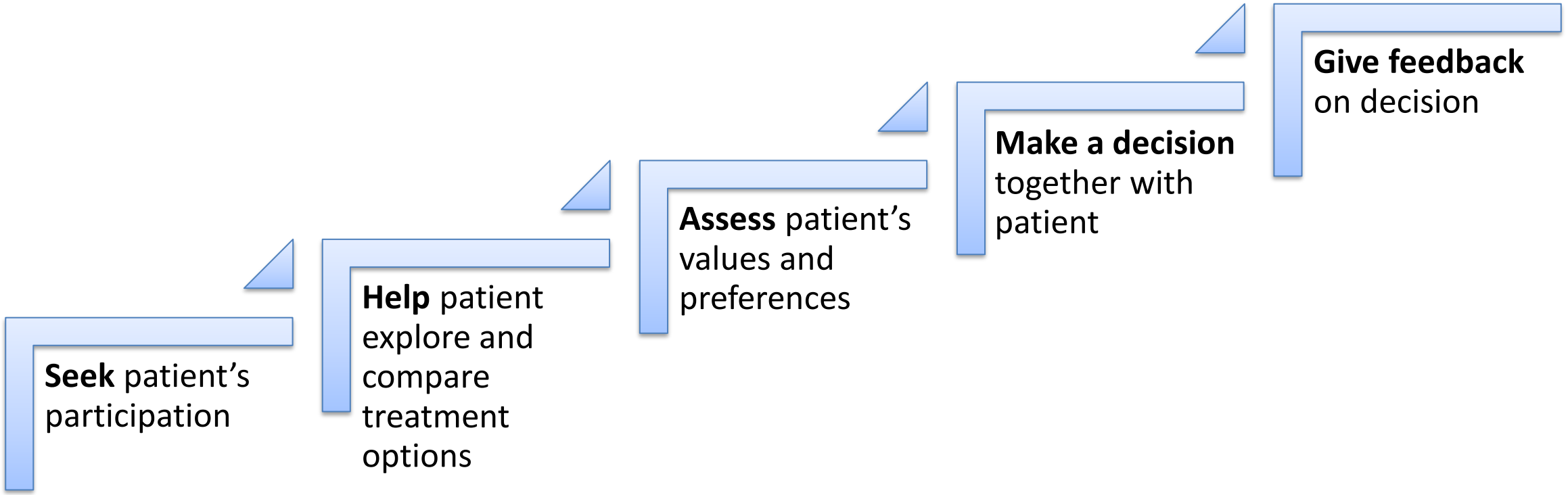
→ Severe co-morbidities

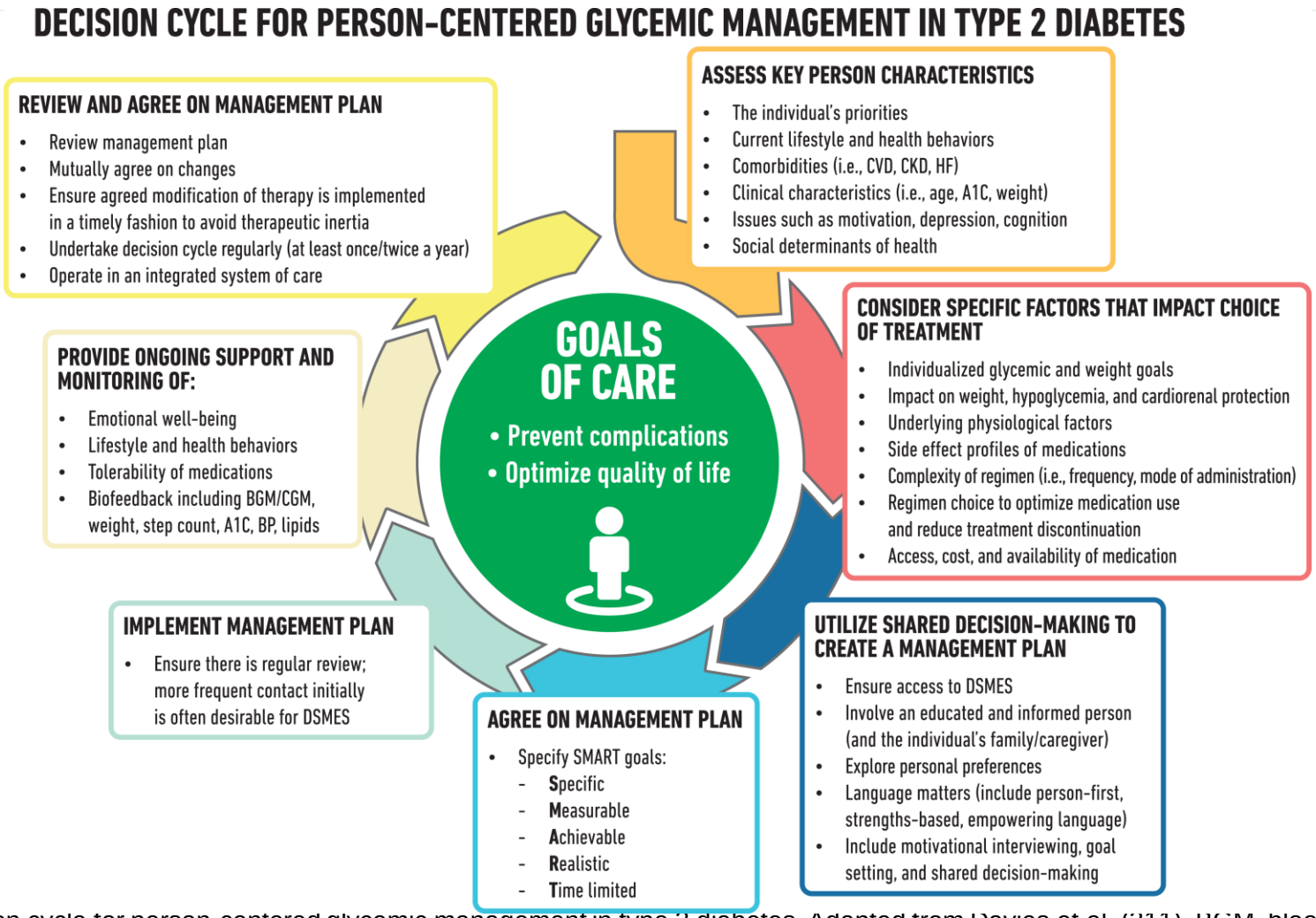
→ Severe vascular complications

→ Preference for less burden of treatment

→ Limited support/access to resources

Goals for shared decision-making in diabetes





Figure

Decision cycle for person-centered glycemic management in type 2 diabetes. Adapted from Davies et al. (211). BGM, blood glucose monitoring; BP, blood pressure; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CVD, atherosclerotic cardiovascular disease; DSMES, diabetes self-management education and support; HF, heart failure.

Person-centered glycemic management

ASSESS KEY PERSON CHARACTERISTICS

- The individual's priorities
- Current lifestyle and health behaviors
- Comorbidities (i.e., CVD, CKD, HF)
- Clinical characteristics (i.e., age, A1C, weight)
- Issues such as motivation, depression, cognition
- Social determinants of health

CONSIDER SPECIFIC FACTORS THAT IMPACT CHOICE OF TREATMENT

- Individualized glycemic and weight goals
- Impact on weight, hypoglycemia, and cardiorenal protection
- Underlying physiological factors
- Side effect profiles of medications
- Complexity of regimen (i.e., frequency, mode of administration)
- Regimen choice to optimize medication use and reduce treatment discontinuation
- Access, cost, and availability of medication

Person-centered glycemic management

UTILIZE SHARED DECISION-MAKING TO CREATE A MANAGEMENT PLAN

- Ensure access to DSMES
- Involve an educated and informed person (and the individual's family/caregiver)
