به نام خداوند جان و خرد

دکتر نادر طاهری فوق تخصص غدد بالغین

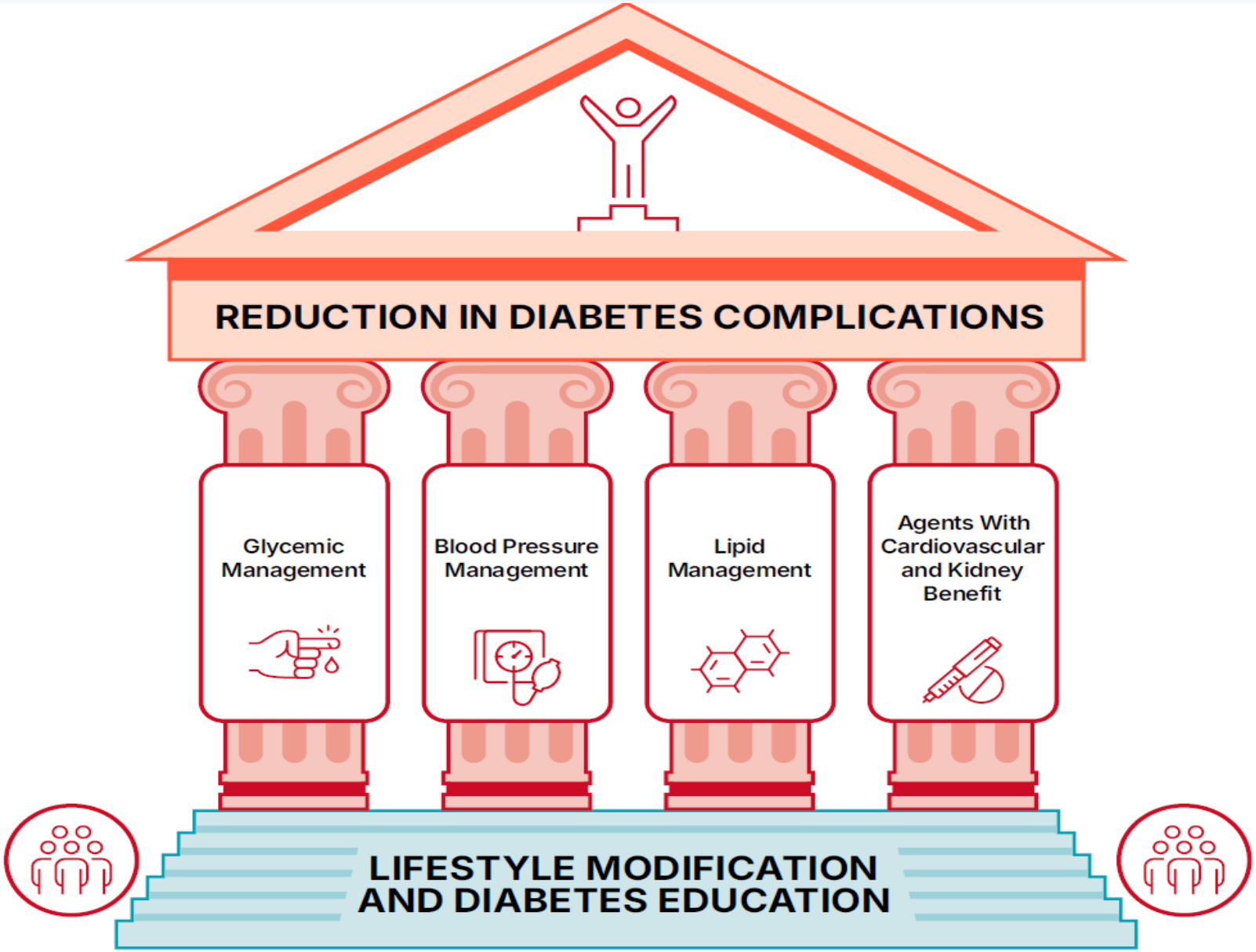

Figure 10.1—Multifactorial approach to reduction in risk of diabetes complications.

