BEYOND METFORMIN: HOW TO CHOOSE THE NEXT TREATMENT FOR DIABETES

GUIDELINE BASED MANAGEMENT OF TYPE 2 DIABETES in 2024

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METABOLISM, ENDOCRINOLOGY & NUTRITION

Disclosures

- Advisory boards for Abbott Diabetes Care

Objectives

To understand how to incorporate therapies for weight management in individuals with diabetes without cardiorenal disease

To learn how to use appropriate therapies for cardiorenal disease in individuals with diabetes

To review updates in diabetes for 2024

Case 1 A

- 60 year old individual with 5 years of type 2 diabetes, no complications
- Diabetes regimen – metformin ER 1000mg twice daily
- Reports weight gain of 15 lbs, BMI 33 kg/m^2
- A1C 8.6-9% over recent 12 months

In addition to referring to diabetes self management education, which of the following should you recommend now?

1. Sulfonylurea
2. DPP4 inhibitor (a gliptin)
3. SGLT2 inhibitor (a flozin)
4. Daily injectable GLP-1 receptor agonist
5. Weekly injectable GLP-1 receptor agonist
6. Oral GLP-1 receptor agonist

Case 1 B

- 60 year old individual presents to establish care
- Has hypertension treated with losartan
- BMI 26 kg/m^2
- Lab testing shows A1C of 8.6% and fasting blood glucose of 160mg/dL

In addition to referring to diabetes self management education, which of the following should you recommend now?

1. Metformin
2. Sulfonylurea
3. DPP4 inhibitor daily (a gliptin)
4. SGLT2 inhibitor daily (a flozin)
5. Daily injectable GLP-1 receptor agonist
6. Weekly injectable GLP-1 receptor agonist

Case 1 C

- 60 year old individual with coronary artery disease, underwent percutaneous intervention 2 years ago
- Has hypertension treated with losartan
- Lab testing shows A1C of 8.6% and fasting blood glucose of 160mg/dL

In addition to referring to diabetes self management education, which of the following should you recommend now?

1. Metformin
2. Sulfonylurea
3. DPP4 inhibitor daily (a gliptin)
4. SGLT2 inhibitor daily (a flozin)
5. Daily injectable GLP-1 receptor agonist
6. Weekly injectable GLP-1 receptor agonist

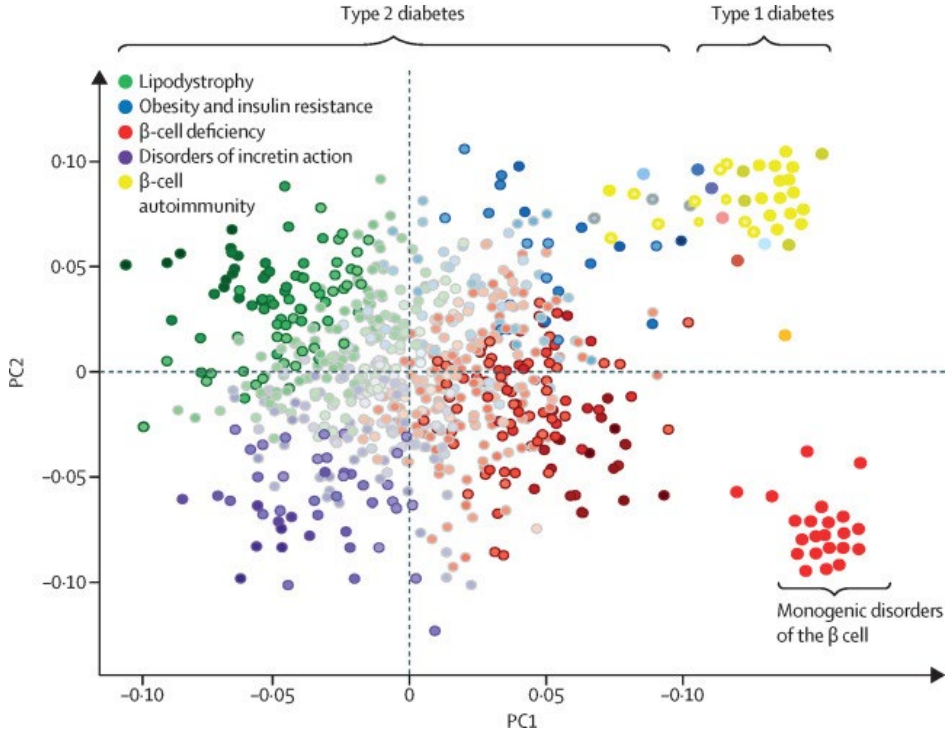
Cases

- Patient 1A - 60 year old with 5 years of type 2 diabetes, no complications with weight gain, on metformin; A1C 8.6-9.2%
- Patient 1B - 60 year old with new diagnosis of diabetes, BMI 26 and A1C 8.6%
- Patient 1C – 60 year old with CAD and new diabetes A1C 8.6%

Diabetes is a chronic and complex disease

- Very clinically **heterogenous** disease

- Variability in
  - age at onset
  - related degree of obesity
  - insulin resistance
  - tendency to develop complications