- Explore personal preferences
- Language matters (include person-first, strengths-based, empowering language)
- Include motivational interviewing, goal setting, and shared decision-making

AGREE ON MANAGEMENT PLAN

- Specify SMART goals:
  - Specific
  - Measurable
  - Achievable
  - Realistic
  - Time limited

Person-centered glycemic management

IMPLEMENT MANAGEMENT PLAN

- Ensure there is regular review; more frequent contact initially is often desirable for DSMES

PROVIDE ONGOING SUPPORT AND MONITORING OF:

- Emotional well-being
- Lifestyle and health behaviors
- Tolerability of medications
- Biofeedback including BGM/CGM, weight, step count, A1C, BP, lipids

REVIEW AND AGREE ON MANAGEMENT PLAN

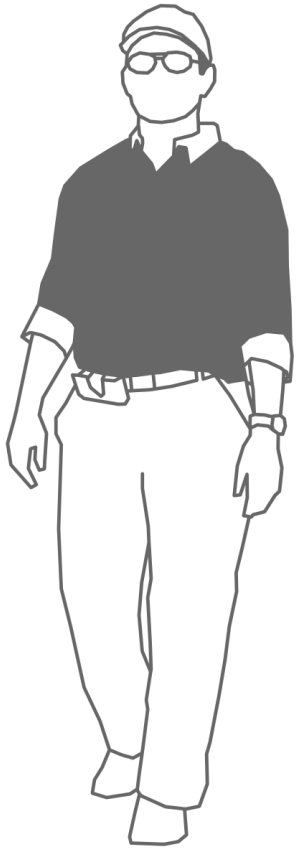
- Review management plan
- Mutually agree on changes
- Ensure agreed modification of therapy is implemented in a timely fashion to avoid therapeutic inertia
- Undertake decision cycle regularly (at least once/twice a year)
- Operate in an integrated system of care

Medication List

Class/Medication
biguanide
metformin (Glucophage)
SGLT-2 inhibitors (flozins)
canagliflozin (Invokana)
empagliflozin (Jardiance)
dapagliflozin (Farxiga)
ertugliflozin (Steglatro)
GLP-1 receptor agonists
liraglutide (Victoza)
semaglutide (Ozempic)
dulaglutide (Trulicity)
exenatide (Bydureon)
lixisenatide (Adlyxin)
semaglutide (Rybelsus)
exenatide (Byetta)

Case Study: Angus

- 45 year old recently diagnosed with type II diabetes
- HgBA1C=8.5 despite 3 months of lifestyle changes
- What will drive your decision in choosing a medication?



