PRINCIPLES OF THE AACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

1.	Lifestyle modification underlies all therapy.
2.	Maintain or achieve optimal weight.
3.	Choice of antihyperglycemic therapy reflects glycemic targets, ASCVD, CHF, CKD, overweight/obesity, and NAFLD.
4.	Choice of therapy includes ease of use and access.
5.	Optimal A1C is ≤6.5% or as close to normal as is safe and achievable for most patients.
6.	Individualize all glycemic targets (A1C, GMI, TIR, FBG, PPG).
7.	Get to goal as soon as possible (adjust ≤3 months).
8.	Avoid hypoglycemia.
9.	CGM is highly recommended to assist patients in reaching goals safely.
10.	Comorbidities must be managed for comprehensive care.

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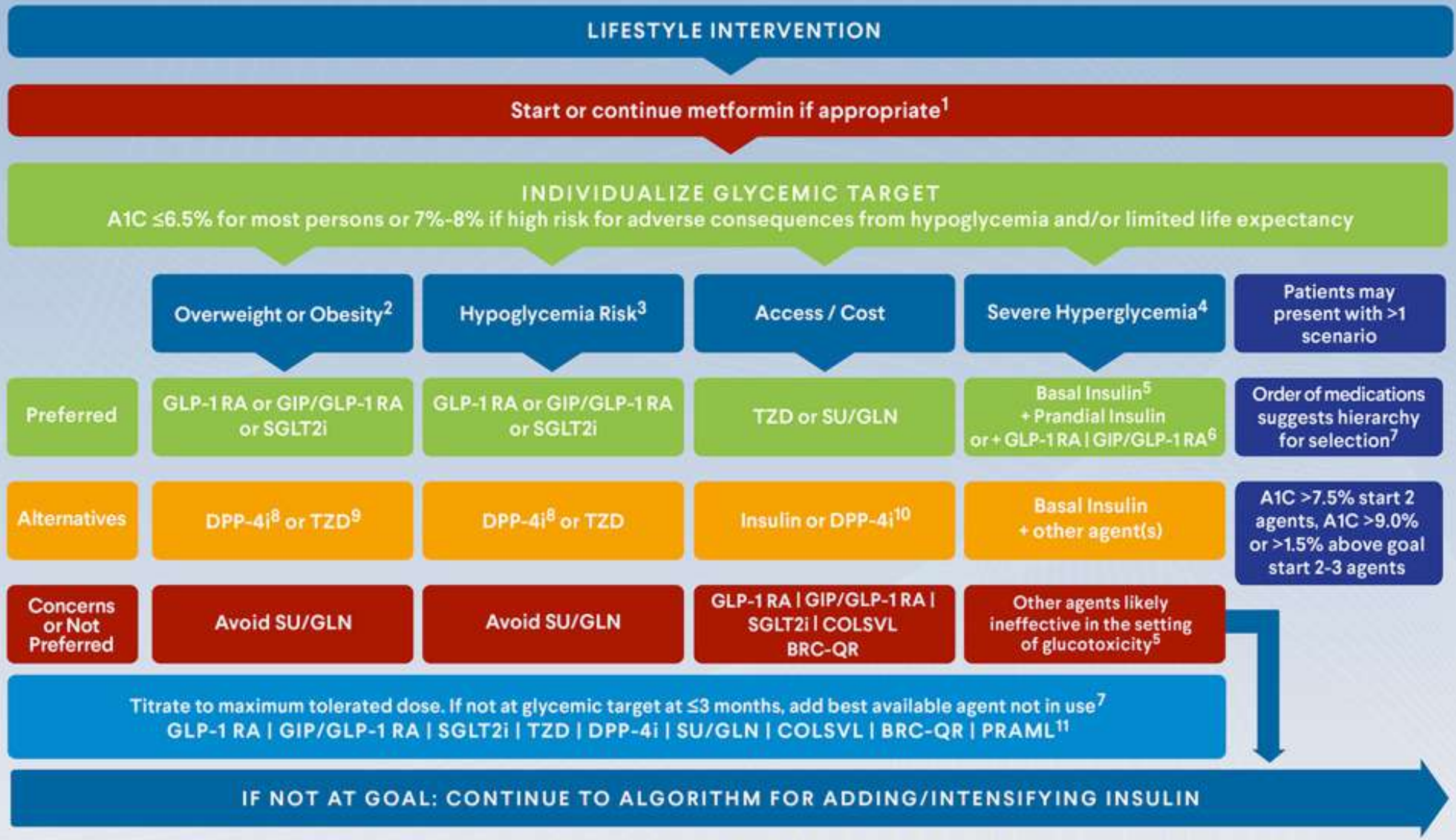
Algorithm Figure 1-Principles