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Standards of Care in Diabetes - 2025 Diabetes Care 2025;48(Suppl. 1):

Pharmacologic Therapy for Adults with Type 2 Diabetes

- ***Hba1c Target***
- ***Cardiovascular & kidney benefit (cardiorenal benefit)***,
- Weight Neutral or Weight benefit,
- hypoglycemia risk,
- Cost & Access,
- Combination therapy,
- Patient preference,

ADA 2025

- When A1C is ≥1.5% above the individualized glycemic goal, many individuals require ***dual-combination therapy*** to achieve their goal A1C level .

- **Initial** combination therapy considered in people presenting with A1C levels 1.5–2.0% above their individualized goal.

- Each new class of oral agents, when added to metformin generally lowers A1C by approximately 0.7–1.0%.

- *ADA,2025*

آقای 50ساله، کارمند، با سابقه 4 ساله دیابت نوع دو، تحت درمان با مت فورمین 500 (روزی 3 عدد) از قبل، 2 هفته پیش از سی سی یو به دلیل سکته قلبی ترخیص شده است .

آزمایشات بعد از سکته قلبی :

BMI : 28 kg/m^2 FBS : 101 Hb A_1C : 7% Cr : 0/9 LFT : N T.F.T: N

LDL : 60 UA CR : 21 EF : 60 % FIB4 : 1.2

ته چشم : Normal

توضیح شما جهت ادامه درمان داروئی چیست ؟

الف – ادامه مت فورمین روزی 3 عدد با توجه به Hb A_1C: 7%

ب – اضافه کردن مهار کننده SGL2 به مت فورمین

ج – اضافه کردن لیراگلوتاید به مت فورمین

د – موارد ب و ج هر دو بسته به ترجیح بیمار

Cardiovascular Disease and Type 2 Diabetes

- **Introduce SGLT2 inhibitors or GLP-1 RAs in people with CVD,**
- ***at A1C goal*** **(independent of metformin) for cardiovascular benefit.**
-

ADA 2025

خانم 60 ساله با دیابت نوع دو و پرفشاری خون از 8 سال قبل تحت درمان با زیپمت50/1000 روزی 2 عدد با مشخصات ذیل به شما مراجعه کرده است :

FBS : 110 Hb A_1C : 7.2 TSH : N LFT : Normal Cr : 0.9

UA CR : 40 در 2 نوبت به فاصله 2 ماه

ته چشم : Mild NPDR FIB4 : 1.2 BMI : 28kg/m^2

بهترین درمان داروئی در بیمار فوق چیست ؟

الف – افزایش دوز ترکیب مت فورمین – سیتا گلیپتین به با توجه به Hb A_1C بیمار 50/1000

ب – اضافه کردن امپا گلیفلوزین 25 به ترکیب مت فورمین – سیتا گلیپتین 50/500

ج – اضافه کردن دیابزید 30 به درمان قبلی بیمار

د – اضافه کردن لیراگلوتاید به ترکیب داروئی بیمار

In adults with T2DM and CKD **(eGFR 20–60 and/or albuminuria),**
an SGLT2 inhibitor or GLP-1 RA should be used for both glycemic management (irrespective of A1C) and for slowing progression of CKD and reduction in cardiovascular events .

The glycemic benefits of SGLT2 inhibitors reduced at eGFR <45 mL/min/1.73 m^2.

In adults with T2DM and advanced CKD (eGFR <30),
a GLP-1 RA preferred for glycemic management due to lower risk of hypoglycemia and for cardiovascular event reduction.

ADA,2025

CASE 3

آقای 60 ساله، کارمند بازنشسته، سابقه 4 سال دیابت نوع دو و چاق (BMI : 31 kg/m^2) با آزمایشات ذیل مراجعه کرده است :

FBS : 100	Hb A_1C : 6.9%	CR : 0.9	TSH : N
LDL : 70	ALT : 54	AST : 40	UA CR : N
PLT : 200,000	BP : 135/85	ته چشم : Normal	

پزشک وی با توجه به چاقی، اندکس FIB-4 را محاسبه کرده و چون FIB-4، عدد 1/4 بوده جهت وی فیبرواسکن درخواست کرده که متاسفانه فیبرواسکن *F-3* بوده است .