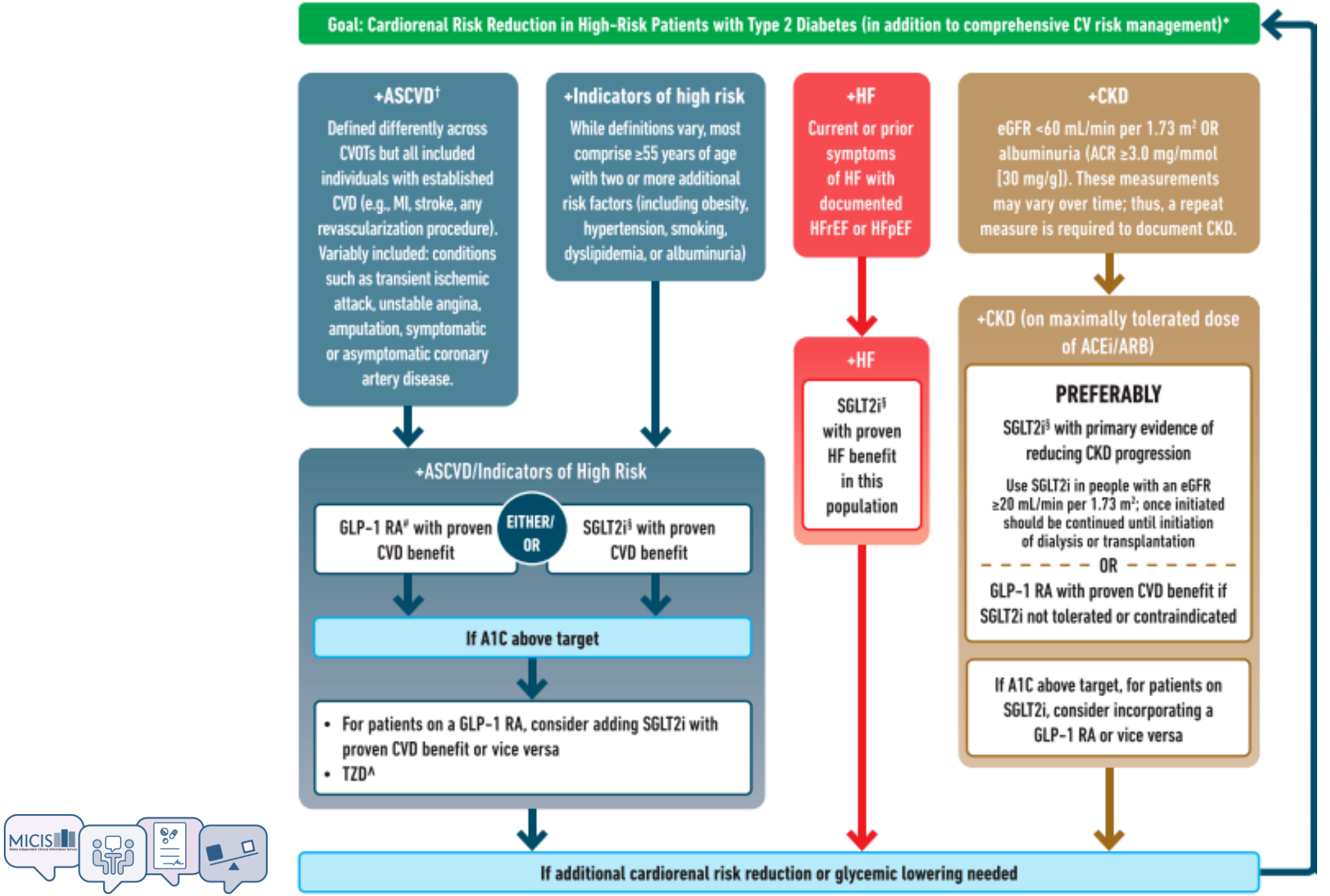
Evidence of Benefit

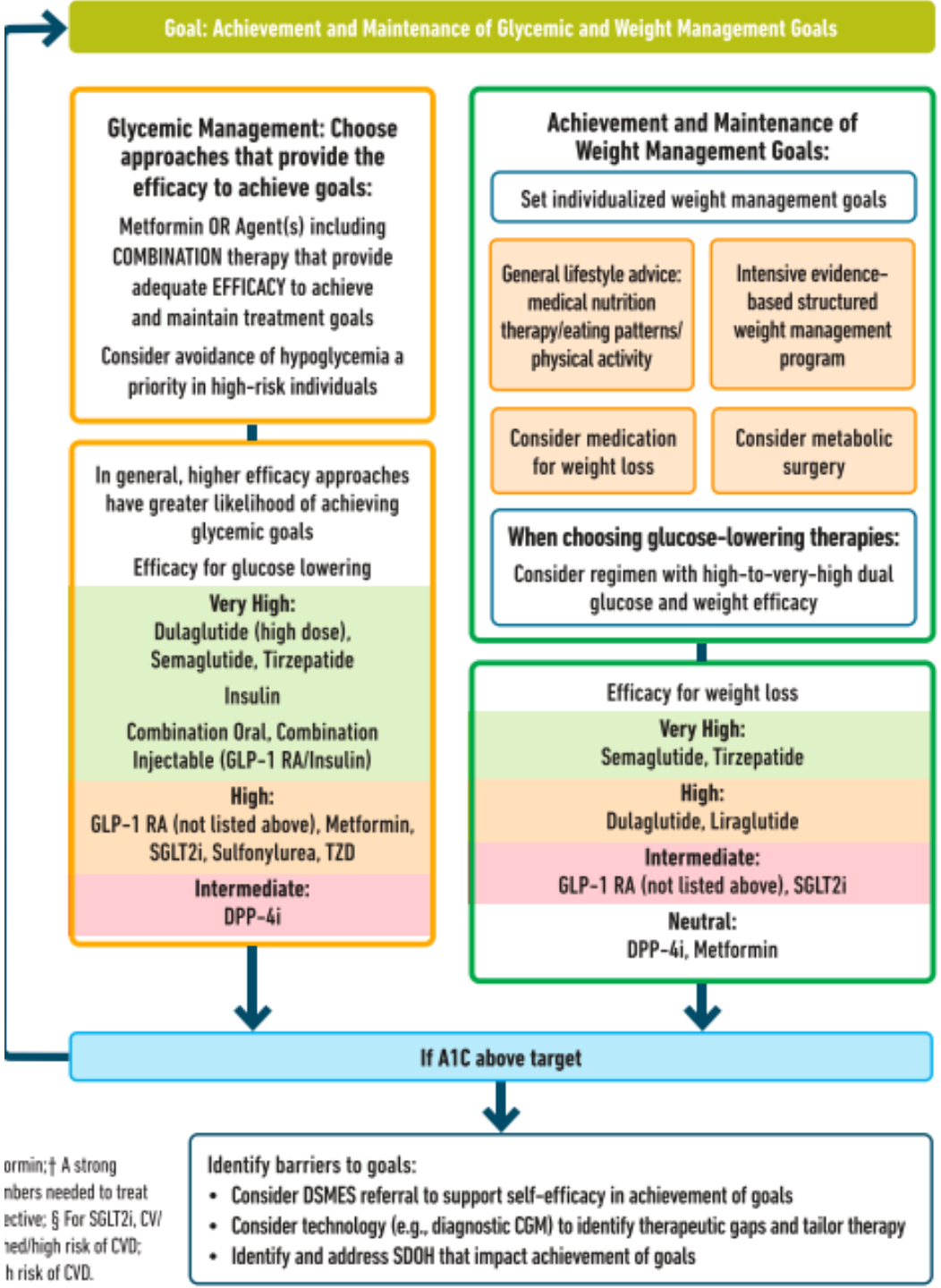
	ASCVD	Heart failure	Chronic kidney disease**	Overweight or obesity	All other patients
Sodium-glucose co-transporter 2 inhibitor (SGLT-2i)	✓	✓	✓		
Glucagon-like peptide-1 receptor agonist (GLP-1 RA)	✓		✓	✓	
Biguanide (metformin)					✓