GLUCOSE-CENTRIC ALGORITHM FOR GLYCEMIC CONTROL



[1]Take with food with dose titration for enhanced tolerance. [2]See also COMPLICATIONS-CENTRIC MODEL FOR THE CARE OF PERSONS WITH OVERWEIGHT/OBESITY and PROFILES OF WEIGHT-LOSS MEDICATIONS table. [3]Evaluate for issues leading to hypoglycemia or hypoglycemia unawareness and manage with patient-centered strategies. [4]If A1C >10% and/or BG ≥300 with symptomatic hyperglycemia, reduce glucose/A1C as promptly and safely as possible. [5]See also ALGORITHM FOR ADDING/INTENSIFYING INSULIN. [6]GLP-1 RA requires titration phase which can delay glycemic control. After glucose toxicity is resolved,consider adding other agents. [7]See also PROFILES OF ANTIHYPERGLYCEMIC MEDICATIONS table. [8]GLP-1 RA and DPP-4i should not be combined. [9]TZD can cause fluid retention but have benefit for NAFLD, CVD prevention, dyslipidemia. [10]Access/Cost are dependent on location of the market. Insulin costs vary widely with devices (e.g., pens versus vials) and formulations (e.g., analogues versus combinations such as 70/30). [11]PRAML is used as an adjunct with prandial insulin.

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Algorithm Figure 7-Glucose-Centric Glycemic Control

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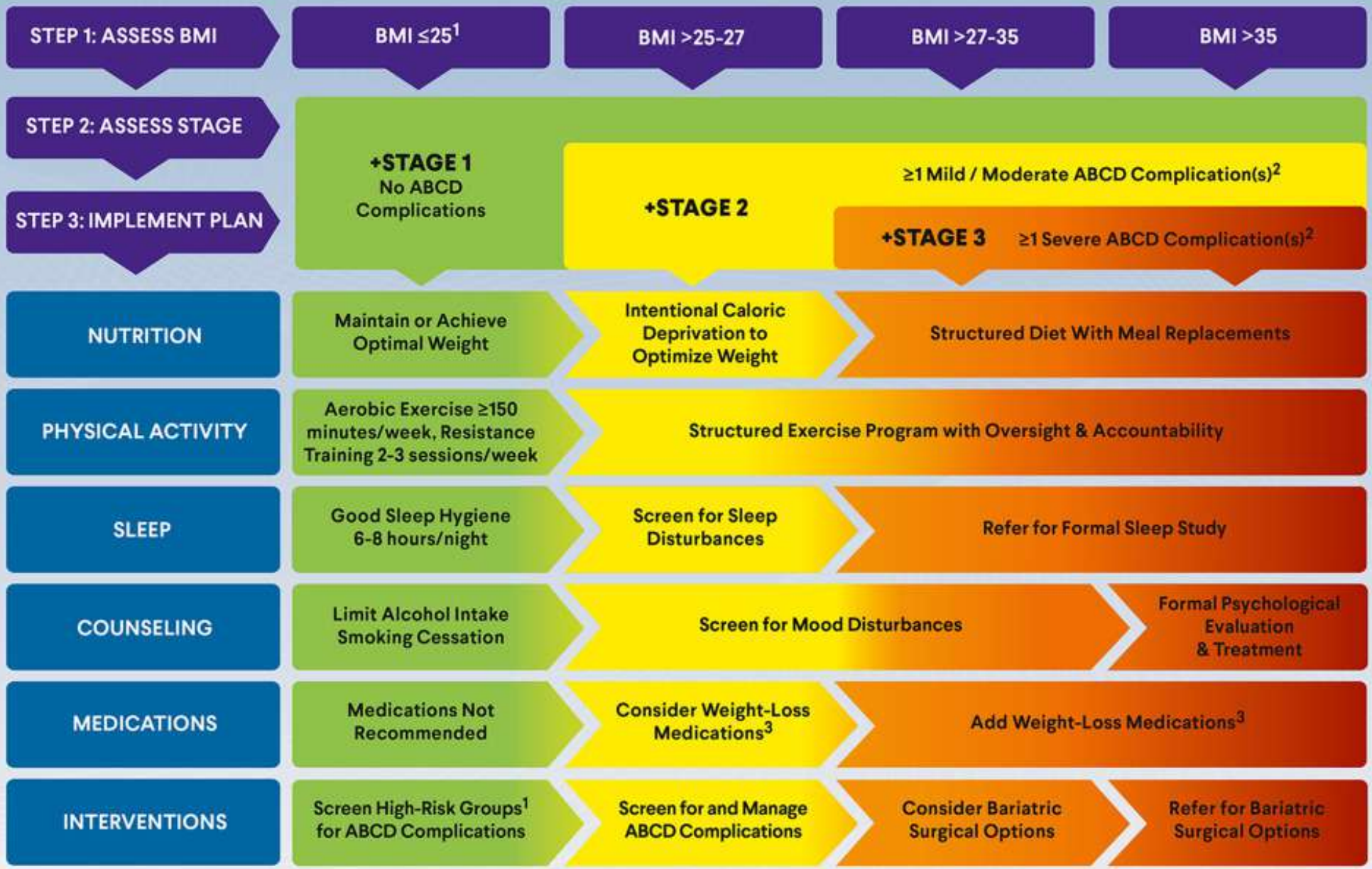
COMPLICATIONS-CENTRIC MODEL FOR THE CARE OF PERSONS WITH OVERWEIGHT/OBESITY (ADIPOSITY-BASED CHRONIC DISEASE)