بهترین تصمیم درمانی چیست ؟

الف – ادامه مت فورمین و کاهش وزن حداقل 7 درصد

ب – اضافه کردن امپا گلیفلوزین 25 به مت فورمین

ج – اضافه کردن پیتوز 15 به مت فورمین

د – اضافه کردن لیراگلوتاید به مت فورمین

ه – الف و ج یا د ، بسته به ترجیح بیمار

T2DM AND MASH

In adults with T2DM and MASH (F2 AND F3 in fibroscan) :

pioglitazone, a GLP-1 RA, or a dual GIP and GLP-1 RA preferred for glycemic management due to potential beneficial effects on MASH.

Combination therapy with pioglitazone plus a GLP-1 RA can be considered for the treatment of hyperglycemia .

Table 2—MASLD nomenclature, histological grades, and fibrosis staging

Nomenclature	Definition
Steatotic liver disease (SLD)	• An "umbrella" term encompassing different disease subcategories, characterized by predominantly hepatic macrovesicular steatosis
Metabolic dysfunction–associated steatotic liver disease (MASLD)*	• Presence of SLD with at least one metabolic risk factor (overweight or obesity or waist circumference >95th percentile, hypertension, prediabetes or type 2 diabetes, elevated triglycerides, or low HDL cholesterol) and either no alcohol consumption or consumption in amounts not likely to directly lead to liver outcomes (<20 g/day for women, <30 g/day for men)
Metabolic dysfunction–associated steatotic liver (MASL)	• Steatosis with either no or minimal lobular inflammation and without ballooning and alcohol consumption below thresholds noted above
Metabolic dysfunction–associated steatohepatitis (MASH)	• Presence of steatohepatitis and at least one metabolic risk factor for SLD and no alcohol consumption or consumption in amounts not considered likely to cause liver outcomes by itself as noted above
At-risk MASH	• Steatohepatitis (with histological MASLD activity score [MAS] ≥4) and fibrosis stage ≥F2 (i.e., people who are at a higher risk of developing future cirrhosis) (see below)
MASLD activity score (MAS)**	• Sum of scores for steatosis (0–3) plus hepatocellular ballooning (0–2) plus lobular inflammation (0–3)
Fibrosis stages	• Based on severity and distribution of scar tissue
	• Mild fibrosis: stage F1 (i.e., fibrosis in hepatic sinusoids in pericellular location)
	• Moderate fibrosis: stage F2 (i.e., sinusoidal and portal fibrosis)
	• Advanced fibrosis: stage F3 (i.e., bridging fibrosis, usually central-to-portal or central-to-central bridges) or stage F4 (cirrhosis)**
Clinically significant fibrosis	• Fibrosis stage ≥F2

*The definition of MASLD implies either no alcohol consumption or consumption in amounts not considered to lead to liver outcomes by itself. **Extensive disruption of liver architecture with regenerative nodules with encirclement by fibrotic bands.