ADA 2023 Treatment Algorhythm

https://diabetesjournals.org/view-large/figure/4482963/dc23S009f3.tif

https://diabetesjournals.org/care/issue/46/Supplement_1 Chapter 9, page 8 (Figure 9.3)


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 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/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 adding SGLT2i with proven CVD benefit or 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 1.73 m²; 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-1 RA or vice versa
If additional cardiorenal risk reduction or glycemic lowering needed



ormin;† A strong
nbers needed to treat
ective; § For SGLT2i, CV
ned/high risk of CVD;
h risk of CVD.

So let’s start with a GLP-1!

GLP-1s

(glucagon-like peptide agonists)

- FDA approved in 2005-2017
- **Nickname:** the “tides”
- **Mechanism of action:** works in the pancreas to increase glucose dependent insulin secretion as an incretin mimetic, decreases glucagon, decreases GI emptying, increases satiety

What benefits would we expect from a GLP-1?

GLP-1s

(glucagon-like peptide agonists)

Benefits (newer drugs studied more/more evidence):

- decreased mortality
- decreased MACE (major adverse cardiac events)
- possible slowed progression of CKD
- weight loss

What side effects are most common with a GLP-1?

GLP-1s

(glucagon-like peptide agonists)

Side effects:

- GI: nausea, vomiting, diarrhea, constipation
- decreased appetite
- tolerance

What are some tips for using GLP-1s?

GLP-1s

(glucagon-like peptide agonists)

- Always start with a low dose, including after a period of abstinence
- Wait 4-6 weeks before increasing dose
- Eat smaller, more frequent, low fat meals slowly
- Monitor glycemic control and decrease insulin if necessary
- Check baseline and periodic creatinine; electrolytes if significant ongoing GI symptoms

Indication: Obesity

GLP-1s	DM	Obesity
semaglutide subq	Ozempic ™	Wegovy ™
liraglutide	Victoza ™	Saxenda ™
tirzepatide	Mounjaro™	Zepbound ™

- Other drugs in class (and certain brand versions) likely being used off-label
- Studies of benefits in obesity without DM ongoing

https://micismaine.org/education-topics/clinical-toolkit/

Medications for Type 2 Diabetes

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GLP-1s (glucagon-like peptide agonists)

FDA approved in 2005-17 **NICKNAME: the "tides"**

MECHANISM OF ACTION: works in the pancreas to increase glucose dependent insulin secretion as an incretin mimetic, decreases glucagon, decreases GI emptying, increases satiety

BENEFITS (see individual drug information, newer drugs studied more): decreased mortality, decreased MACE (major adverse cardiac events), possible slowed progression of CKD

CONTRAINDICATIONS: Personal/family hx medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 (MEN-2, black box warning); use with relative caution with hx gastric surgery, gastroparesis, hx pancreatitis

DRUG INTERACTIONS: Insulin (monitor glycemic control, consider

SIDE EFFECTS:

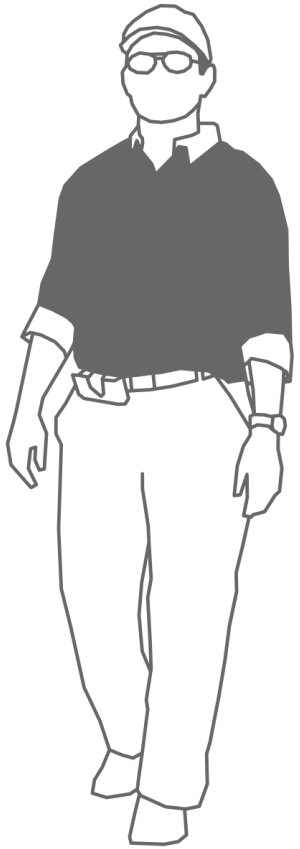
Common: GI: nausea, vomiting, diarrhea, constipation, decreased appetite; tolerance;

Rare: thyroid C-cell tumor, MEN-2, pancreatitis, AKI, retinopathy, gallbladder disease

ADVICE TO COUNTER GI SIDE EFFECTS:

Case Study: Angus

- 45 year old with type II diabetes
- Taking a GLP-1 for one year
- Recent hospital stay for NSTEMI
- Any changes to diabetes regimen?



SGLT-2s

(sodium-glucose co-transporter-2 inhibitors)

- FDA approved in 2013-4
- **Nickname:** the “flozins”
- **Mechanism of action:** works in the kidney to increase urinary glucose excretion by decreasing glucose resorption

What benefits would we expect from a SGLT-2?

