

FROM FOOD SIGNALS TO ORGAN PROTECTION

New Pharmacological Advances
in Diabetes and CKM Care

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Disclosures

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- No relevant financial relationship to disclose.

How investigational content will be handled

- Regulatory status will be stated at the point of discussion.
- Investigational efficacy data will be separated from FDA-approved indications, and surrogate/biomarker findings will be distinguished from patient-important outcomes.

Learning objectives

- **Differentiate** mechanisms, evidence, regulatory status, and major safety considerations across established and emerging diabetes/CKM therapies.
- **Apply** a phenotype- and complication-directed approach incorporating glycemia, obesity, ASCVD, HF, CKD, metabolic liver disease, hypoglycemia risk, frailty, burden, affordability, and preferences.
- **Evaluate** new trial findings by separating patient-important cardiovascular/kidney outcomes from surrogate endpoints and exploratory evidence.
- **Develop** patient-centered education and monitoring strategies addressing adverse effects, hypoglycemia, nutrition, lean mass/function, access, and investigational therapies.

Section 01

Meeting Our Patient...

One patient. Five competing priorities.

Patient snapshot

- TT, male, 64 years old
- T2D for 12 years
- A1c: 8.9%; BMI: 37 kg/m²
- Prior MI; HFpEF with exertional limitation
- eGFR: 48 mL/min/1.73m²; UACR: 380 mg/g
- Current: metformin, insulin glargine, lisinopril, atorvastatin (max tolerable doses)
- 2 symptomatic hypoglycemia episodes in the past month

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Clinical priorities

1. Reduce recurrent cardiovascular risk
2. Slow CKD progression
3. Reduce heart-failure events
4. Improve weight and glycemia management
5. Reduce hypoglycemia and treatment burden

The challenge

At the end of this session, build an integrated plan:

- What would you **ADD**?
- What would you **REDUCE**?
- What would you **MONITOR**?

****** What evidence justifies each decision?

Section 02

Framing Our Discussion

Food is information, not just calories

1 | Nutrient sensing

Carbohydrate, fat, and protein are detected by **intestinal enteroendocrine cells** through nutrient transporters, ion channels, and G-protein-coupled receptors.

The endocrine response begins while **nutrients are still being processed in the gut**.



2 | Hormone release

Gut-derived signals:

- GIP
- GLP-1
- PYY / CCK

Responding to food →
insulin release

Satiety &
Digestion
hormones

Pancreatic meal signals:

- Insulin
- Amylin
- Glucagon



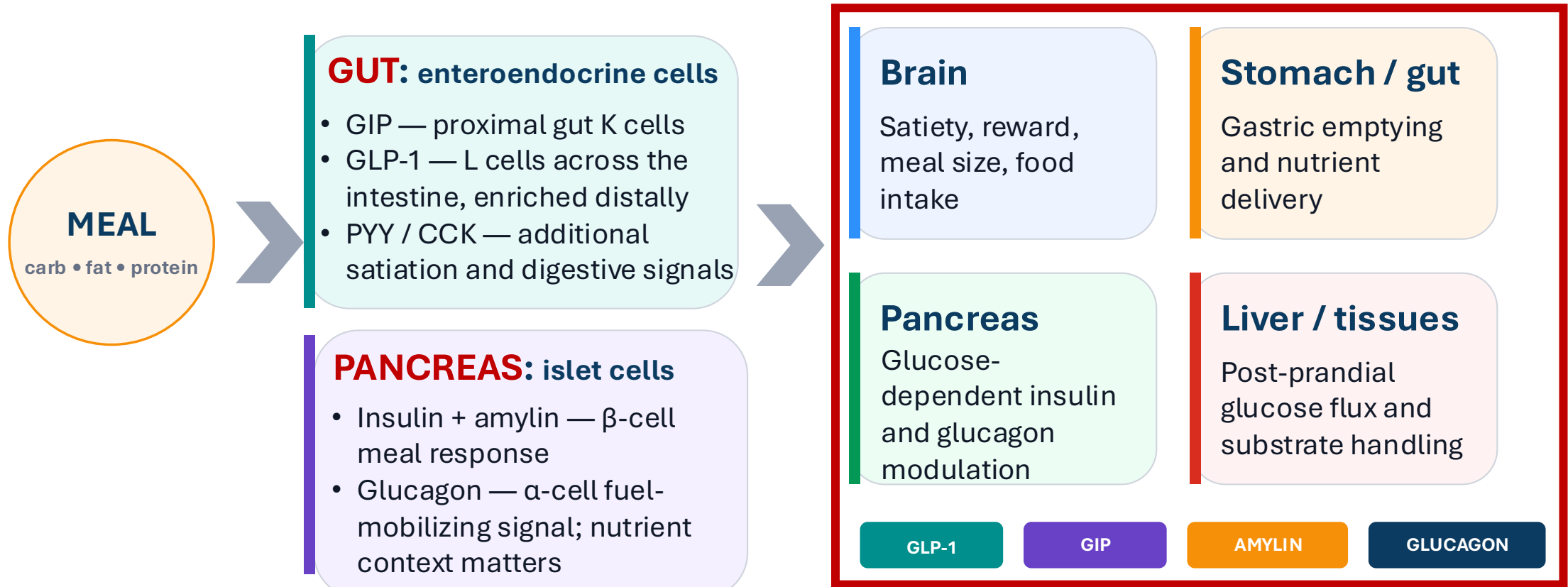
3 | Coordinated response

These signals help coordinate:

- Insulin and glucagon secretion
- Gastric emptying
- Satiety and meal termination
- Hepatic substrate handling
- Post-prandial glucose and energy balance

Modern metabolic pharmacology amplifies, prolongs, or combines these native meal signals.

A meal activates a gut–brain–pancreas signaling network

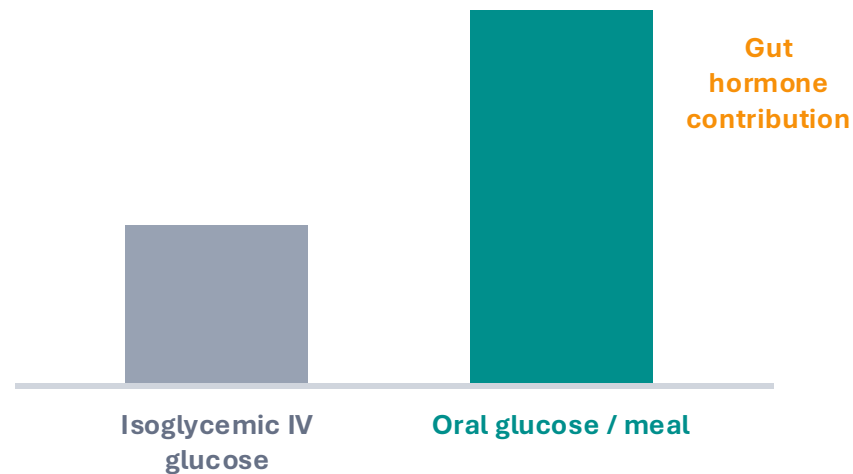


The major “food-signal” pathways are now being translated into metabolic therapeutics.

Same glycemia, different insulin response: The incretin effect

Oral nutrient exposure produces a ***larger*** **insulin response** than iso-glycemic IV glucose because the gut contributes an endocrine signal.

Conceptual insulin secretory response



Conceptual illustration, not patient-level trial data.