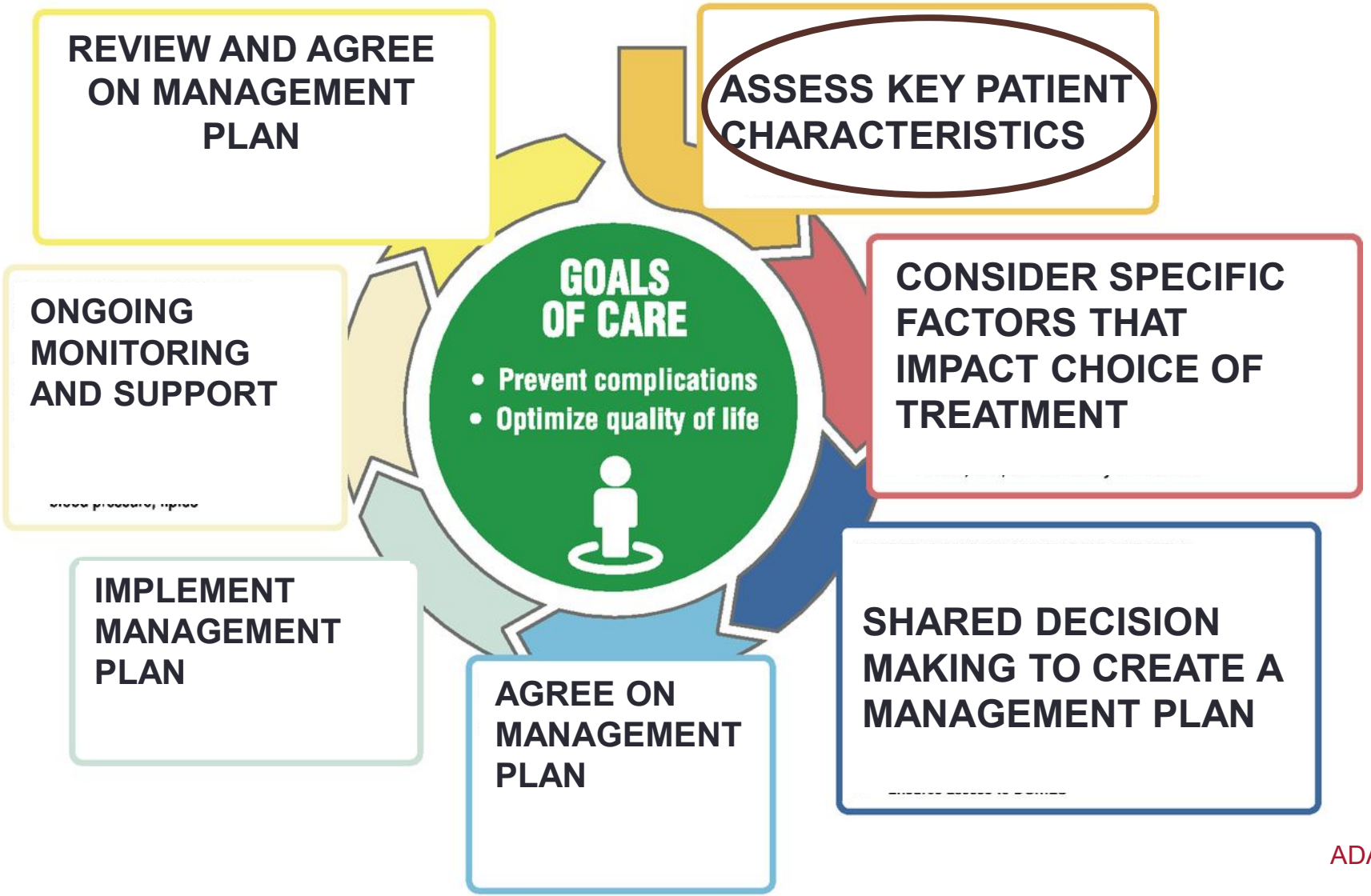
Leslie RD et al Lancet Diabetes Endocrinol Nov 2023

Person-centered approach to diabetes management

- Goals – to prevent or delay complications and maintain quality of life
- Management involves -
  - multifactorial behavioral modification
  - pharmacological treatments
  - management of blood glucose levels, weight, cardiovascular risk factors, comorbidities, and complications
  - Care needs to be delivered in an organized and structured way

- Involves an **individualized and personalized approach** to enhance engagement in self-care activities

Decision cycle for patient-centered glycemic management in Type 2 diabetes



ADA/EASD 2022

ADA Algorithm for Type 2 Diabetes Treatment – 2024

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY 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 Individuals 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)

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

+HF
SGLT2i§ with proven HF benefit in this population

+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.

+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

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

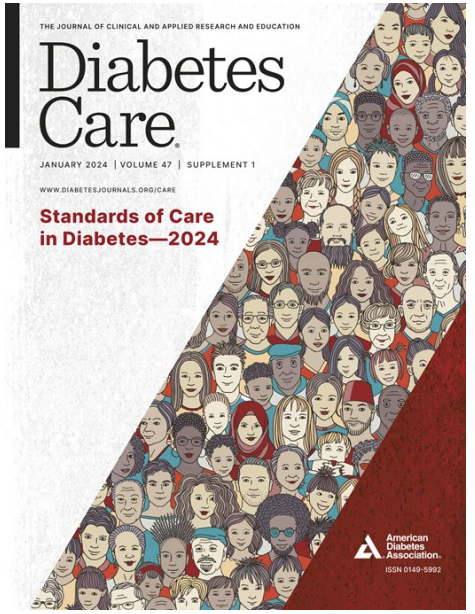
Intermediate:
GLP-1 RA (not listed above), SGLT2i

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.



Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2024. Diabetes Care 47: S158-178*

Appropriate Glucose-lowering Medication Selection in type 2 diabetes in 2024

Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2024*. *Diabetes Care 47: S158-178*