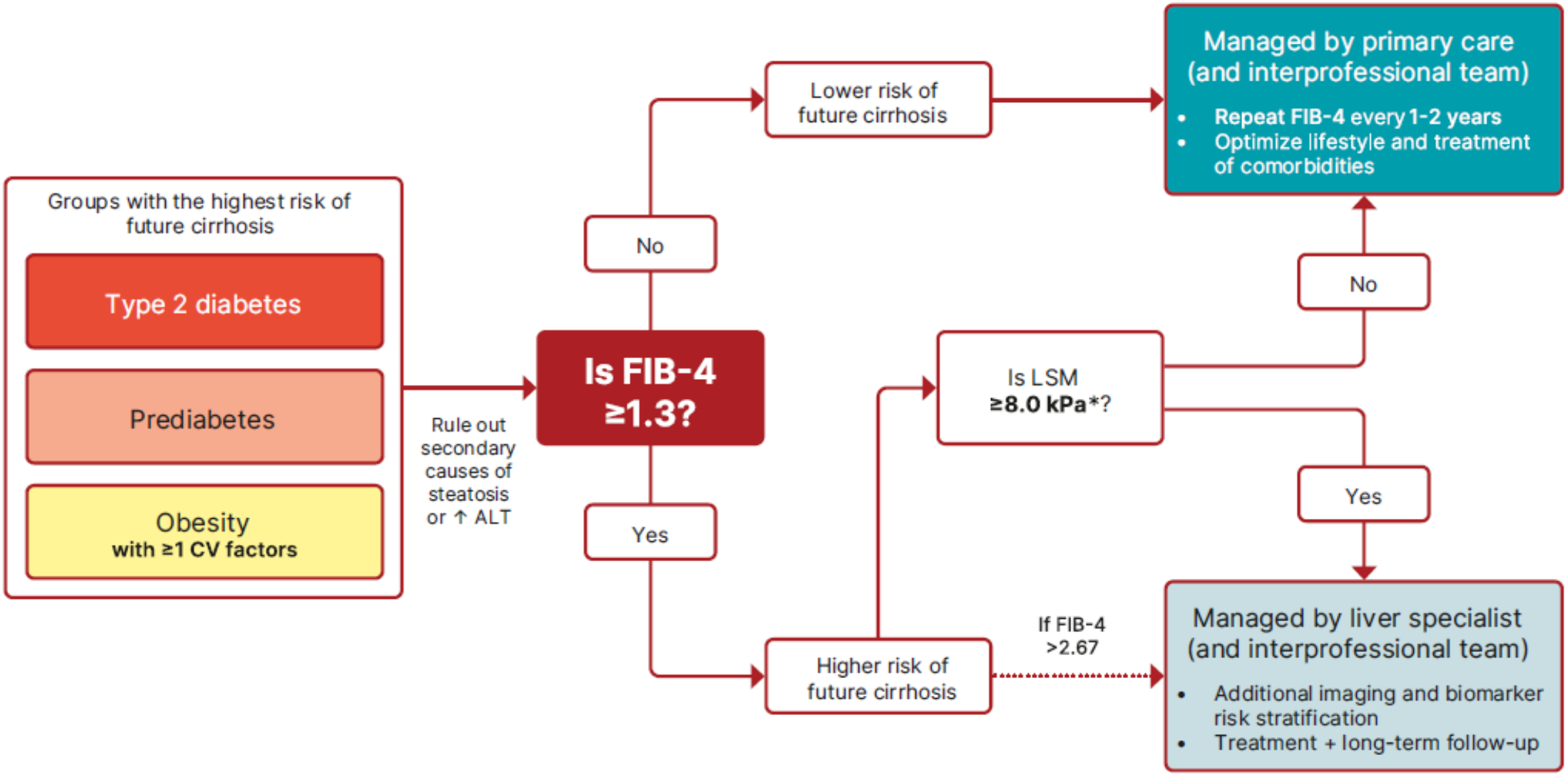