[1]BMI 23 to 25 kg/m^2 may be considered overweight for South Asian, Southeast Asian, and East Asian adults; [2]ABCD complications can include prediabetes, dyslipidemia, hypertension, NAFLD/NASH, ASCVD, CHF and HFpEF, CKD, OSA, OA, asthma/reactive airways disease, GERD, urinary incontinence, PCOS, hypogonadism, and reduced fertility. [3]See PROFILES OF WEIGHT-LOSS MEDICATIONS table.

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Algorithm Figure 2-ABCD

PROFILES OF ANTIHYPERGLYCEMIC MEDICATIONS

	MET	GLP-1 RA	DUAL GIP/ GLP-1 RA	SGLT2i	TZD	INSULIN (basal & basal bolus)	DPP-4i	SU	GLN	AGi	COLSVL	BRC	PRAML
EFFICACY FOR GLUCOSE LOWERING	++	+++	+++	++	++	+++/++++	+	++	+	+	+	+	+
ASCVD MACE	Neutral	Benefit[1,3]	Safe	Benefit[2]	Neutral[3]	Neutral	Neutral	Possible Increased Risk	Neutral	Insufficient Evidence	Neutral[3]	Safe	Insufficient Evidence
ASCVD CHF		Unclear		Reduced Risk	Moderate to Severe[4]	Moderate	Moderate[4]						
ASCVD STROKE		Benefit[5]		Possible Benefit[2]	Benefit	Neutral	Neutral						
CKD	CKD3a/3b[6]	Benefit[7]	Insufficient Evidence	Benefit	Neutral	Increased hypoglycemia risk with impaired renal function	Neutral	Increased hypoglycemia risk with impaired renal function		Not recommended SCR >2 mg/dL or CrCl <25	Neutral	Neutral	Neutral
RENAL ADJUSTMENT	Not with CKD4 eGFR <30[8]	Exenatide not recommended eGFR <45		Check medication-specific eGFR thresholds[8]			Adjust Dose[9]						
HYPOGLYCEMIA RISK[14]	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate to Severe	Neutral	Moderate to Severe	Mild	Neutral	Neutral	Neutral	Neutral
WEIGHT	Slight loss	Loss	Loss	Loss	Gain[4]	Gain	Neutral	Gain	Neutral	Neutral	Neutral	Neutral	Loss
NAFLD	Neutral	Benefit	Benefit	Potential Benefit	Benefit	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Benefit
GI ADVERSE SYMPTOMS	Mild to Moderate	Moderate[10]	Moderate[10]	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate	Mild	Moderate	Moderate
OTHER CONSIDERATIONS		Medullary Thyroid Carcinoma/ MEN2	Medullary Thyroid Carcinoma/ MEN2	GU infections DKA[11] Fracture Risk[12]	Fracture Risk		Rare Arthralgias/ Myalgias						
ACCESS/COST	$	$$$	$$$	$$$	$	$ - $$$[13]	$-$$	$	$-$$	$-$$	$$$	$$$	$$$

■ Possible benefits ■ Use with caution ■ Likelihood of adverse events ■ Neutral, not studied, insufficient evidence