≈50–70%

of the insulin response to oral glucose in healthy people can be attributed to incretin signaling.

GIP

Strong physiologic incretin signal in individuals without T2D; ***insulinotropic action is markedly impaired in T2D.***

GLP-1

- Insulinotropic and glucagon-suppressing actions **remain pharmacologically exploitable in T2D**;
- Slows gastric emptying and reduces appetite.

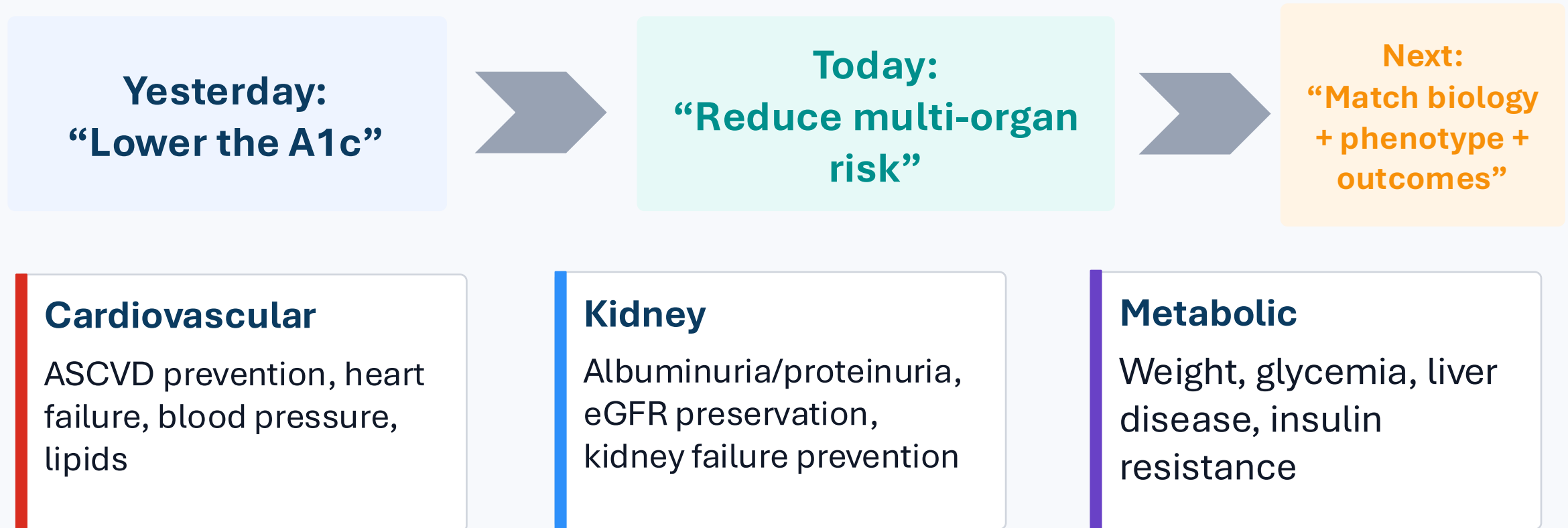
Clinical pearl: in T2D, the defect is not simply “too little GLP-1”; impaired incretin action is central.

Engineering food signals, not just lowering glucose

Native signal	Physiologic role	Pharmacologic translation	2026 clinical context
GLP-1	Insulin ↑ • glucagon ↓ • satiety ↑ • gastric emptying ↓	Long-acting GLP-1 receptor agonists ; oral small-molecule GLP-1 pathway now also possible	Established therapeutic platform with glycemic, weight, and agent-specific CV/kidney outcomes
GIP + GLP-1	Complementary incretin and central/metabolic signaling	Dual agonism: tirzepatide	Established dual-receptor therapy; outcome evidence depends on indication and dose
GIP + GLP-1 + glucagon	Adds glucagon-receptor biology to incretin signaling and appetite control	Triple agonism: retatrutide	<i>Investigational</i> ; Phase 3 program ongoing and not regulator-approved as of Sept 2026
Amylin	Meal termination • gastric emptying ↓ • postprandial glucagon ↓	Pramlintide; next-generation long-acting amylin and amylin/GLP-1 strategies	Pramlintide established; newer long-acting / combination programs remain investigational

Conceptual leap: modern therapy can selectively amplify one signal or deliberately combine several meal-response pathways.

The therapeutic target has changed



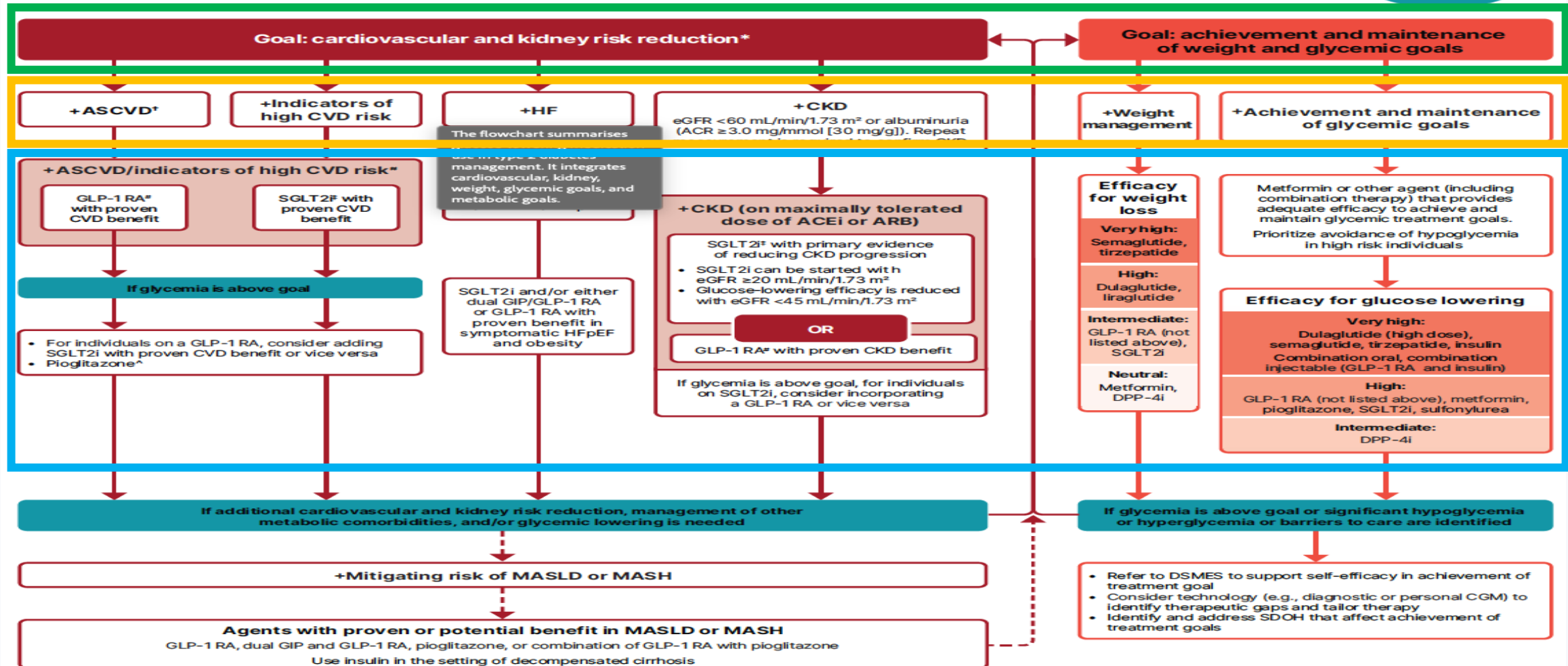
ADA 2026 T2DM Treatment Algorithm

Use of glucose-lowering medications in the management of type 2 diabetes

(For recommendations for specific conditions, including non-glucose-lowering medications, refer to pertinent sections)