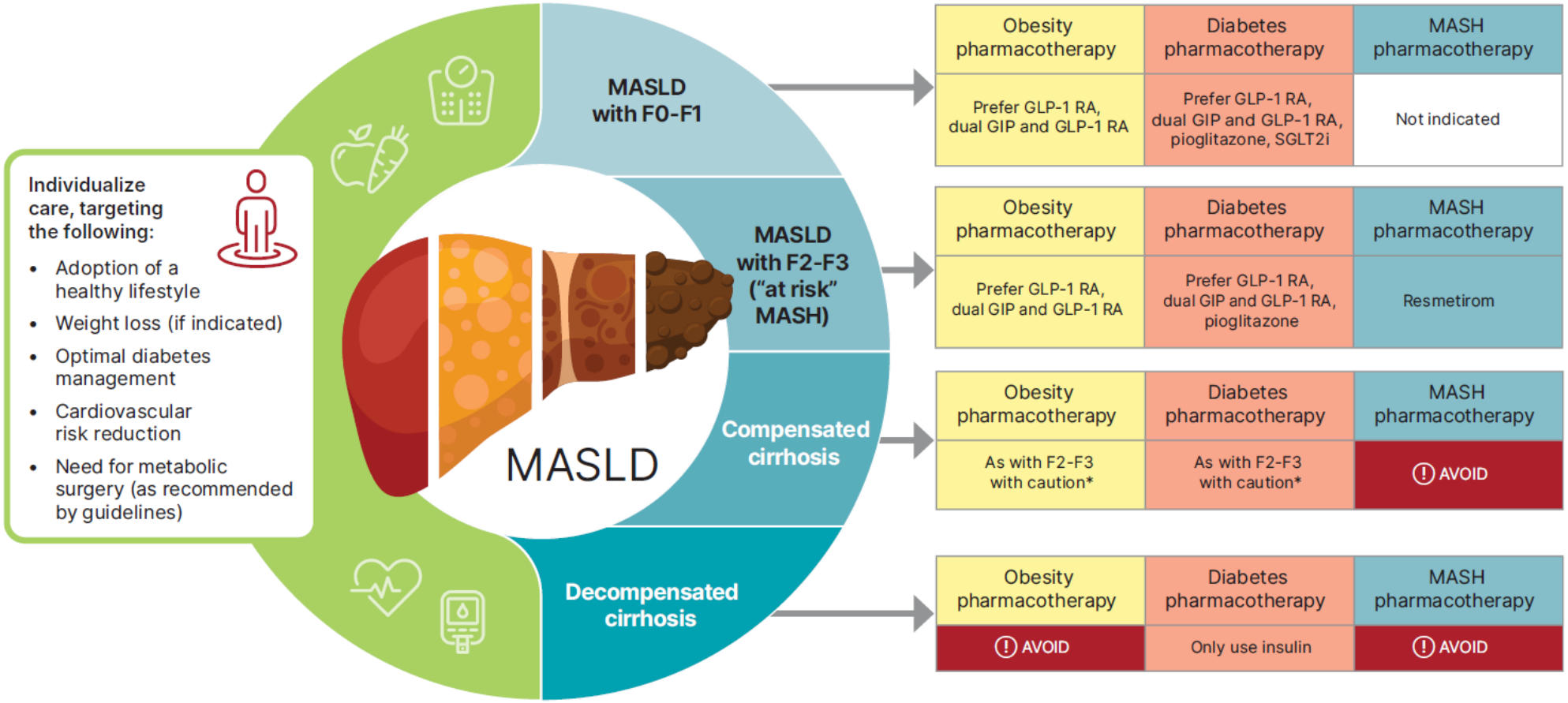