Cases

- **Patient 1A - 60 year old with 5 years of type 2 diabetes, no complications with weight gain, BMI 33, on metformin; A1C 8.6-9.2%**
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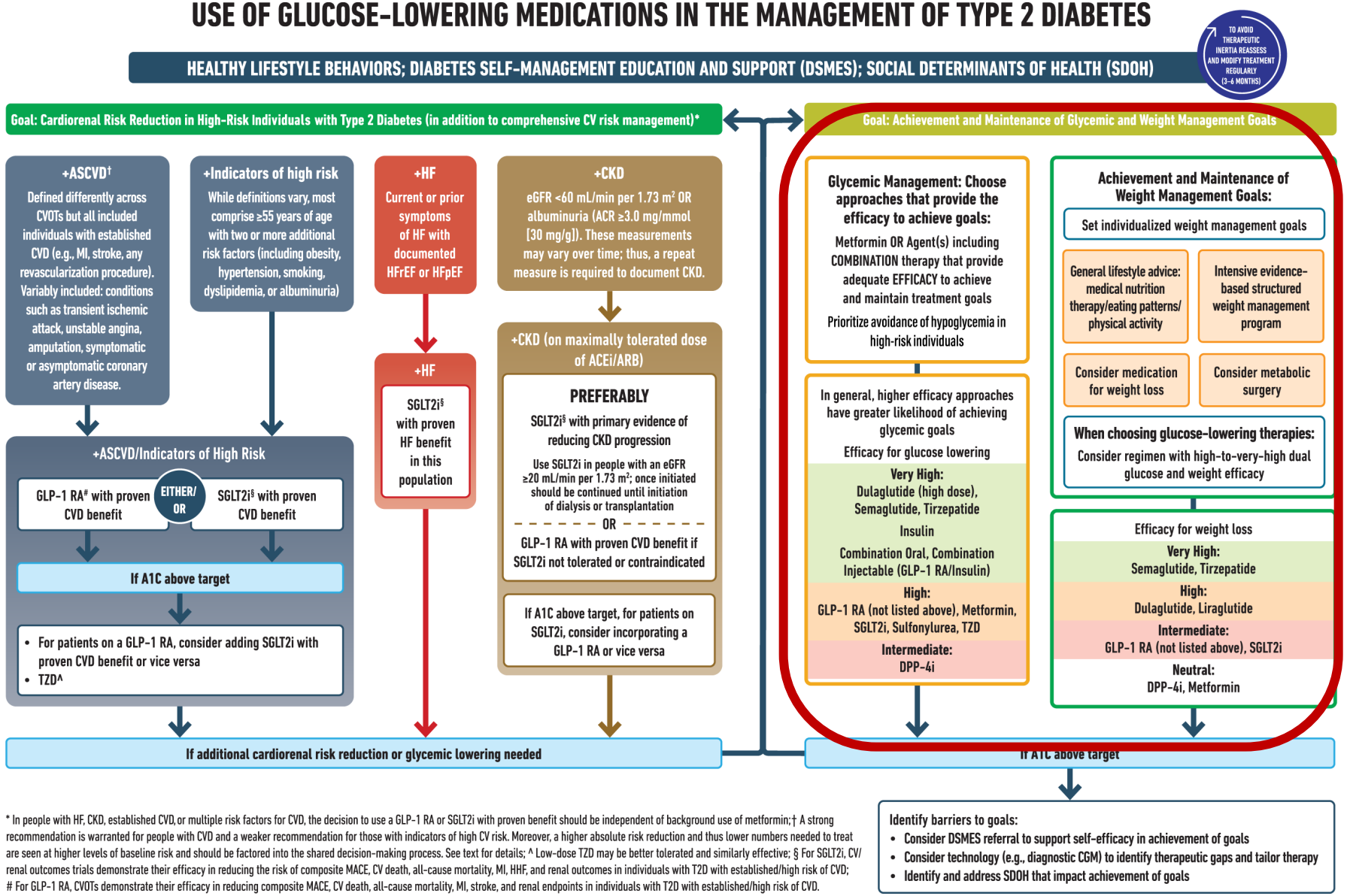
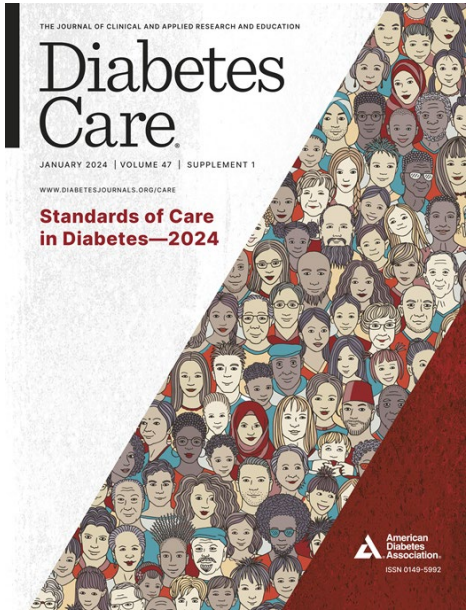
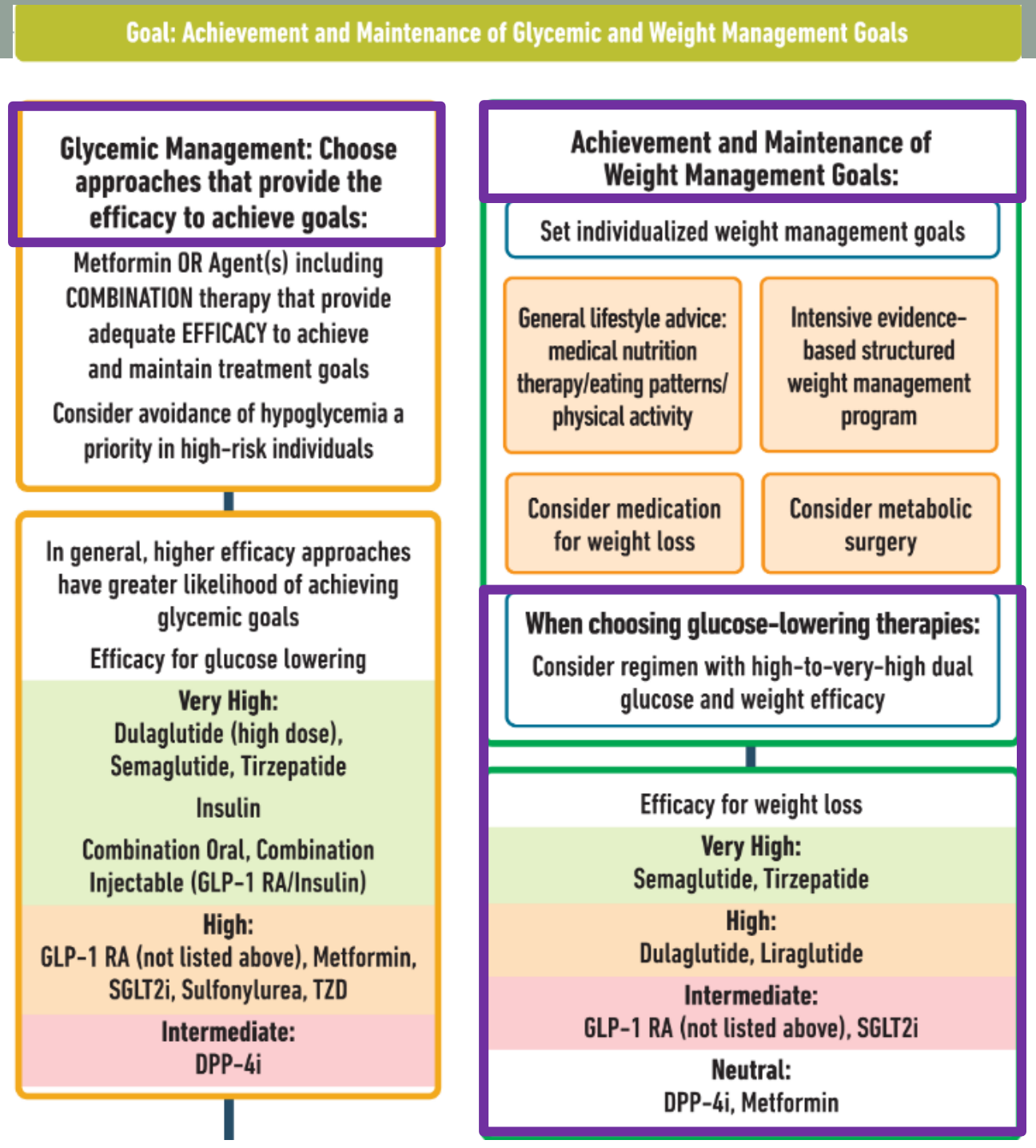
ADA Algorithm for Type 2 Diabetes Treatment – 2024





Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2024. Diabetes Care 47: S158-178*

- Patient's goals
  - Weight loss
  - Glycemic management



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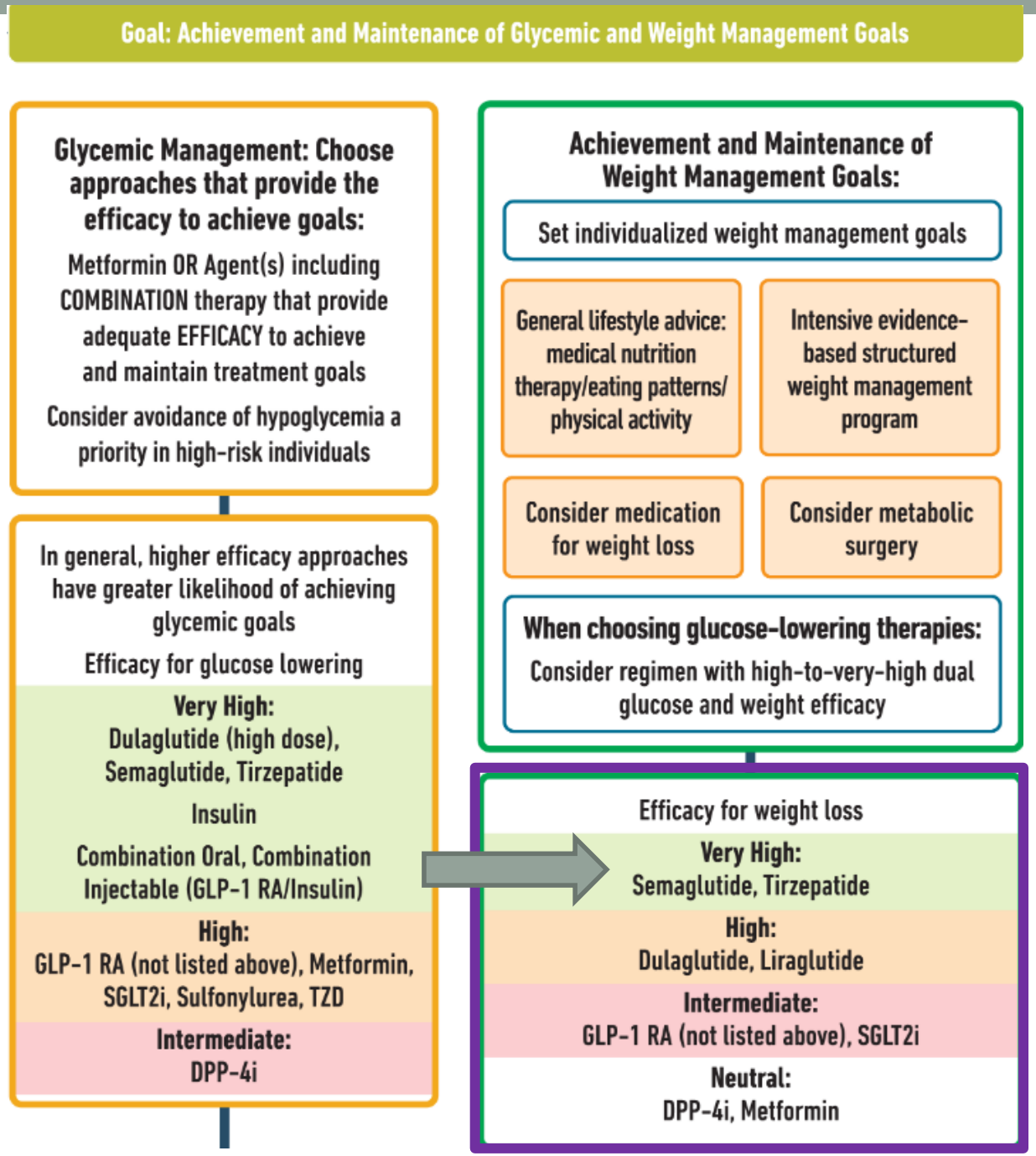