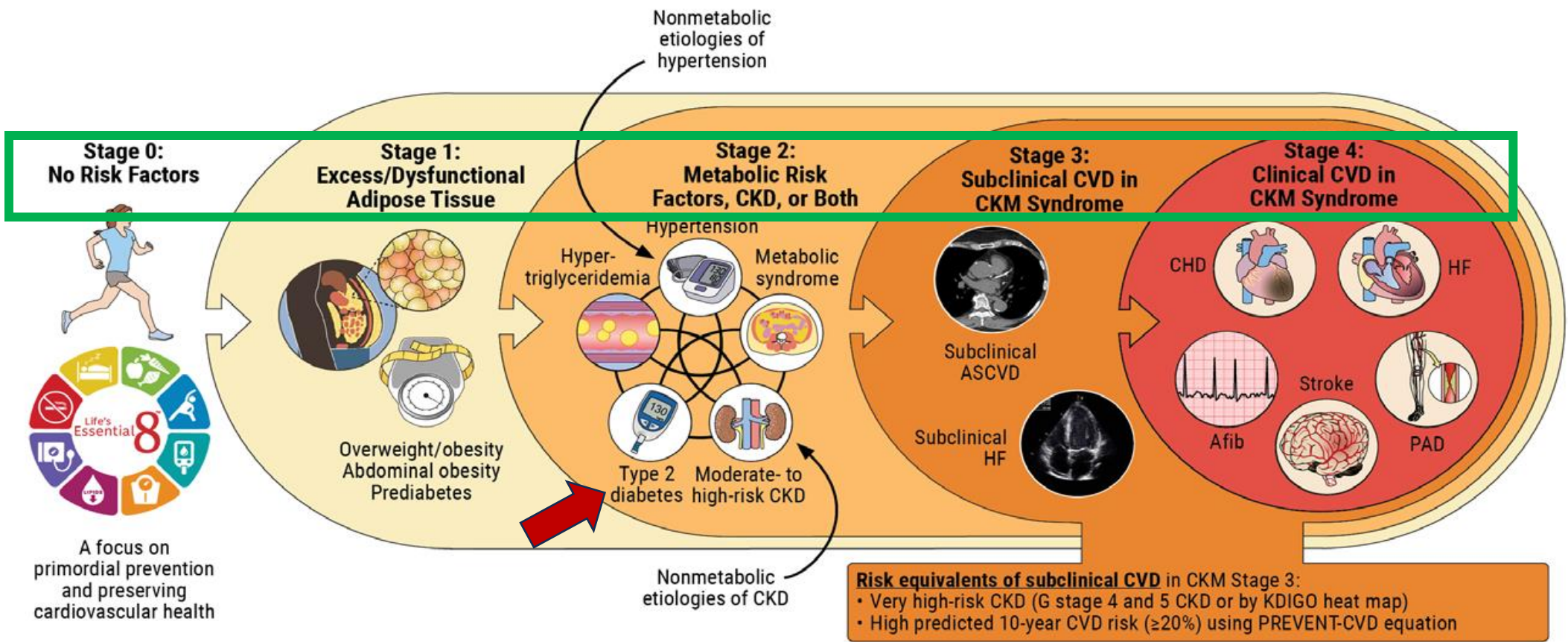
Healthy lifestyle behaviors; diabetes self-management education and support; social determinants of health

To avoid therapeutic inertia, reassess and modify treatment regularly (3–6 months)



Stages of CKM Syndrome

Stages of CKM Syndrome



Ndumele CE, Rodriguez F, Dixon DL, Khan SS, Mukherjee D, Bajaj M, Bangalore S, Bozkurt B, Breathett K, Clarke SL, de Boer IH, Ellison DH, Evangelista LS, Heffron SP, Kazi DS, Kulshreshtha A, Lingvay I, Low Wang CC, Mercado CA, Morton JM, Neeland IJ, Pagidipati N, Powell-Wiley TM, Rangaswami J, Rao G, Reza N, Saeed A, St. Peter W, Starks JB, Sterling M, Talbot AW, Tran AH, Tuttle KR, VanWagner LB, Vest AR, Virani SS. 2026 AHA/ACC/ADA/ASN guideline for the prevention, detection, evaluation, and management of cardiovascular-kidney-metabolic syndrome: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2026;153:e50–e158. doi: 10.1161/CIR.0000000000001453

Diabetes Care[®]



Management of Type 2 Diabetes, 2026. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Melanie J. Davies, Vanita R. Aroda, Mandeep Bajaj, Nuha A. ElSayed, Francesco Giorgino, Jennifer Green, Rita R. Kalyani, Nisa M. Maruthur, Chantal Mathieu, Sylvia E. Rosas, Peter Rossing, Tommy Slater, Tsvetalina Tankova, Pinar Topsever, Apostolos Tsapas, and John B. Buse