Figure 2—Diagnostic algorithm for risk stratification and the prevention of cirrhosis in individuals with MASLD. *In the absence of LSM, consider the blood-based ELF test as a diagnostic alternative. If ELF score is ≥9.8, a referral to a liver specialist is recommended, as there is a high risk of MASH with advanced liver fibrosis. Adapted from "Standards of Care of Diabetes—2025" (59).

Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) Treatment Algorithm



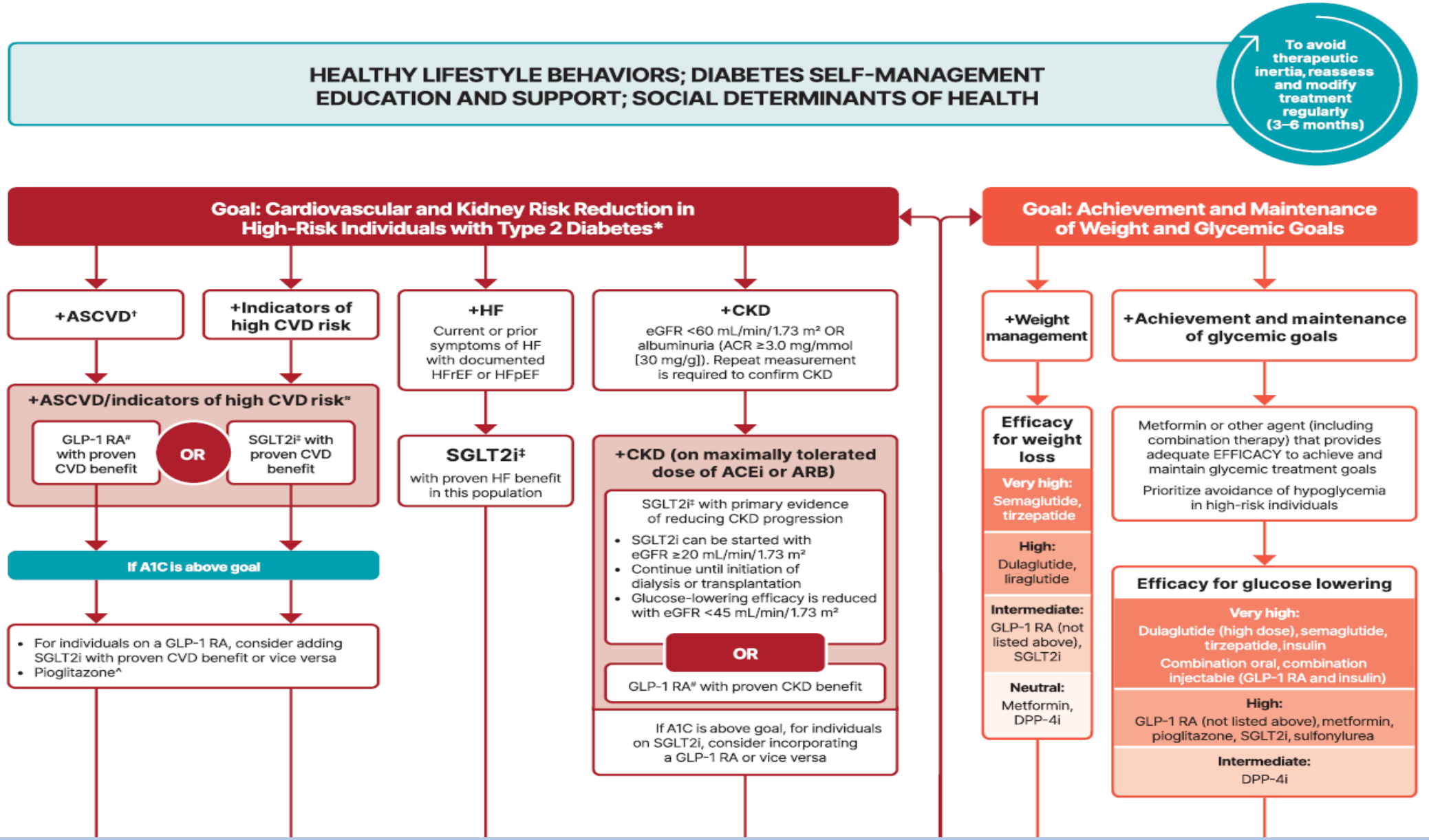
	Obesity pharmacotherapy	Diabetes pharmacotherapy	MASH pharmacotherapy
MASLD with F0-F1	Prefer GLP-1 RA, dual GIP and GLP-1 RA	Prefer GLP-1 RA, dual GIP and GLP-1 RA, pioglitazone, SGLT2i	Not indicated
MASLD with F2-F3 ("at risk" MASH)	Prefer GLP-1 RA, dual GIP and GLP-1 RA	Prefer GLP-1 RA, dual GIP and GLP-1 RA, pioglitazone	Resmetirom
Compensated cirrhosis	As with F2-F3 with caution*	As with F2-F3 with caution*	ⓘ AVOID
Decompensated cirrhosis	ⓘ AVOID	Only use insulin	ⓘ AVOID

*Individualized care and close monitoring needed in compensated cirrhosis given limited safety data available.