SGLT-2s

(sodium-glucose co-transporter-2 inhibitors)

BENEFITS (not all drugs in class have data on all benefits, see individual drug information)

- decreases mortality
- decreases MACE (major adverse cardiac events)
- slows progression of CKD,
- decreases hospitalization in HFrEF (heart failure, EF<40%)
- Benefit in other heart failure types
- Lowers blood pressure

What side effects are most common with a SGLT-2?

SGLT-2s

(sodium-glucose co-transporter-2 inhibitors)

SIDE EFFECTS:

- Common: increased urinary frequency and volume resulting in
  - Thirst
  - Hypovolemia
  - acute kidney injury
  - Orthostatic hypotension
- infection (genital mycotic, UTI),
- DKA-euglycemic

SGLT-2s

(sodium-glucose co-transporter-2 inhibitors)

INCREASED RISK FACTORS FOR DKA:

- acute serious illness
- surgery & colonoscopy (hold 3d prior)
- low carbohydrate diet (i.e. keto)
- Fasting
- sudden decrease in insulin dose
- hx of DKA
- alcohol use
- type 1 DM
- age >65

What are some tips for using SLGT-2s?

SGLT-2s

(sodium-glucose co-transporter-2 inhibitors)

- Counsel patients to drink significantly more water
- Recheck Na, K, Cr at 4 weeks
- Use lowest starting dose, consider increase after 4 week labs (stop if GFR decreases 30%, smaller decreases common)
- Monitor blood pressure and volume status

https://micismaine.org/education-topics/clinical-toolkit/

Medications for Type 2 Diabetes

Maine Independent Clinical Information Service, 2023

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SGLT-2s (sodium-glucose co-transporter-2 inhibitors)

FDA approved in 2013-4 **NICKNAME: the "flozins"**

MECHANISM OF ACTION: works in the kidney to increase urinary glucose excretion by decreasing glucose resorption

BENEFITS **(not all drugs in class have data on all benefits, see individual drug information)**: decreases mortality, decreases MACE (major adverse cardiac events), slows progression of CKD, decreases hospitalization in HFrEF (heart failure, EF<40%), benefit in HFpEF (heart failure, EF>40%), lowers blood pressure

INCREASED RISK FACTORS FOR DKA: acute serious illness, surgery & colonoscopy (hold 3d prior), low carbohydrate diet (i.e. keto), fasting, sudden decrease in insulin dose, hx of DKA, alcohol use, type 1 DM, age >65

CONTRAINDICATIONS: severe renal or hepatic impairment (check individual drug dosing and GFR parameters)

DRUG INTERACTIONS: monitor diuretics and anti-hypertensives,

SIDE EFFECTS:

Common: increased urinary frequency and volume (resulting in thirst, hypovolemia, acute kidney injury, orthostatic hypotension), infection (genital mycotic, UTI), DKA-euglycemic

Rare: Fournier's gangrene, acute pancreatitis, increased fracture (canagliflozin), amputation (canagliflozin)

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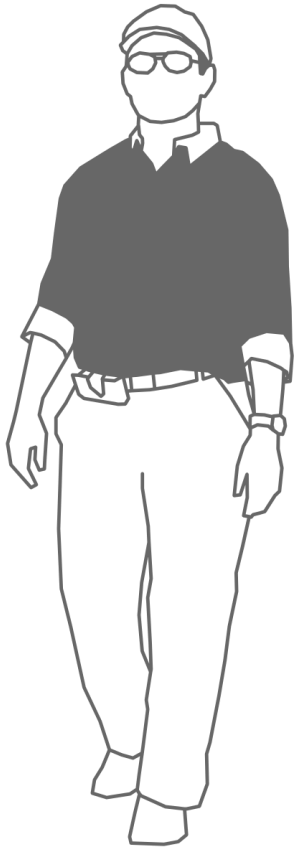
Case Study: Atticus

- 65 year old with type II diabetes for 20 years
- Taking basal insulin for two years
- Started on SGLT-2
- Two episodes of symptomatic hypoglycemia with glucose of 60 and 50 in past week
- Considerations?



Modifiable and non-modifiable risk factors for hypoglycemia

Modifiable	Non-modifiable
Irregular eating habits	Longer duration of diabetes
Insulin	Frailty or older age
Sulfonylureas, meglitinides	Cognitive impairment
Polypharmacy (e.g., non-selective beta-blockers)	Chronic kidney disease or hepatic dysfunction
Alcohol use	Hypoglycemia unawareness

Source: Veterans Administration materials, p.16, https://www.pbm.va.gov/PBM/AcademicDetailingService/Documents/Academic_Detailing_Educational_Material_Catalog/IB_1402_Diabetes_CG.pdf

Hypoglycemia increases risk of:

- Cardiovascular events
- Cardiovascular mortality
- All-cause mortality
- Falls
- Car crashes