Diabetes Care 2026;**49(00)**:1–45 | <https://doi.org/10.2337/dci26-0141>

A HOLISTIC ANTICIPATORY INTEGRATED CARE APPROACH ADDRESSING TYPE 2 DIABETES AND ITS ASSOCIATED LONG-TERM CONDITIONS

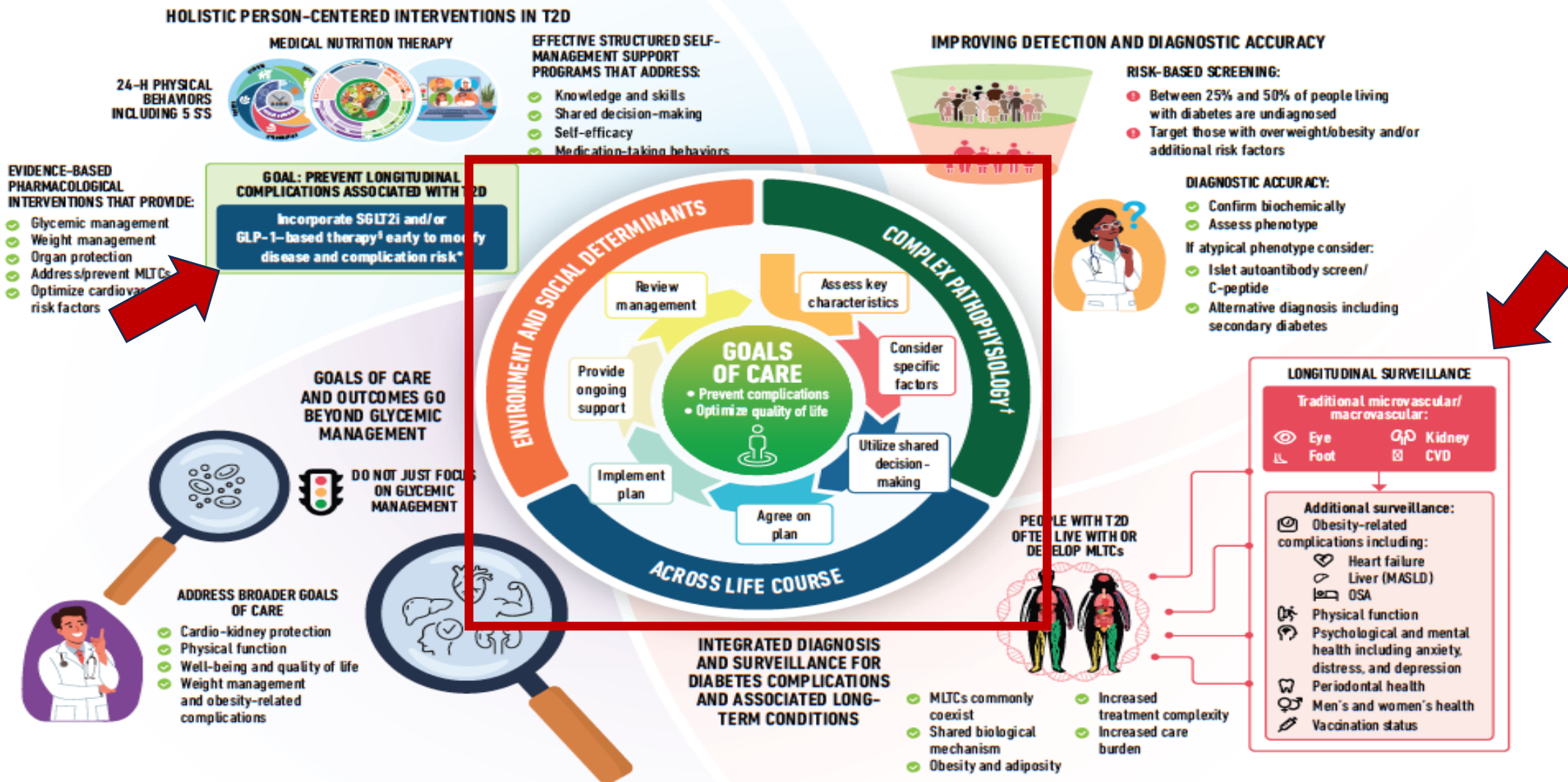


Figure 1—A holistic anticipatory integrated care approach addressing type 2 diabetes and its associated long-term conditions. *Use combination therapy based on target achievement and individual CVD and CKD risk. †Includes GLP-1 RA and the dual GLP-1/GIP agonist tirzepatide. ‡Dominantly driven by excess adiposity. MASLD, metabolic dysfunction-associated steatotic liver disease; MLTCs, multiple long-term conditions; OSA, obstructive sleep apnea; T2D, type 2 diabetes.

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

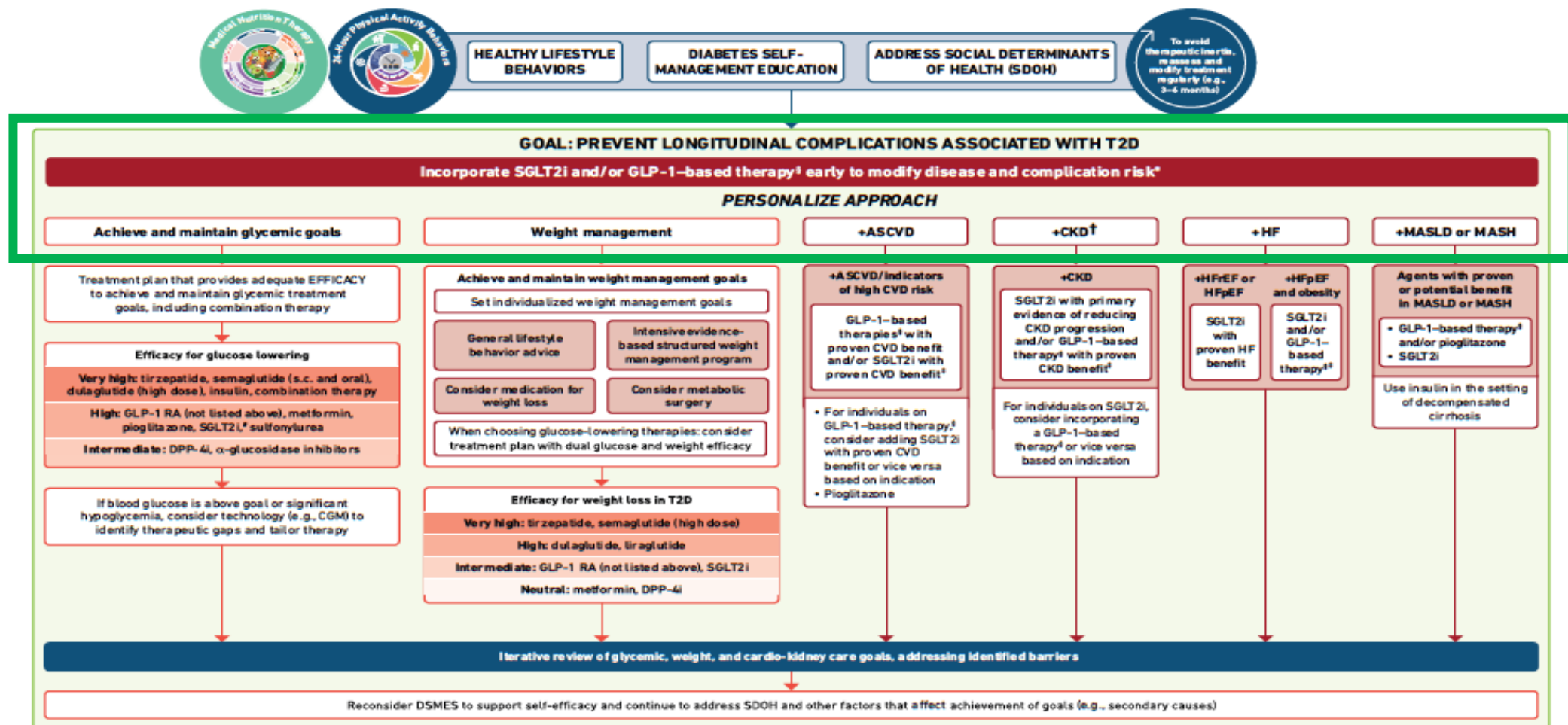


Figure 4—Use of glucose-lowering medications in the management of type 2 diabetes. *Use combination therapy based on target achievement and individual CVD and CKD risk. †eGFR <60 mL/min per 1.73 m² and/or albuminuria (UACR ≥3.0 mg/mmol [30 mg/g]). Repeat measurement is required to confirm CKD. ‡While evidence does not suggest simultaneous introduction of a GLP-1-based therapy with SGLT2i, evidence indicates that each will have benefit toward outcome risk reduction. §Includes GLP-1 RA and the dual GLP-1/GIP agonist tirzepatide. #Glucose-lowering efficacy is intermediate to high, dependent on eGFR. ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitor; CKD, chronic kidney disease; DSMES, diabetes self-management education and support; DPP-4i, dipeptidyl peptidase 4 inhibitor; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MASLD, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; OSA, obstructive sleep apnea; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes.