Figure 4.3—Metabolic dysfunction–associated steatotic liver disease (MASLD) treatment algorithm. F0-F1, no to minimal fibrosis; F2-F3, moderate fibrosis; F4, cirrhosis; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; MASH, metabolic dysfunction–associated steatohepatitis; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Standards of Care in Diabetes - 2025. *Diabetes Care* 2025;48(Suppl. 1):S59-S85

Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes



Standards of Care in Diabetes - 2025 Diabetes Care 2025;

Table 9.2—Features of medications for lowering glucose in type 2 diabetes

Medication (route of administration)	Glucose-lowering efficacy[1]	Hypoglycemia risk	Weight effects[2]	CV effects		Kidney effects		MASH effects	Clinical considerations and adverse effects
				Effect on MACE	Effect on HF	Progression of CKD	Dosing/use considerations*		
Metformin (oral)	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	• Contraindicated with eGFR <30 mL/min/ 1.73 m^2	Neutral	• GI side effects: mitigate with slow dose titration, extended-release formulations, and administration with food. • Potential for vitamin B12 deficiency: monitor and replete as appropriate.
SGLT2 inhibitors (oral)	Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	• See labels of individual agents for dosage considerations for kidney function • Glucose-lowering effect is minimal at eGFR <45 mL/min/1.73 m^2 and lower; continue for cardiovascular and kidney benefit until dialysis or transplantation	Unknown	• DKA risk in individuals with insulin deficiency (rare in T2D): discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentations (including euglycemic DKA); mitigate risk with sick-day planning; discontinue before scheduled surgery (e.g., 3-4 days), during critical illness, or during prolonged fasting. • Genital mycotic infections: mitigate risk with genital hygiene and avoid use in high-risk individuals. • Necrotizing fasciitis of the perineum (Fournier gangrene): rare; prompt treatment if suspected. • Intravascular volume depletion: attention to volume status and blood pressure, particularly when ill or fasting; adjust other volume-contracting agents as applicable; monitor kidney function upon initiation.

9. Pharmacologic Approaches to Glycemic Treatment

(route of administration)	lowering efficacy[1]	Hypoglycemia risk	Weight effects[2]	Effect on MACE	Effect on HF	Progression of CKD	Dosing/use considerations*	MASH effects	Clinical considerations and adverse effects
GLP-1 RAs (SQ; semaglutide also available in oral formulation)	High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ) Neutral: exenatide once weekly, lixisenatide	Neutral	Benefit for renal end points in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ) Demonstrated benefit for progression of CKD for semaglutide (SQ)	• See labels of individual agents for dosage considerations for kidney function • No dose adjustment for dulaglutide, liraglutide, or semaglutide • Monitor kidney function when initiating or escalating doses in individuals with kidney impairment reporting severe adverse GI reactions	Potential benefit	• Thyroid C-cell tumors identified in rodents; human relevance not determined. • Ileus: risk level is not well established; provide guidance on discontinuation prior to surgical procedures. • Pancreatitis: acute pancreatitis has been reported, but causality has not been established. Do not initiate if at high risk for pancreatitis, and discontinue if pancreatitis is suspected. • Biliary disease: evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected; avoid use in at-risk individuals. • Diabetic retinopathy: close monitoring of retinopathy in those at high risk (older individuals and those with longer duration of T2D [≥10 years]). • Impact on drug absorption: orally administered drug absorption may be impaired during dose titration (including of oral contraceptives). • GI side effects: counsel on potential for GI side effects; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g. stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for those experiencing GI challenges. Not recommended for individuals with gastroparesis.
Dual GIP and GLP-1 RA (SQ)	Very high	No	Loss (very high)	Under investigation	Under investigation	Under investigation	• See labels of individual agents for dosage considerations for kidney function • No dose adjustment • Monitor kidney function when initiating or escalating doses in individuals with kidney impairment reporting severe adverse GI reactions	Potential benefit	
DPP-4 inhibitors (oral)	Intermediate	No	Neutral	Neutral	Neutral (potential risk: saxagliptin)	Neutral	• Dose adjustment required based on kidney function (sitagliptin, saxagliptin, alogliptin) • No dose adjustment required for linagliptin	Unknown	• Pancreatitis has been reported, but causality has not been established. Discontinue if pancreatitis is suspected. • Postmarketing concerns about joint pain (consider discontinuing if debilitating and other treatment options are feasible) and bullous pemphigoid (discontinue if suspected).