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- Patient's goals
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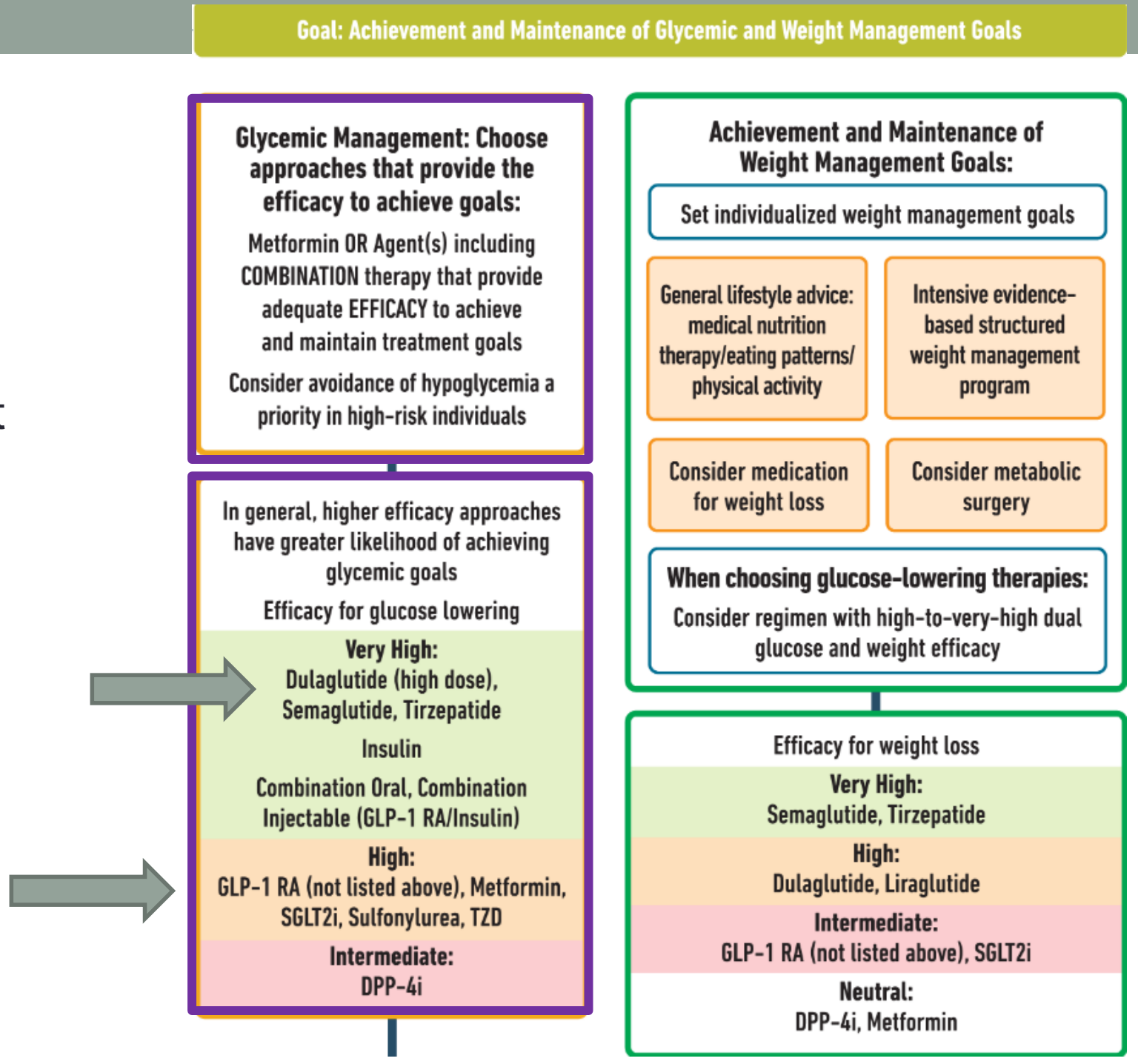

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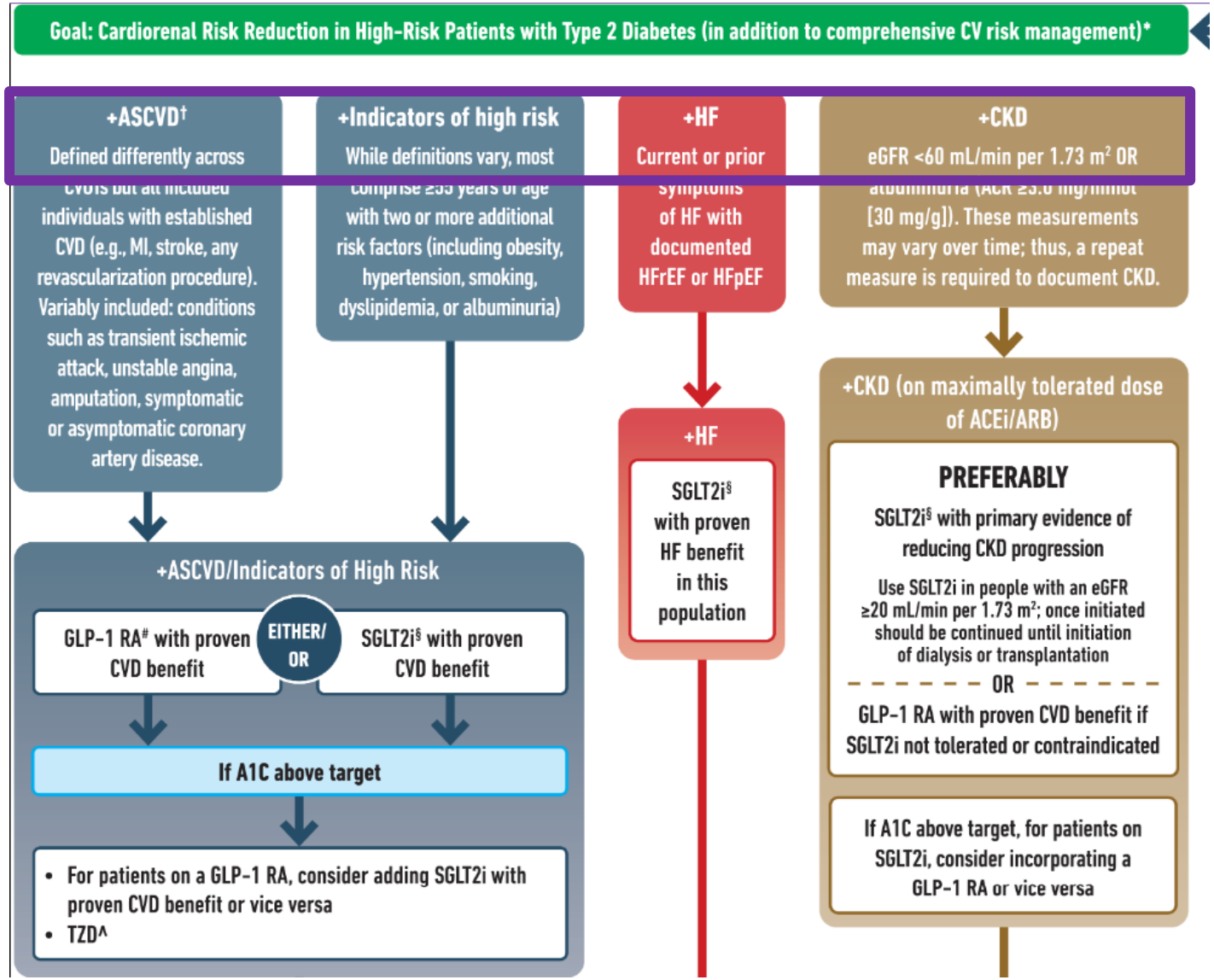
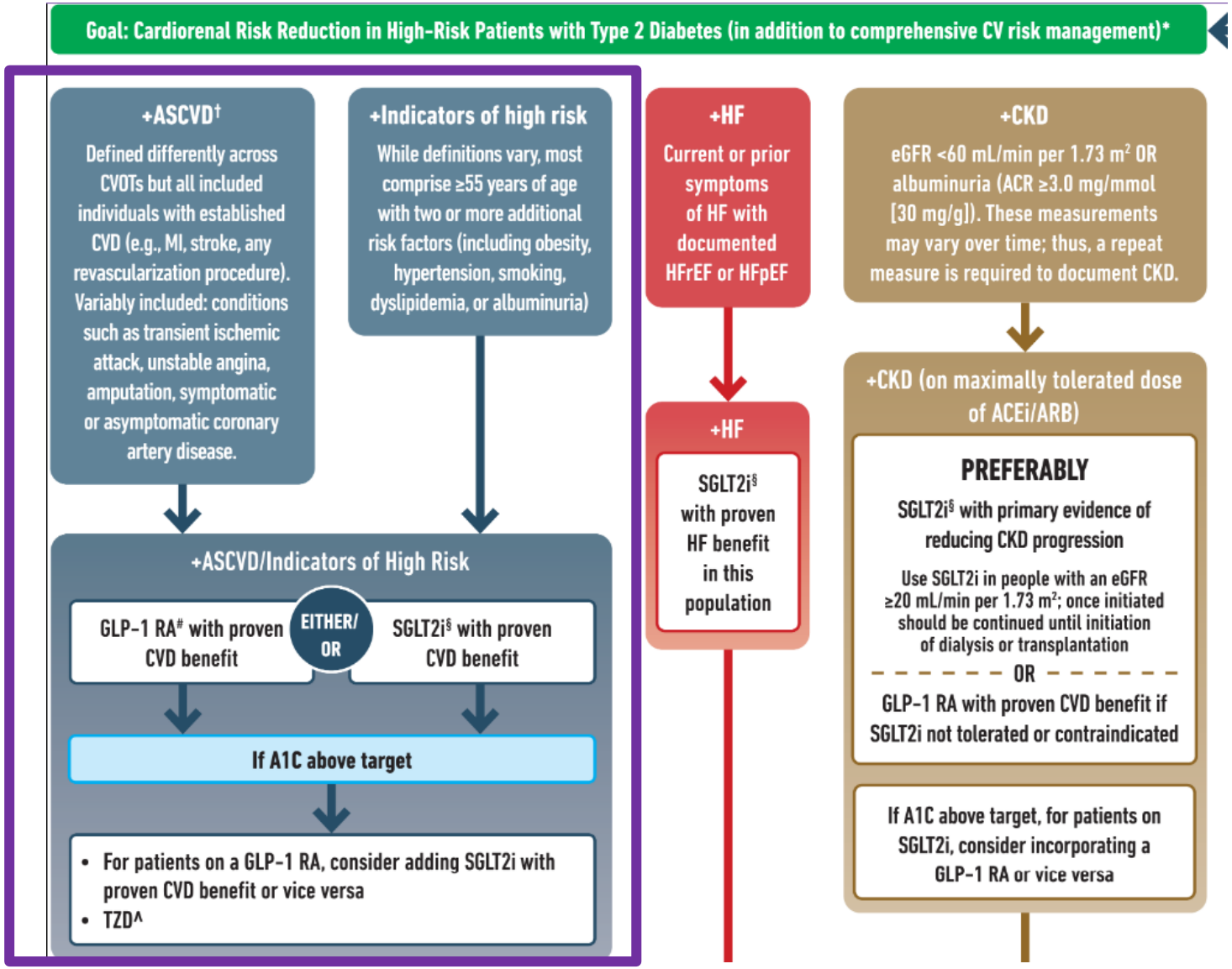
Appropriate Glucose-lowering Medication Selection in T2D