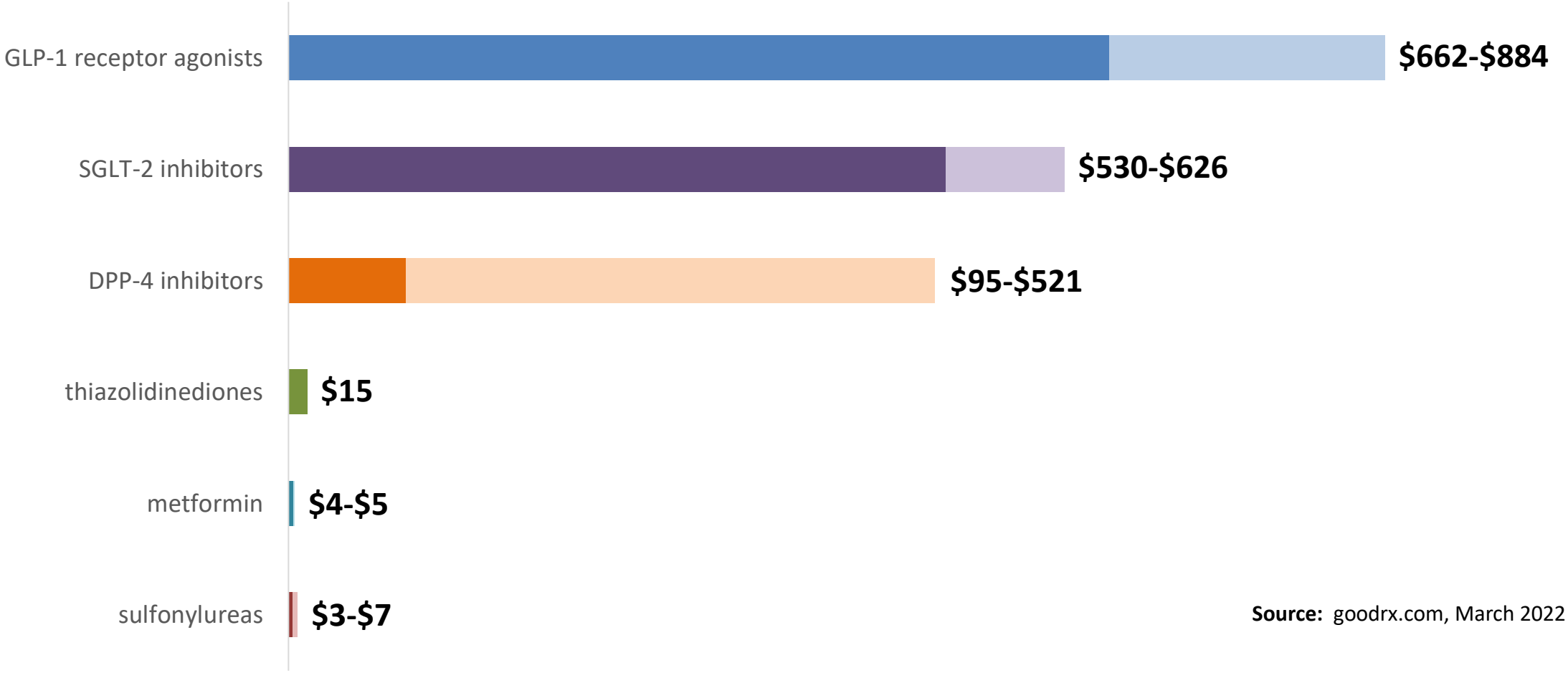
- Rule of 15: if less than 70, consume 15g carbs 4-6oz juice/soda, wait 15 min, recheck (if over 100, proceed with snack/meal), if not repeat

Patient handout: https://www.cdc.gov/diabetes/basics/low-blood-sugar-treatment.html

Continuous Blood Glucose Monitoring

- Can help patients achieve target glucose levels & improve quality of life
- Most insurance coverage based on insulin use or hypoglycemic events
- Some patients choose to purchase sensors/use coupons
- Target ranges/warnings can be individualized
- For those on insulin, can increase hypoglycemia awareness

Costs of medications



Source: goodrx.com, March 2022

Comprehensive care in patients with diabetes

- Antiplatelet recommendations

Antiplatelet therapy

Primary prevention (no CVD)

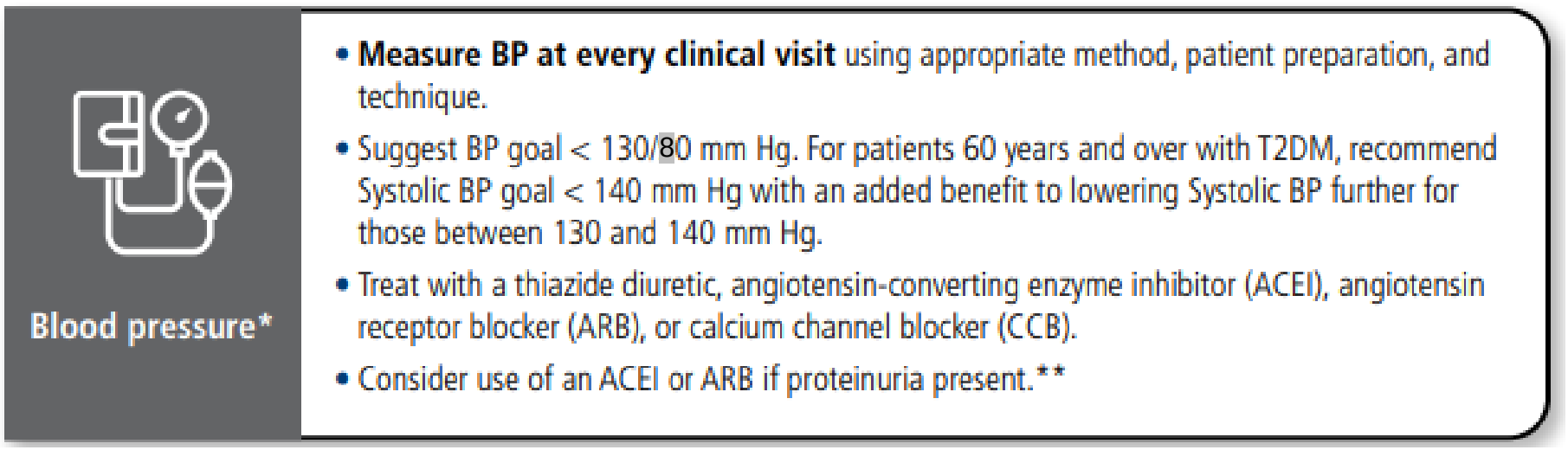
- Balance risk and benefits. In older adults (e.g., ≥ 70 years), risk appears to outweigh benefit.