[1]GLP-1 RA MACE benefits with liraglutide, semaglutide, dulaglutide. [2]SGLT2i MACE benefits with empagliflozin, canagliflozin. Possible benefit for hemorrhagic stroke. [3]GLP-1 RA, TZD, COLSVL can lower LDL. [4]TZDs increase fluid retention and edema and are contraindicated in persons with NYHA Class III/IV CHF. There is Increased risk of hospitalization for CHF with saxagliptin, and limited experience for persons with NYHA Class II/IV CHF with alogliptin [5]GLP-1 RA stroke benefits observed with semaglutide and dulaglutide. [6]CKD3a no adjustment with monitoring, CKD3b decrease dose and do not initiate, CKD4 contraindicated. Hold for acute kidney injury, IV contrast. [7]Dulaglutide, semaglutide decrease CKD progression. [8]The eGFR thresholds for initiation and/or continuation of therapy in CKD vary among SGLT2i. Check medication-specific eGFR levels. [9]Only linagliptin does not require adjustment. [10]Slow titration, portion control, and consider reducing to prior tolerated dose. [11]Precipitants include significant current illness, surgery, inappropriate or rapid insulin dose reduction. [12]Reported with canagliflozin, dapagliflozin. [13]Cost varies widely with devices (e.g., pens), formulations (e.g., analogues), and combinations (e.g., 70/30). [14]SIngle-agent risks of hypoglycemia may be low but increases when combined with other agents.

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Algorithm Figure 9-Antihyperglycemic Medications

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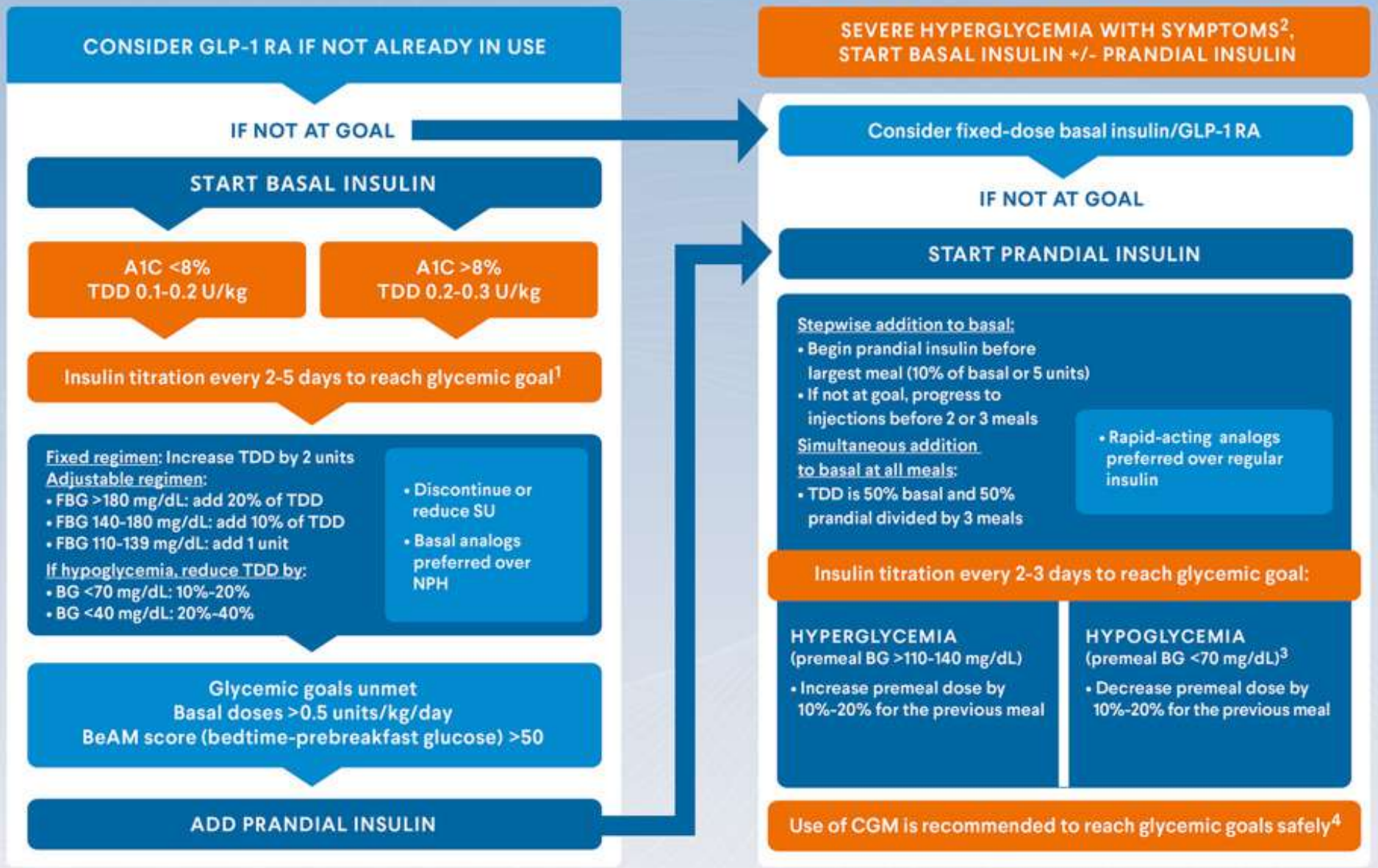
ALGORITHM FOR ADDING/INTENSIFYING INSULIN