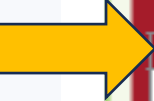
Section 03

Discussing Pharmacotherapies

USE OF GLUCOSE-LOWERING MEDICATIONS EARLY IN CARE

GOAL: PREVENT LONGITUDINAL COMPLICATIONS ASSOCIATED WITH T2D

Incorporate SGLT2i and/or GLP-1–based therapy[§] early to modify disease and complication risk^{***}



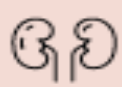
Phenotype	SGLT2i [†]	GLP-1–based therapy ^{†‡}
 Glucose-lowering efficacy	+	++
 Weight-lowering efficacy	+	++
 ASCVD/high-risk ASCVD	**	**
 CKD	**	**
 HF		
-HFrEF	**	
-HFpEF [‡]	**	**
 MASH/MASLD [§]	*	**

Figure 5— Use of glucose-lowering medications early in care. **Outcomes evidence. *Improvement in markers. ++Highest efficacy. +High efficacy. ***Use combination therapy based on target achievement and individual CVD and CKD risk. ¶Pioglitazone may be considered. †Where evidence and/or label indicate (Table 1). ‡Trials of GLP-1–based therapies only included participants with a BMI ≥30 kg/m². §Includes GLP-1 RA and the dual GLP-1/GIP agonist tirzepatide. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T2D, type 2 diabetes.

Start with the phenotype—not the drug list

ASCVD / high CV risk

- **GLP-1 RA or dual** incretin with ***demonstrated CV benefit(s)***
- **SGLT2 inhibitor** when CKD/HF coexists

Heart failure

- **SGLT2 inhibitor** foundational
- Consider phenotype-specific add-ons (e.g., **finerenone** in HFpEF indication)

CKD / albuminuria

- **SGLT2 inhibitor + renin-angiotensin** system therapy
- **nsMRA**
- **GLP-1 RA** with ***kidney-outcome evidence*** when appropriate

Obesity / MASLD-MASH

- Potent **incretin-**based therapy
- Align indication, weight-loss goal, liver status, nutrition and lean-mass plan

Frailty / hypoglycemia / burden

- De-intensify risky agents
- Simplify dosing
- Prioritize function, safety, and feasibility

2026 pharmacotherapy landscape

Class	Primary signal	Organ-outcome evidence	U.S. status
GLP-1 RA	GLP-1	ASCVD; kidney (semaglutide); obesity; MASH	Established
Dual GIP/GLP-1	GIP + GLP-1	Glycemia/weight; CV outcomes; HFpEF/obesity	Established
SGLT2 inhibitors	Renal glucose / sodium transport	HF + CKD + CV risk reduction	Established
nsMRA (finerenone)	Mineralocorticoid receptor	CKD/T2D + HFmrEF/HFpEF	Established
Once-weekly basal insulin	Insulin receptor	Glycemic efficacy; convenience	Awikli (icodec) approved March 2026 Onswik (efsitora) approved September 2026
Triple agonists / amylin combinations	Multi-receptor	Weight/metabolic endpoints; outcomes pending	Investigational

Clinical pearl: approval ≠ outcome evidence for organ protection, and outcome evidence ≠ an approved indication.

ADA Standards of Care—2026; FDA Prescribing Information for Wegovy, Ozempic, Mounjaro, Zepbound, Kerendia, and Awikli (current labels accessed Sept 2026).

A. GLP-1 receptor agonists: more than a glucose story

Metabolic effects

- Glucose-dependent insulin secretion
- Reduced glucagon (glucose-dependent)
- Delayed gastric emptying
- Appetite/satiety signaling
- Clinically meaningful weight reduction

Outcome evidence

- Multiple GLP-1 RAs reduce MACE in high-risk T2D populations
- **Semaglutide has dedicated kidney-outcome evidence in T2D + CKD and cardiovascular-outcome evidence in obesity without diabetes**

Safety focus

- GI adverse effects
- Gallbladder disease
- Dehydration-related kidney injury risk
- Rare pancreatitis
- Retinopathy signal with rapid glycemic improvement in susceptible individuals

MACE, major adverse cardiovascular event

Marso SP, et al. N Engl J Med. 2016;375:1834-1844. Lincoff AM, et al. N Engl J Med. 2023;389:2221-2232. Perkovic V, et al. N Engl J Med. 2024;391:109-121.

Semaglutide: one molecule, multiple organ indications

T2D + ASCVD

- **SUSTAIN-6**
established cardiovascular benefit
- Current Ozempic (injectable and oral) labeling includes reduction of MACE in adults with T2D and established CVD

T2D + CKD

- **FLOW:**
semaglutide (injectable Ozempic) reduced the composite risk of major kidney disease events / CV death versus placebo in high-risk T2D + CKD

Obesity + CVD

- **SELECT:**
semaglutide 2.4 mg reduced MACE in adults with overweight/obesity and established CVD without diabetes
- FDA approved 7.2 mg Wegovy dose in March 2026.

MASH

- Wegovy 2.4 mg weekly (injectable) received FDA accelerated approval (2025) for noncirrhotic MASH with moderate-to-advanced fibrosis, consistent with stages F2 to F3
- Confirm fibrosis stage and label criteria

Wegovy injection: weight + CV risk reduction + MASH

Wegovy tablets: weight + CV risk reduction

B. Dual GIP/GLP-1 agonism: *tirzepatide*

What it does well

- Large reductions in A1c and **body weight** across **SURPASS/SURMOUNT** programs
- Efficacy must be paired with proactive GI, nutrition, and hypoglycemia planning

Cardiovascular outcomes

- **SURPASS-CVOT** compared tirzepatide with dulaglutide in T2D + ASCVD
- Tirzepatide met noninferiority for MACE and generated additional cardiorenal analyses
- 8/28/2026 – **FDA approved Mounjaro to reduce MACE in adults with T2D at high CV risk.**

HFpEF + obesity

- **SUMMIT** showed clinically important benefit in people with HFpEF and obesity, including fewer worsening-HF/CV-death events and improved health status.

C. The incretin/amylin landscape is moving fast

NEW IN 2026: Foundayo (orforglipron) —
once-daily oral nonpeptide GLP-1 RA;
FDA-approved April 1, 2026 for chronic weight management (not T2D).

Retatrutide

- GIP + GLP-1 + glucagon receptor agonist
- Investigational
- Phase 3 obesity/T2D programs – TRIUMPH-1, 2, and 3 (positive outcomes)
- Phase 3 moderate-to-severe OSA & obesity or overweight +/- T2D

CagriSema

- Cagrilintide (amylin analog) + semaglutide
- Late-stage obesity/T2D program; verify regulatory status
- Still investigational

Zenagamide

(formerly known as amycletin)

- GLP-1 + amylin receptor co-agonism
- Clinical development; investigational

Clinical rule: do not translate weight-loss magnitude into “organ protection” unless outcomes trials establish patient-important benefit.

D. SGLT2 inhibitors: the CKM “organ-protection backbone”

Kidney

- Reduce intraglomerular pressure
- Slow CKD progression
- Benefit extends beyond glucose lowering and into lower eGFR ranges depending on product/indication

Heart failure

- Consistent reduction in HF hospitalization across reduced and preserved ejection fraction phenotypes, including people with and without diabetes

Safety / counseling

- Genital mycotic infection
- Volume depletion
- ***Rare euglycemic DKA***
- Temporary hold during prolonged fasting/major illness/surgery
- Monitor renal function and volume status

E. Finerenone: nonsteroidal MRA from diabetic CKD into heart failure

CKD + T2D

FIDELIO-DKD and **FIGARO-DKD** demonstrated kidney and cardiovascular benefit on top of standard care in albuminuric CKD associated with T2D.