Secondary prevention (has CVD)

- Use antiplatelet therapy (e.g., aspirin) in most patients unless contraindicated.
- Use clopidogrel 75mg in patients with an aspirin allergy.

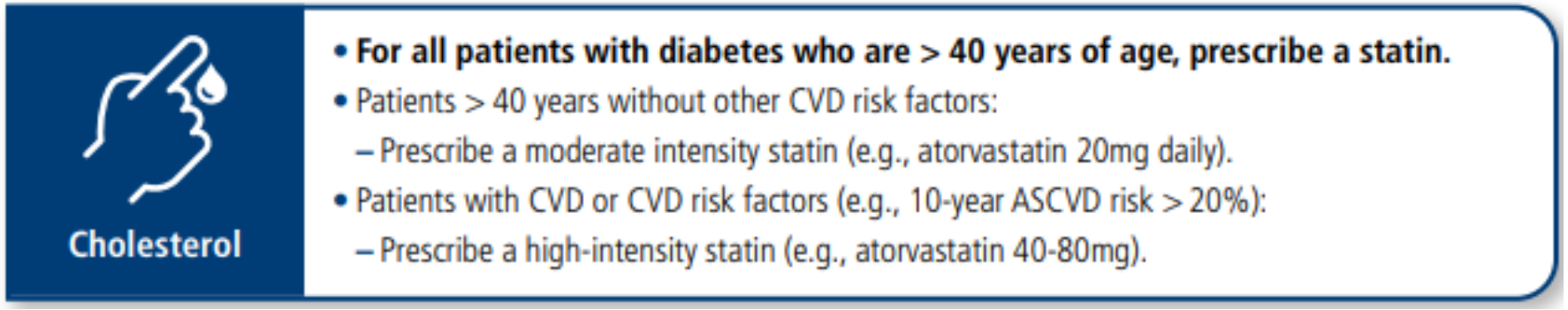
Comprehensive care in patients with diabetes

- Blood pressure recommendations



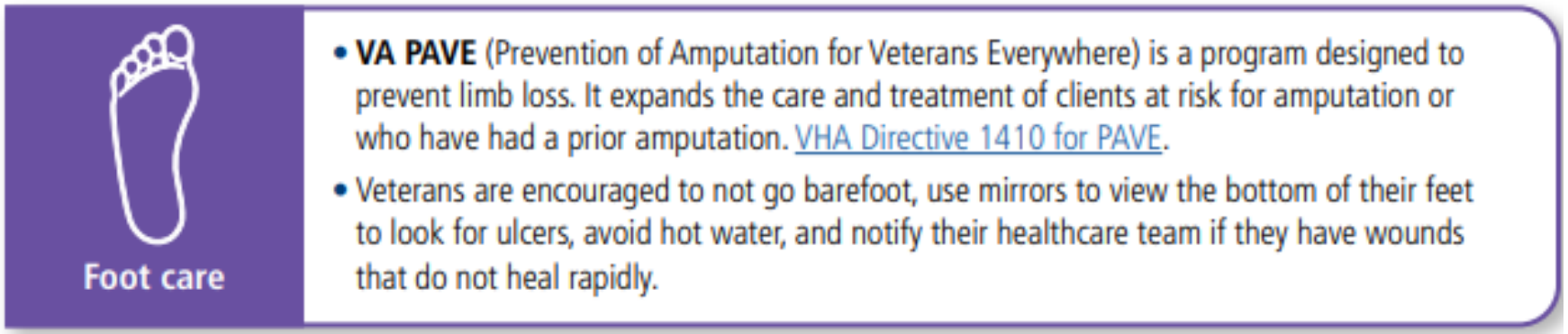
Comprehensive care in patients with diabetes

- Cholesterol



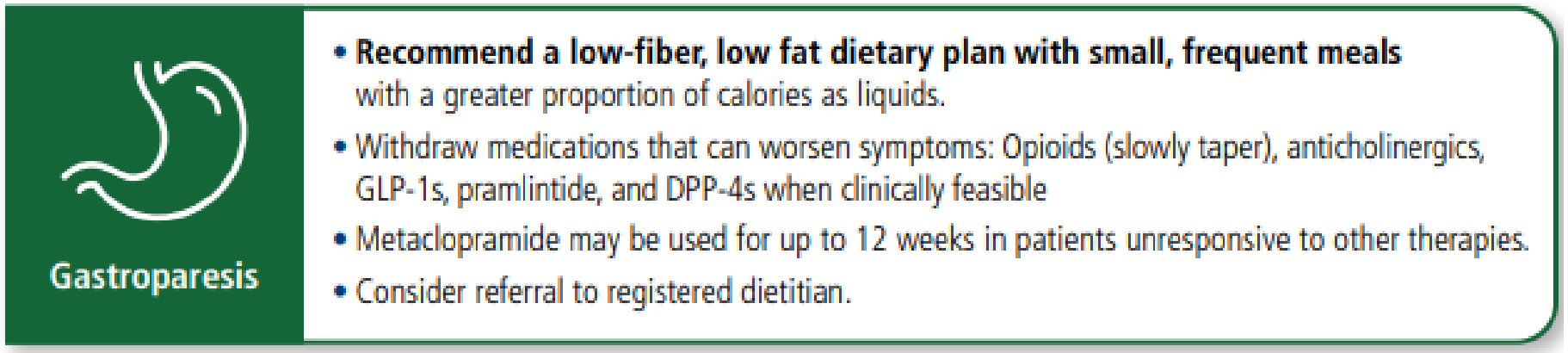
Comprehensive care in patients with diabetes

- Feet



Comprehensive care in patients with diabetes

- Gastroparesis



Comprehensive care in patients with diabetes

- Kidney disease

Nephropathy

- **Determine eGFR** at diagnosis and annually thereafter.
- **Obtain a urine albumin-to-creatinine ratio** at diagnosis and annually thereafter.
- Prescribe an ACEI or ARB in Veterans with diabetes, hypertension, and elevated urinary albumin >30 mg/g Cr (e.g., spot urinary to albumin creatinine ratio (UACR)) and/or an eGFR <60 mL/min/1.73 m^2.