- Risk stratifiers
  - ASCVD
  - Heart failure
  - CKD

Appropriate Glucose-lowering Medication Selection in T2D



- ASCVD or indicators of high risk
- GLP-1RA with proven benefit

OR

- SGLT2i with proven CVD benefit

Cases – individualized management

- Patient 1A - 60 year old with 5 years of type 2 diabetes, no complications with weight gain, BMI 33, on metformin; A1C 8.6-9.2%
- *GLP-1RA with weight benefit – semaglutide or tirzepatide, dulaglutide, liraglutide*

- Patient 1B - 60 year old with new diagnosis of diabetes, BMI 26 and A1C 8.6%
- *Metformin or combination therapy*

- Patient 1C – 60 year old with CAD and new diabetes
- *GLP-1RA with proven benefit (semaglutide or liraglutide)*

Why these changes?

- Numerous RCTs have demonstrated ASCVD benefit of several SGLT2 inhibitors and GLP-1RAs
- SGLT2 inhibitors also decrease risk of heart failure hospitalization and CKD progression
- Emerging data suggests combination of these 2 agents will provide an additive benefit in CV and kidney outcomes
- Non-insulin injectables preferred over insulin
  - Efficacy of GLP-1RAs are equivalent or greater than basal insulin
  - Lower risk of hypoglycemia
  - Potent weight loss
- Combination therapy (rather than traditional stepwise approach) is superior to sequential addition (metformin +DPP4i)