Standards of Care in Diabetes - 2025 Diabetes Care 2025;

Medication (route of administration)	Glucose-lowering efficacy[1]	Hypoglycemia risk	Weight effects[2]	CV effects		Kidney effects		MASH effects	Clinical considerations and adverse effects
				Effect on MACE	Effect on HF	Progression of CKD	Dosing/use considerations*		
Pioglitazone (oral)	High	No	Gain	Potential benefit	Increased risk	Neutral	• No dose adjustment required • Generally not recommended in kidney impairment due to potential for fluid retention	Potential benefit	• Increased risk of HF and fluid retention. Do not use in the setting of HF. • Risk of bone fractures. • Bladder cancer: do not use in individuals with active bladder cancer, and use caution in those with prior history of bladder cancer.
Sulfonylureas (2nd generation) (oral)	High	Yes	Gain	Neutral	Neutral	Neutral	• Glyburide: generally not recommended in CKD • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	Unknown	• FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide); glimepiride shown to be CV safe (see text). • Use with caution in individuals at risk for hypoglycemia, particularly if in combination with insulin.
Insulin (human) (SQ; regular insulin also available as inhaled formulation) Insulin (analogs) (SQ)	High to very high	Yes	Gain	Neutral	Neutral	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	Unknown	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs • Risk of hypoglycemia and duration of activity increases with the severity of impaired kidney function. • Refer to device-specific instructions for insulins compatible with different delivery systems (i.e., pumps, connected insulin pens, insulin patches).

Table 5.5—Changes in medications during fasting

Medication name	Risk of hypoglycemia	Timing	Total daily dose
Metformin, SGLT2 inhibitor, DPP-4 inhibitor, GLP-1 receptor agonist, acarbose, or pioglitazone	Low	• If once daily, then take at main mealtime. • If twice daily, then split dose between the two meals. • If once weekly, no change of time.	• No change
New generation sulfonylurea (glimepiride and gliclazide)	Low to moderate	• If once daily, then take at main mealtime. • If twice daily, then split dose between the two meals.	• Reduce dose if glucose levels are within individualized goal range and if no hypoglycemia or hyperglycemia is present at baseline.
Older generation of sulfonylurea (glyburide)	Moderate to high	• Take at time of main meal	• Replace with newer-generation sulfonylurea or reduce dose by 50%.
Basal insulin	Moderate to high	• For longer-acting basal analogs (glargine 300 or degludec), no need to change timing. • For other basal insulins, take at beginning of breaking fast meal.	• Choose the insulin with lower risk of hypoglycemia among the class. • Reduce dose by 25–35% if not well managed.
Prandial insulin	High	• At mealtime	• Reduce dose of insulin for the meal followed by fasting (35–50%). • For other meals, insulin dose should match carbohydrate intake.
Mixed insulin and insulin coformulations	High	• If once daily, then take at main mealtime. • If twice daily, then split dose between the two meals	• Reduce dose of insulin for the meal followed by fasting (35–50%). • For other meals, no change of dose.

DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; SGLT2, sodium–glucose cotransporter 2.

Facilitating Positive Heath Behaviors and Well-being to Improve Health Outcomes:
Standards of Care in Diabetes - 2025. *Diabetes Care* 2025;48(Suppl. 1):S86-S127


ORHADI ANAAZ