CKD + T1D

09/2026 – **FDA label includes CKD associated with type 1 diabetes**

HFmrEF / HFpEF

- **FINEARTS-HF** expanded evidence into HF with mildly reduced or preserved EF
- Current U.S. labeling includes heart-failure risk reduction

Safety / monitoring

- **Hyperkalemia** is the key risk
- Check **potassium** and **kidney function** before initiation and after dose changes
- Account for interacting drugs and concurrent RAAS blockade

Not all “benefits” are the same

Evidence type	Example	How to talk about it
Patient-important outcome	MACE, HF hospitalization, kidney failure, CV death	Directly relevant to patients; anchors treatment priorities
Validated intermediate endpoint	Sustained eGFR decline	Useful but interpret within trial definition and population
Surrogate / biomarker	A1c, body weight, liver enzymes, hs-CRP, albuminuria/UACR change in some contexts	Biologically informative; does not automatically prove fewer hard events
Exploratory analysis	Post hoc subgroup, exploratory endpoint, or exploratory composite	Hypothesis-generating unless prespecified and robustly replicated

Clinical habit to build: ask “What endpoint moved and was that endpoint clinically meaningful?”

Fleming TR, Powers JH. Stat Med. 2012;31:2973-2984. Young CF. Lecture objective emphasizing patient-important vs surrogate outcomes. 2026.

F. Once-weekly basal insulin is now a real clinical choice

What changed

Awiqli (insulin icodec) received U.S. approval in 2026 for once-weekly basal insulin dosing for ***type 2 diabetes***.

The pharmacology requires clinicians to think in weekly units.

Potential value

Lower injection frequency may reduce treatment burden for selected adults, especially when daily basal administration is a barrier.

Clinical caution

- Long-action profile changes the consequences of titration errors and hypoglycemia
- Initiation/conversion instructions are product-specific; education is essential.

Section 04

What Would You Do?

Case 1: T2D + obesity + established ASCVD

Patient snapshot

- 58 years old
- A1c 8.2% on metformin
- BMI 36 kg/m²
- Prior MI
- eGFR 78; UACR 18 mg/g
- No HF symptoms

Priorities

1. Reduce recurrent CV risk
2. Achieve meaningful weight loss
3. Improve glycemia
4. Avoid hypoglycemia
5. Choose a sustainable therapy

Therapeutic direction

- Favor an incretin-based therapy with demonstrated **CV benefit** and high **weight efficacy**.
- Add/retain other risk-reduction therapies according to **blood pressure, lipids, kidney status**, and individual tolerability.

Case 2: T2D + albuminuric CKD

Patient snapshot

- 66 years old
- A1c 7.5%
- eGFR 42 mL/min/1.73m²
- UACR 420 mg/g
- On ACE inhibitor
- K⁺ 4.6 mmol/L

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Priorities

1. Slow kidney progression
2. Reduce HF/CV events
3. Control potassium risk
4. Avoid therapeutic inertia

Therapeutic direction

- **SGLT2 inhibitor** as a foundational organ-protective therapy (if eligible) + **optimized RAAS blockade**.
- Consider **finerenone** for persistent albuminuria with acceptable potassium, and **GLP-1 RA** with kidney-outcome evidence when clinically appropriate.

Case 3: obesity + HFpEF + T2D

Patient snapshot

- 71 years old
- BMI 39 kg/m²
- HFpEF with recent congestion (hospitalization)
- A1c 7.1%
- eGFR 61
- Marked exercise limitation

Priorities

1. Prevent worsening HF
2. Improve symptoms/function
3. Reduce weight safely
4. Preserve lean mass
5. Minimize volume depletion

Therapeutic direction

- **SGLT2 inhibitor** remains foundational.
- In obesity-related HFpEF, **tirzepatide** outcome data support considering potent weight-directed therapy when appropriate.
- **Finerenone** may be relevant under current HF indication and potassium/eGFR criteria.

Case 4: older adult with frailty and recurrent hypoglycemia

Patient snapshot

- 82 years old
- A1c 6.4%
- Basal-bolus insulin + sulfonylurea
- Two falls in 6 months (hypoglycemia-associated)
- Reduced appetite
- Lives alone

Priorities

1. Prevent hypoglycemia
2. Simplify regimen
3. Preserve function / nutrition
4. Align goals with life expectancy and preferences

Therapeutic direction

- Relax **glycemic targets** when appropriate
- **Remove agents** that create avoidable hypoglycemia
- **Simplify insulin**
- Do not pursue aggressive weight loss when frailty, malnutrition, or sarcopenia risk dominates.

Section 05

Exploring other targets

A. Metabolic liver disease is now part of diabetes pharmacotherapy

Screen the phenotype

- T2D and obesity increase risk for advanced metabolic liver disease
- Use non-invasive fibrosis risk assessment (**FIB-4 and liver elastography**) and appropriate **referral rather than relying on aminotransferases alone**

Treat the biology

- **Weight reduction** remains central
- **Semaglutide** has an FDA MASH indication under accelerated approval for defined noncirrhotic fibrosis stages (F2 and F3)
- **Resmetirom** is another liver-directed option outside the diabetes drug classes

Avoid overclaiming

- Improved liver enzymes, imaging, or histology are **not** interchangeable with hard liver outcomes
- State what the trial actually measured: Not to turn a positive MASH trial into a claim that is stronger than the evidence.

MASH: SCREEN → STAGE → REFER

In T2D, clinically important fibrosis can be present even when aminotransferases are normal

1 | Start with **FIB-4**

- Screen adults with T2D or prediabetes, especially with obesity, other cardiometabolic risk factors, or established CVD
- **FIB-4 uses age, AST, ALT, and platelet count.**
- A value **<1.3 generally indicates lower risk;**
>2.67 warrants direct liver-specialist referral without additional testing

2 | Escalate if FIB-4: 1.3 – 2.67

- Use **LSM** by transient elastography (preferred) or the ELF test
- LSM <8.0 kPa supports lower advanced-fibrosis risk; LSM ≥8.0 kPa or ELF ≥9.8 should prompt gastroenterology/hepatology referral
- ***In adults ≥65 years, higher FIB-4 cutoffs (~1.9–2.0) may be appropriate***

3 | Reassess longitudinally

- ***Do not use ALT alone*** as a screening strategy
- ***Patients at lower risk can usually remain in non-specialty care with repeat fibrosis-risk assessment about every ≥2 years***
- Refer higher-risk, discordant, or clinically concerning cases

ELF, Enhanced Liver Fibrosis; LSM, Liver stiffness measurement.

American Diabetes Association Professional Practice Committee. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Care in Diabetes—2026. Diabetes Care. 2026;49(Suppl 1).