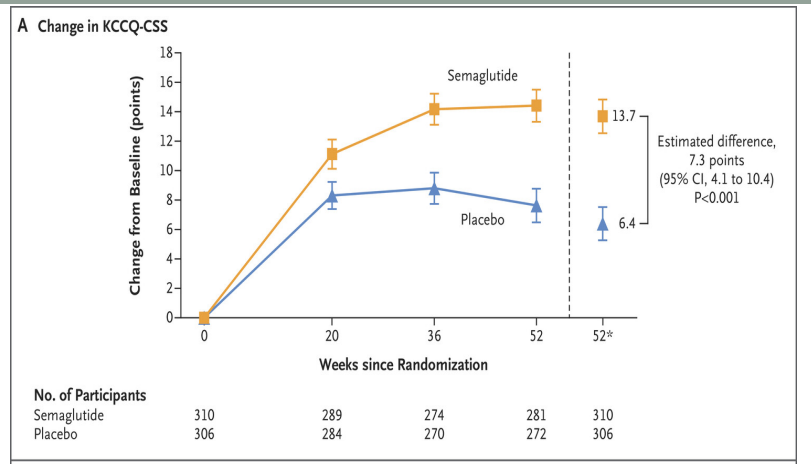
Updates for 2024

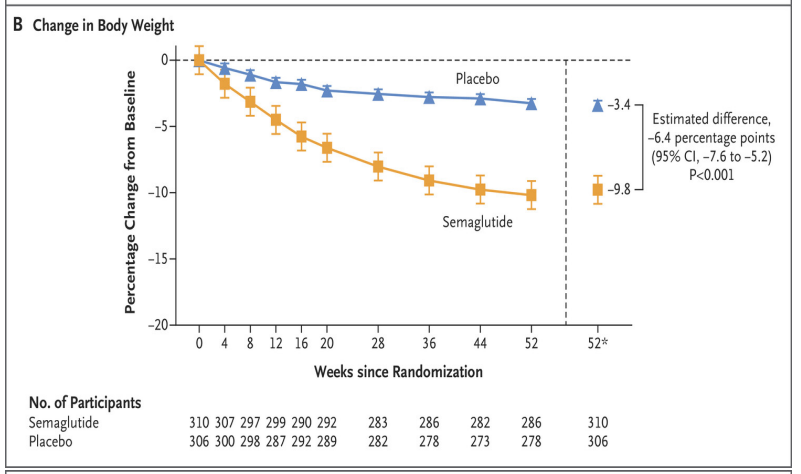
- Its all about the GLP-1RAs…

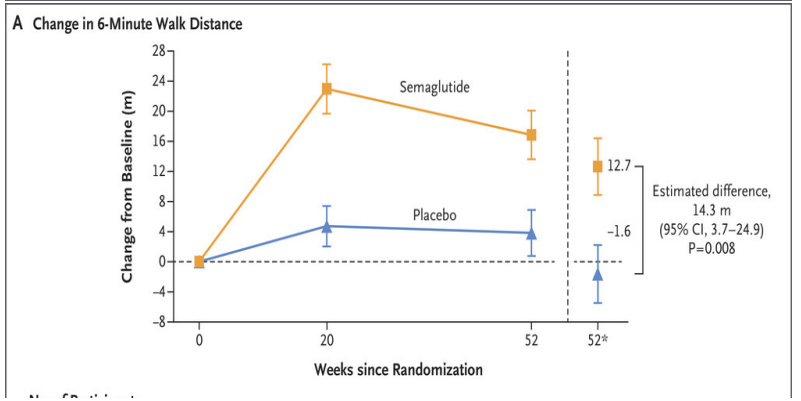
STEP-HFpEF DM

- Heart failure with preserved ejection fraction is very common, esp in people with obesity
- People with HFpEF has high prevalence of T2D

- Semaglutide 2.4mg weekly vs placebo for 52 weeks
- n= 616, 52 wks
- Decrease in heart failure symptoms and physical limitation + weight loss



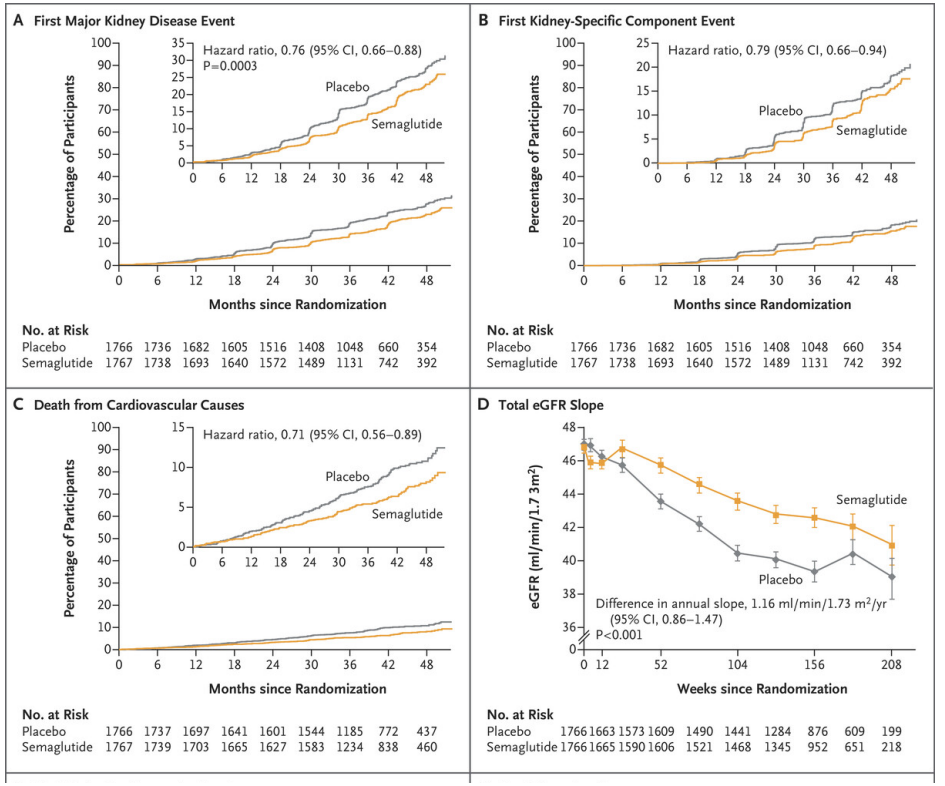




Kosiborod M et al NEJM 2024

FLOW trial - semaglutide on progression of CKD, kidney and CV mortality in T2D

- N = 3533 adults with T2D and CKD
- Semaglutide 1mg vs placebo
- Age 67, 30% women, 3.4y
- Primary end-point – major kidney events- a composite of onset of kidney failure (initiation of dialysis, renal transplantation, or eGFR <15) or a 50% reduction of eGFR from baseline or death from kidney of CV causes
- Hazard ratio, 0.76; 95% CI 0.66 to 0.88; P=0.0003) , RRR 24%
- Results were independent of SGLT2 inhibitor use



Perkovic V et al NEJM 2024; Mann JFE et al Nat Medicine 2024

Recent issues with GLP-1RA

- Availability/ shortage (as of Oct 2024)

- Dulaglutide – in shortage
- Semaglutide – in shortage (all available except for 1 dose)
- Liraglutide – in shortage in some doses
- Tirzepatide – resolved
- (Even when a medication is available, patients may not always be able to immediately fill their prescription at a particular pharmacy. This is true for refrigerated products and products with multiple dose strengths, due to factors like ordering practices and incentives, cold chain logistical considerations, and retailer capacity constraints. Patients may experience variability at a particular pharmacy location regardless of whether a drug is in shortage)

Dealing with shortages of GLP-1RAs

- Have patients call around pharmacies
- Use a lower dose of same agent
- Switch to a different agent