Comprehensive care in patients with diabetes

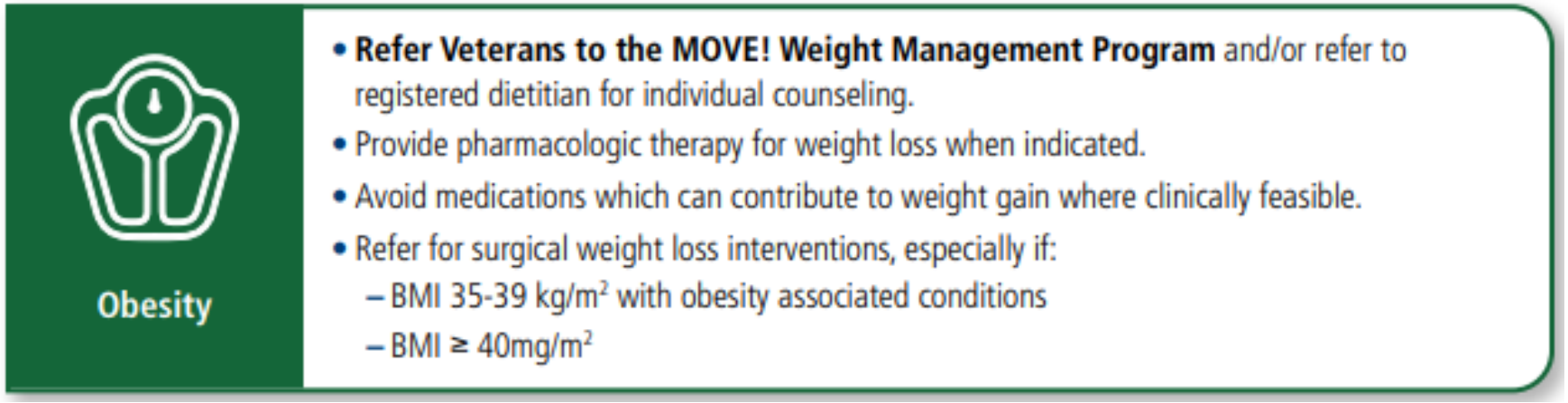
- Neuropathy

Neuropathy

- **Comprehensive foot exam,** including:
  - Visual inspection (e.g., skin integrity, toe nails, callouses, deformities, ulcers)
  - Determination of temperature, vibration, or pinprick sensation, and 10-g monofilament exam
- Optimize glycemic control for symptoms of autonomic neuropathy and overall health.
- Prescribe duloxetine, gabapentin, or pregabalin for neuropathic pain in accordance with VA PBM clinical guidance.

Comprehensive care in patients with diabetes

- Obesity



Comprehensive care in patients with diabetes

- Retinopathy

Retinopathy

- **All Veterans should have a dilated retinal exam or retinal imaging** to detect retinopathy.
- Screen at least every other year for Veterans with no retinopathy on prior exams.
- More frequent screenings required if risk factors for progression of retinopathy are present (e.g., pregnancy).
- Follow-up for retinopathy should occur in conjunction with an eye care professional.

Comprehensive care in patients with diabetes

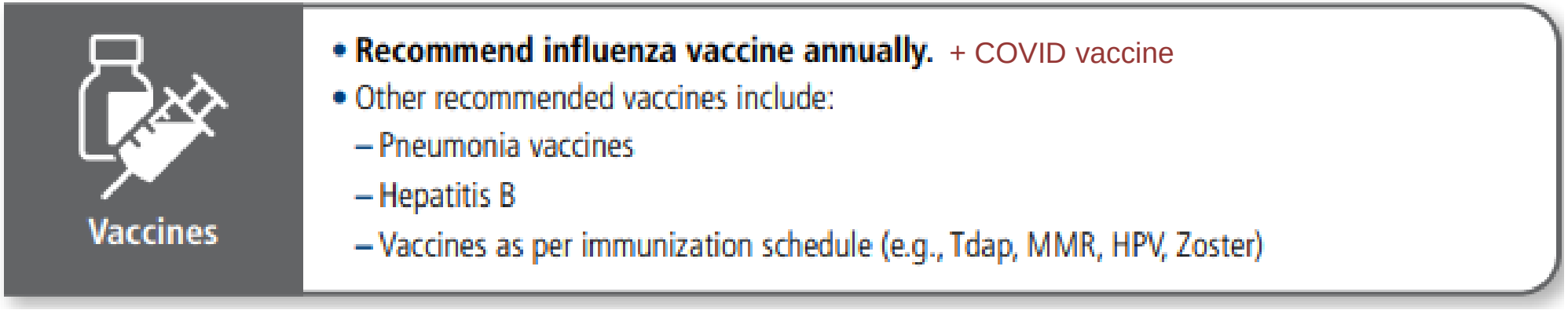
- Smoking

Tobacco

- **Drug therapy** using nicotine replacement, bupropion, or varenicline significantly improves cessation rates.
- Adding counseling programs to pharmacotherapy further increases the chances for success.
- Contact your tobacco cessation clinician to learn about programs available at your facility.
- Veterans can also be referred to the Veteran tobacco quitline at **1-855-QUIT-VET**.

Comprehensive care in patients with diabetes

- Vaccines



Summary

- Lifestyle management remains the cornerstone of managing prediabetes and diabetes
- Choose medications based on co-morbidities
- Adjust A1C targets to avoid hypoglycemia
- Use guidelines to provide comprehensive care for people with diabetes

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