MASH THERAPY: TWO APPROVED PATHS, DIFFERENT BIOLOGY

One amplifies a food signal; the other directly targets hepatic thyroid-hormone signaling

Amplify GLP-1 signaling

SEMAGLUTIDE 2.4 mg weekly

- FDA accelerated approval (2025) for adults with MASH and moderate-to-advanced fibrosis
- **ESSENCE** at Week 72: MASH resolution without worsening fibrosis 62.9% vs 34.3%; ≥1-stage fibrosis improvement without worsening MASH 36.8% vs 22.4%
- Also addresses obesity and cardiometabolic risk

Target the liver directly

RESMETIROM once daily

- FDA accelerated approval (2024) for adults with noncirrhotic MASH and F2–F3 fibrosis
- **MAESTRO-NASH** (100 mg, 52 weeks): MASH resolution 29.9% vs 9.7%; fibrosis improvement 25.9% vs 14.2%
- Monitor for *hepatotoxicity*, gallbladder events, and clinically relevant drug interactions

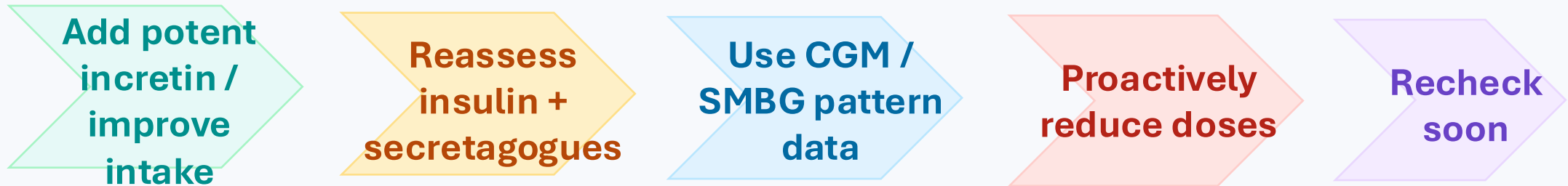
Next wave: still investigational

- **TIRZEPATIDE: SYNERGY-NASH** phase 2 showed MASH resolution in 44–62% vs 10% with placebo and fibrosis improvement in ~51–55% vs 30%
- **SURVODUTIDE:** glucagon/GLP-1 dual agonist remains investigational for MASH, with phase 3 development ongoing

Histologic MASH endpoints are NOT equivalent to demonstrated reduction in cirrhosis, hepatic decompensation, transplantation, or mortality.

FDA. Wegovy approval for MASH (Aug 15, 2025); FDA. Rezdiffra approval (Mar 14, 2024). Sanyal AJ, et al. N Engl J Med. 2025;392:2089–2099. Harrison SA, et al. N Engl J Med. 2024;390:497–509. Loomba R, et al. N Engl J Med. 2024;391:299–310.

B. Potent therapy should trigger medication subtraction, not just addition



Who is at **highest** risk?

Older adults; CKD; prior severe hypoglycemia; inconsistent food intake; cognitive impairment; insulin/sulfonylurea use; recent rapid A1c improvement

Practical message

When a new agent lowers glucose without intrinsic hypoglycemia, the hypoglycemia risk often comes from the ***therapies already on board.***

C. Weight loss is NOT the same as healthy tissue loss

Assess

- Recent unintentional weight loss
- Appetite
- Protein intake
- Resistance activity
- Frailty
- *Sarcopenia* risk
- GI adverse effects
- Food insecurity

Protect

- Adequate protein and micronutrients
- Resistance exercise when feasible
- Slower titration when intake is compromised
- Coordinate with nutrition and rehabilitation professionals

Monitor

- Weight trajectory + strength/function, not weight alone
- In older adults or advanced disease, excessive loss may conflict with functional goals

Section 06

Ensuring Safety & Access

WHAT TO ANTICIPATE BEFORE THE PRESCRIPTION

A compact safety matrix for clinic

Class	Key adverse-effect domains	High-yield monitoring / counseling
GLP-1 / dual incretin	GI, gallbladder, dehydration, rare pancreatitis	Slow titration; hydration; persistent severe abdominal symptoms; retinopathy risk context
SGLT2 inhibitor	Genital infection, volume depletion, euglycemic DKA	Sick-day / fasting hold; ketone awareness; volume and renal status
Finerenone	Hyperkalemia, renal function changes	K ⁺ / eGFR at baseline and after initiation/ dose changes
Basal insulin	Hypoglycemia, dosing error	Injection technique; glucose patterns; product-specific conversion/titration
Investigational agents	Known + unknown class effects	Explicitly discuss uncertainty and lack of approval

Current US Prescribing Information: Wegovy/Ozempic, Mounjaro/Zepbound, SGLT2 inhibitors, Kerendia, Awiqli; accessed Sept 2026.

Unapproved / compounded incretin products require careful communication

Clarify terms

FDA-approved
commercial product ≠
compounded product
≠
research drug ≠
counterfeit/
fraudulent product

Known risks

- **FDA has warned about dosing errors and fraudulent compounded products labeled as semaglutide or tirzepatide**
- Product quality and concentration may differ

How to counsel

- Use nonjudgmental language
- Ask what product, concentration, source, and dosing device the patient is actually using
- Escalate adverse events and suspected counterfeit products appropriately

The “best” therapy is the one the patient can actually obtain and sustain

Before prescribing

- Coverage / formulary
- Prior authorization criteria
- Deductible / copay
- Supply availability
- Injection / device preference
- Transportation / pharmacy access

During titration

- Early follow-up
- Adverse-effect management
- Refill continuity
- Dose availability
- Nutrition changes
- Hypoglycemia de-intensification

If therapy is interrupted

- Plan for re-initiation / titration when appropriate
- Reassess glycemia / weight / HF volume status
- Avoid unsafe “catch-up” dosing
- Address the cause of interruption

Section 07

Summary & Key Takeaways

Monitoring should follow the risk you are trying to change

Metabolic

- A1c / CGM metrics
- Weight trajectory
- Appetite / food intake
- Liver risk markers when relevant

Cardiovascular

- Symptoms / volume status
- Blood pressure
- Lipids
- HF events
- ASCVD risk-factor management

Kidney

- eGFR
- UACR
- Potassium
- Volume / AKI risk

Humanistic

- Hypoglycemia
- GI burden
- Function / strength
- Affordability
- Preferences / treatment burden

A practical prescribing algorithm

- 1 Define phenotype** ASCVD • HF • CKD • obesity • MASH • frailty
- 2 Name the outcome** MACE • HF hospitalization • kidney failure • function • glycemia
- 3 Match evidence** Choose therapy with demonstrated benefit for that **outcome + phenotype**
- 4 Subtract risk** De-intensify hypoglycemia / avoid interactions / plan sick-day holds
- 5 Protect function** Nutrition • protein • resistance activity • lean mass
- 6 Make it sustainable** Access • burden • preferences • follow-up

Synthesis based on ADA Standards of Care—2026, current FDA labeling, and landmark outcomes trials cited throughout this presentation.

Five take-home messages

- 1 Treat the **phenotype**, not just A1c.
- 2 Anchor “**benefit**” to patient-important outcomes.
- 3 Layer complementary **organ-protective** mechanisms when indicated.
- 4 Proactively manage **hypoglycemia, nutrition, lean mass, and treatment burden**.
- 5 State **regulatory status clearly**, especially for rapidly evolving metabolic therapies.

Section 08

Returning to the Opening Clinical Case

Build the integrated CKM treatment plan

Protect organs first

- Start an **SGLT2 inhibitor** with demonstrated HF and kidney benefit, unless contraindicated
- Continue/maximize **ACE inhibitor or ARB therapy** for albuminuric CKD as tolerated
- Optimize established ASCVD risk-reduction therapy

Address obesity + glycemia

- Add an **incretin-based therapy** with outcome evidence appropriate to the phenotype
- Match the specific agent to ASCVD evidence, weight goals, tolerability, regulatory status, access, and patient preference

Subtract risk + layer care

- Consider **finerenone** for persistent albuminuric CKD when potassium and kidney function permit
- Reassess **basal insulin** as glucose improves; use CGM to reduce hypoglycemia
- Protect **nutrition, lean mass, function, and medication access**

Which therapy is doing which job?