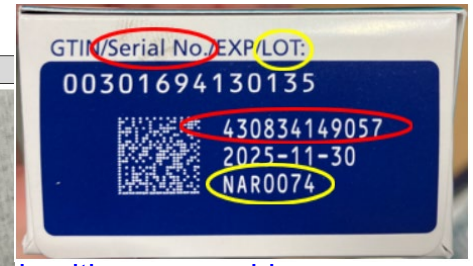
Agent	Frequency	Titration Schedule	Equivalent Doses					
Dulaglutide	Weekly	4 week		0.75 mg	1.5 mg	3 - 4.5 mg		
Semaglutide	Weekly	4 week		0.25 mg*	0.5 mg	1 mg	2 mg	
Liraglutide	Daily	1 week	0.6 mg*	1.2 mg	1.8 mg			
Oral Semaglutide	Daily	4 week	3 mg*	7 mg	14 mg			
Tirzepatide	Weekly	4 week				2.5 mg*	5 mg	7.5 - 15 mg

* Sensitizing dose, no glycemic impact

https://www.mct2d.org/resource-library/glp-1-receptor-agonist-shortages-how-to-support-patients

Compounded GLP-1RA therapies

- Compounding pharmacies are licensed and regulated by pharmacy boards
  - Can make compounded versions of branded drugs on FDA's drug shortage list (but not FDA- approved)
  - Compounders offer semaglutide injectable products in various containers/ packaging, like multiple-dose vials or prefilled syringes. Product concentrations may vary depending on the compounder, and a single compounder may offer multiple concentrations of compounded semaglutide products
  - Instructions may say to administer semaglutide injections in "units" rather than mg or mL
  - Dosing errors – 5-20x more than intended dose due to incorrect measurements, miscalculations
  - Adverse events; GI effects, dehydrations, acute pancreatitis, gallstones
- Counterfeit semaglutide



https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-providers-compounders-and-patients-dosing-errors-associated-compounded (accessed Nov 2, 2024)

GLP-1RA and procedures/ surgeries

June 29, 2023

American Society of Anesthesiologists Consensus-Based Guidance on Preoperative Management of Patients (Adults and Children) on Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists

Girish P. Joshi, M.B.B.S., M.D., Basem B. Abdelmalak, M.D., Wade A. Weigel, M.D., Sulpicio G. Soriano, M.D., Monica W. Harbell, M.D., Catherine I. Kuo, M.D., Paul A. Stricker, M.D., Karen B. Domino, M.D., M.P.H., American Society of Anesthesiologists (ASA) Task Force on Preoperative Fasting

- Delayed gastric emptying with increase in residual gastric volume
- Hold on the day of (on daily GLP-1RA) or the week prior (weekly dosing)
- Delay procedure if GI symptoms present on day of procedure for concerns of regurgitation and pulmonary aspiration
- If no GI symptoms, but GLP-1RA not held, use ‘full stomach’ precautions or consider evaluating gastric volume by ultrasound. If stomach is empty, proceed. If stomach is full, consider delaying the procedure or treat the patient as ‘full stomach’.

GLP-1RA and procedures/ surgeries

Research Letter

FREE

April 22, 2024

Preoperative GLP-1 Receptor Agonist Use and Risk of Postoperative Respiratory Complications

Anjali A. Dixit, MD, MPH[1]; Brian T. Bateman, MD, MS[1]; Mary T. Hawn, MD, MPH[2]; et al

- Patients on GLP-1RA therapy undergoing same-day emergency surgery
- Outcome – aspiration pneumonitis, post-op respiratory failure, and/or admission to ICU
- n=3502, 49% women, 50% with obesity
- No difference in post op respiratory complications (3.5% vs 4%)

Other GLP-1RA studies

- Semaglutide weekly in patients with obesity and knee osteoarthritis – body weight reduction and decrease in pain related to OA (STEP 9 NEJM Oct 2024)
- Semaglutide (ESSENCE) early results in MASH and moderate to advanced liver fibrosis
  - Semaglutide arm demonstrated improvement in fibrosis, resolution of steatohepatitis
- Semaglutide being studied in PAD, neurodegenerative diseases
- SURPASS-CVOT (2025) tirzepatide
- Use in Type 1 diabetes

Updates on insulin

- Once weekly insulin icodec – not approved by FDA (approved as Awiqli in EU, Canada, Australia, Japan, China)
- Once weekly insulin efsitora alfa data published and non-inferior to degludec (Wysham C et al NEJM Sept 2024)
- As of early 2023, price of insulin under the Inflation Reduction Act of 2022, is capped at $35/ each type of insulin per month for Medicare beneficiaries

Continuous glucose monitoring (CGM)

- Libre 2
  - Requires scanning every 8h
  - Measures every minute and stores every 15 min

- Libre 3 plus
  - No scanning
  - Smaller sensor
  - Sends data every minute
  - Reader available

- Dexcom G6
  - Realtime CGM
  - No scanning
  - Measures every 5 min
  - Sensor, transmitter and receiver/app

- Dexcom G7
  - No scanning
  - Measures every 5 min
  - No transmitter

- Eversense 365
  - Implantable CGM
  - Cost?

CGM coverage 2024

- Taking insulin (any kind)
- Have type 1 or type 2 diabetes
- Severe hypoglycemia or recurrent non-severe hypoglycemia despite attempts to modify treatment plan
- Document adherence every 6 months in chart note (use a smartphrase)

- Medicare requires a DME supplier
- Medicaid – some plans still ask for 3+ injections of insulin, but pharmacy benefit

Over-the-counter CGM devices

CGM	Abbott Lingo	Abbott Libre Rio	Dexcom Stelo
Intended patient	No DM	Type 2 DM, not on insulin	Type 2 DM, not on insulin
Duration of sensor	14 day	14 day	15 day
Cost	$49 1 sensor $89 2 sensors $239 6 sensors with subscription	TBD, expected later 2024	$99 1 month supply $89/month with subscription

Key takeaways

1. Type 2 diabetes management in 2024 is now based on individual patient characteristics, assessing cardiorenal risk
2. GLP-1 RAs and GLP1/GIP RAs are highly effective for weight loss and decrease in risk of CVD, CKD
3. Shortages and costs are still a major barrier
4. The road to once weekly insulin continues
5. Continuous glucose monitoring technology is now an important aspect of management of type 2 diabetes
6. Caps on insulin pricing offer hope for our patients

Thank you!

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