- | | | |
|---|-------------------------------|---|
| 1 | SGLT2 inhibitor | HF + kidney protection • modest glycemic effect • monitor volume status and sick-day risk |
| 2 | GLP-1 / dual incretin | Weight + glycemia • cardiovascular benefit depends on agent/evidence • anticipate GI and nutrition issues |
| 3 | Finerenone | Residual albuminuric kidney / CV risk • monitor potassium and eGFR |
| 4 | Insulin adjustment | Reduce hypoglycemia and treatment burden as more potent therapies are layered in |
| 5 | Supportive care | Nutrition • protein adequacy • resistance activity • lean mass • education • access |
| 6 | What changes the plan? | Frailty • cost / coverage • kidney function • potassium • GI tolerance • patient goals and preferences |
-

From food signals to organ protection: what each layer contributes

Therapy / action	Food-signal pathway	Primary clinical job	Key monitoring / discussion
GLP-1 / dual incretin	GLP-1 ± GIP	Weight + glycemia; agent-specific CV / kidney benefit	GI tolerance • intake/protein adequacy • hypoglycemia risk when insulin/secretagogues are present
SGLT2 inhibitor	Not a food-signal pathway	HF + CKD protection; modest glucose effect	Volume status • eGFR • genital effects • sick-day / ketosis education
Finerenone	Not a food-signal pathway	Albuminuric CKD/cardiorenal risk; independently reduces HF events in patients with HF and LVEF ≥ 40%	Hyperkalemia • eGFR • drug interactions • Worsening renal function in HF
Insulin deintensification	Responds to the new metabolic environment	Reduce hypoglycemia and treatment burden	CGM/SMBG pattern • dose reduction • nutrition changes
Nutrition + resistance activity	Actual nutrient input + muscle stimulus	Preserve lean mass, function, and treatment tolerance	Appetite • protein / micronutrient adequacy • strength / frailty • patient goals

Discussion prompt: Which layer changes the patient’s meal-response biology, and which layer protects organs through a different pathway?

Section 09

Returning to the Big Picture: System of Care

Diabetes Care®



Management of Type 2 Diabetes, 2026. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Melanie J. Davies, Vanita R. Aroda, Mandeep Bajaj, Nuha A. ElSayed, Francesco Giorgino, Jennifer Green, Rita R. Kalyani, Nisa M. Maruthur, Chantal Mathieu, Sylvia E. Rosas, Peter Rossing, Tommy Slater, Tsvetalina Tankova, Pinar Topsever, Apostolos Tsapas, and John B. Buse

Diabetes Care 2026;**49(00)**:1–45 | <https://doi.org/10.2337/dci26-0141>

A LEARNING HEALTH SYSTEM FRAMEWORK FOR QUALITY AND OUTCOMES IN T2D

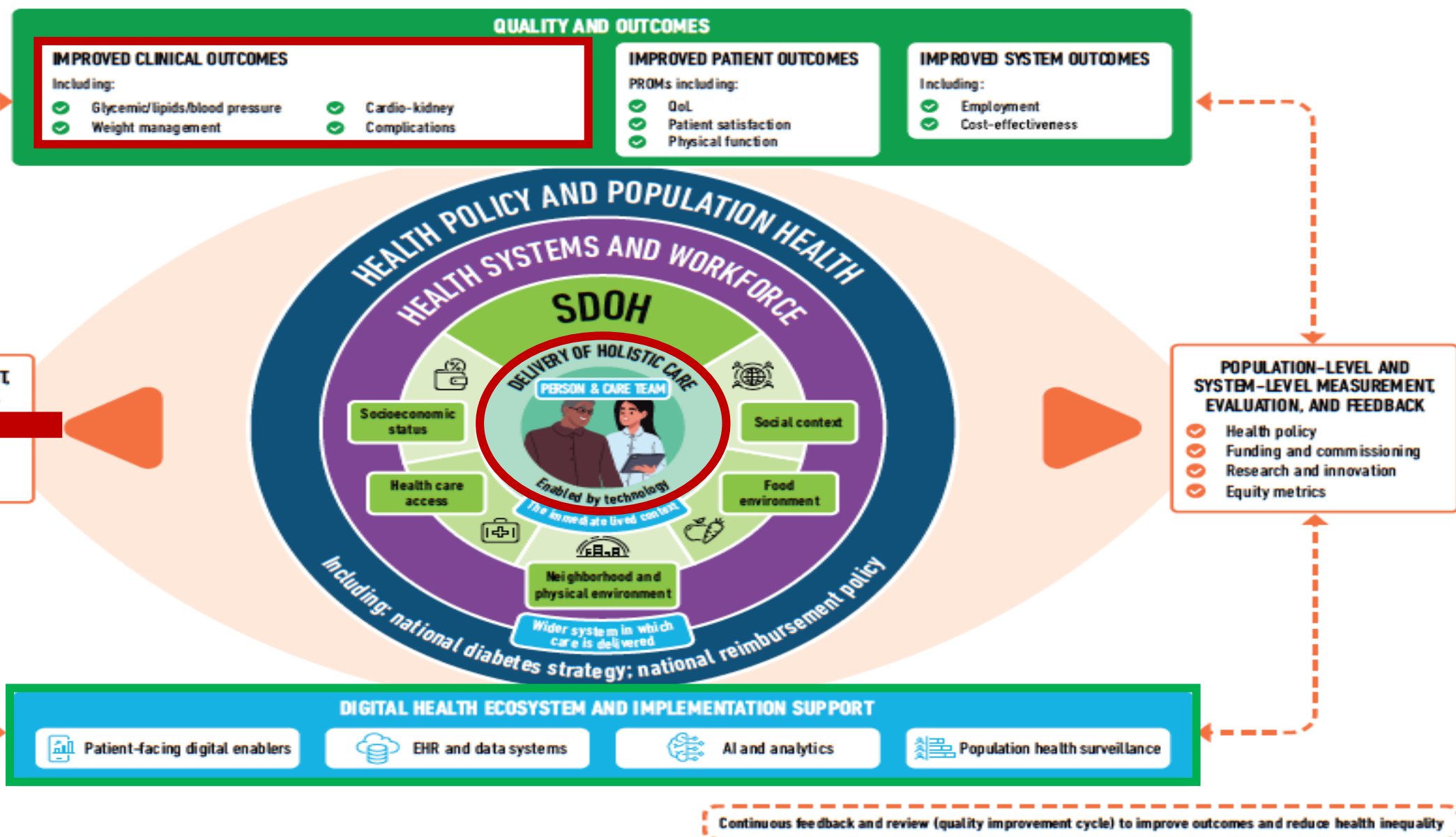


Figure 6—A learning health system framework for quality and outcomes in type 2 diabetes. AI, artificial intelligence; EHR, electronic health record; PROMs, patient-reported outcome measures; QoL, quality of life; T2D, type 2 diabetes.

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Diabetes

Type 2 diabetes and the cardio-renal-metabolic syndrome: The evolving roles of GLP-1 and dual GLP-1/GIP receptor agonists

 Clipper F Young, Namrita George, Alexander Olson, Diana Isaacs  22 mins



Published Online: Aug 25th 2026 touchREVIEWS in Endocrinology. 2026;20(2):1–9:Online ahead of journal publication

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THANK YOU

Questions & Discussion

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From Food Signals to Organ Protection