[1]Glycemic goals: A1C ≤6.5%-7% without hypoglycemia, fasting and premeal glucose <110 mg/dL, A1C should be individualized in people with comorbidities and at high adverse consequences of hypoglycemia and/or limited life expectancy. Longer-acting basal insulins (e.g., glargine U300, degludec U100 or U200) require slower titration ≥3 days because of a longer time to steady state. [2]For symptomatic hyperglycemia with A1C >10% and/or BG ≥300 mg/dL, reduce glucose/A1C as promptly and safely as possible. Consider testing for autoimmune diabetes. GLP-1 RA requires titration phase which can delay glycemic control. [3]Oral administration of rapidly absorbed source of glucose (tablet, fruit juice) if person can safely swallow. If unresponsive or unable to swallow, subcutaneous/intramuscular/intranasal glucagon or glucagon analogue can be given by a trained member of the household. [4]See also American Association of Clinical Endocrinology Clinical Practice Guideline: The Use of Advanced Technology in the Management of Persons with Diabetes Mellitus.

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Algorithm Figure 8-Adding/Intensifying Insulin

PROFILES OF WEIGHT-LOSS MEDICATIONS

	SEMAGLUTIDE	LIRAGLUTIDE	PHENTERMINE/ TOPIRAMATE-ER	NALTREXONE-ER/ BUPROPRION-ER	ORLISTAT	PHENTERMINE[1]
CLASS	GLP-1 RA	GLP-1 RA	Sympathomimetic Amine/Gabaminergic	Opioid-Receptor Antagonist/DA-Norepi Reuptake inhibitor	GI Lipase Inhibitor	Sympathomimetic
WEIGHT LOSS[2]	15%-18%	5%-6%	9%-10%	4%-6%	4%	3%[2]
MECHANISM	Decreased Appetite Delayed Gastric Emptying	Decreased Appetite Delayed Gastric Emptying	Decreased Appetite Increased Satiety	Decreased Cravings Decreased Appetite	Decreased Fat Absorption	Decreased Appetite
DELIVERY	Weekly Subcutaneous Injection	Daily Subcutaneous Injection	Oral	Oral	Oral	Oral
STARTING DOSE	0.25 mg/week	0.6 mg/day	3.75 mg/23 mg daily	8 mg/90 mg daily	120 mg three times daily	15 mg daily
TREATMENT DOSE	2.4 mg/week	3 mg/day	7.5 mg/46 mg daily (maximum 15 mg/92 mg daily)	16 mg/180 mg twice per day	120 mg three times daily	37.5 mg daily[1]
POTENTIAL SIDE EFFECTS	Nausea/Vomiting Diarrhea Constipation Headache Fatigue	Nausea/Vomiting Diarrhea Constipation Headache Fatigue	Restlessness Insomnia Headache Dry Mouth Blurred Vision Tachycardia/BP Elevation Paresthesia Dysgeusia Mental Clouding/Mood Changes	Nausea/Vomiting Diarrhea Constipation Headache Fatigue Insomnia Dry Mouth Blurred Vision Agitation/Mood Changes	Flatulence Fecal Urgency Oily Stools Fat-Soluble Vitamin Drug Malabsorption	Restlessness Insomnia Headache Dry Mouth Tachycardia/BP Elevation
CAUTIONS AND CONTRAINDICATIONS[3]	MTC/MEN2 Tachycardia Pancreatitis/ Gallbladder Disease Diabetic Retinopathy	MTC/MEN2 Tachycardia Pancreatitis/ Gallbladder Disease	Glaucoma Hyperthyroidism Urolithiasis Metabolic Acidosis	Seizure Risk Uncontrolled Hypertension Chronic Opioid Use	Organ Transplant Urolithiasis (Oxalate) Cholestasis	Active CAD Uncontrolled Hypertension Hyperthyroidism Agitated States
ACCESS/COST	$$$	$$$	$$	$$	$$	$

[1]Approved for short term ≤3 months. 15 mg / 30 mg / 37.5 mg phentermine hydrochloride = 12 mg / 24 mg / 30 mg phentermine resin.
[2]Approximate placebo-subtracted with 1 year of therapy except phentermine (12 weeks). [3]All agents are contraindicated in pregnancy/breastfeeding.

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Algorithm Figure 10-Weight-Loss Medications

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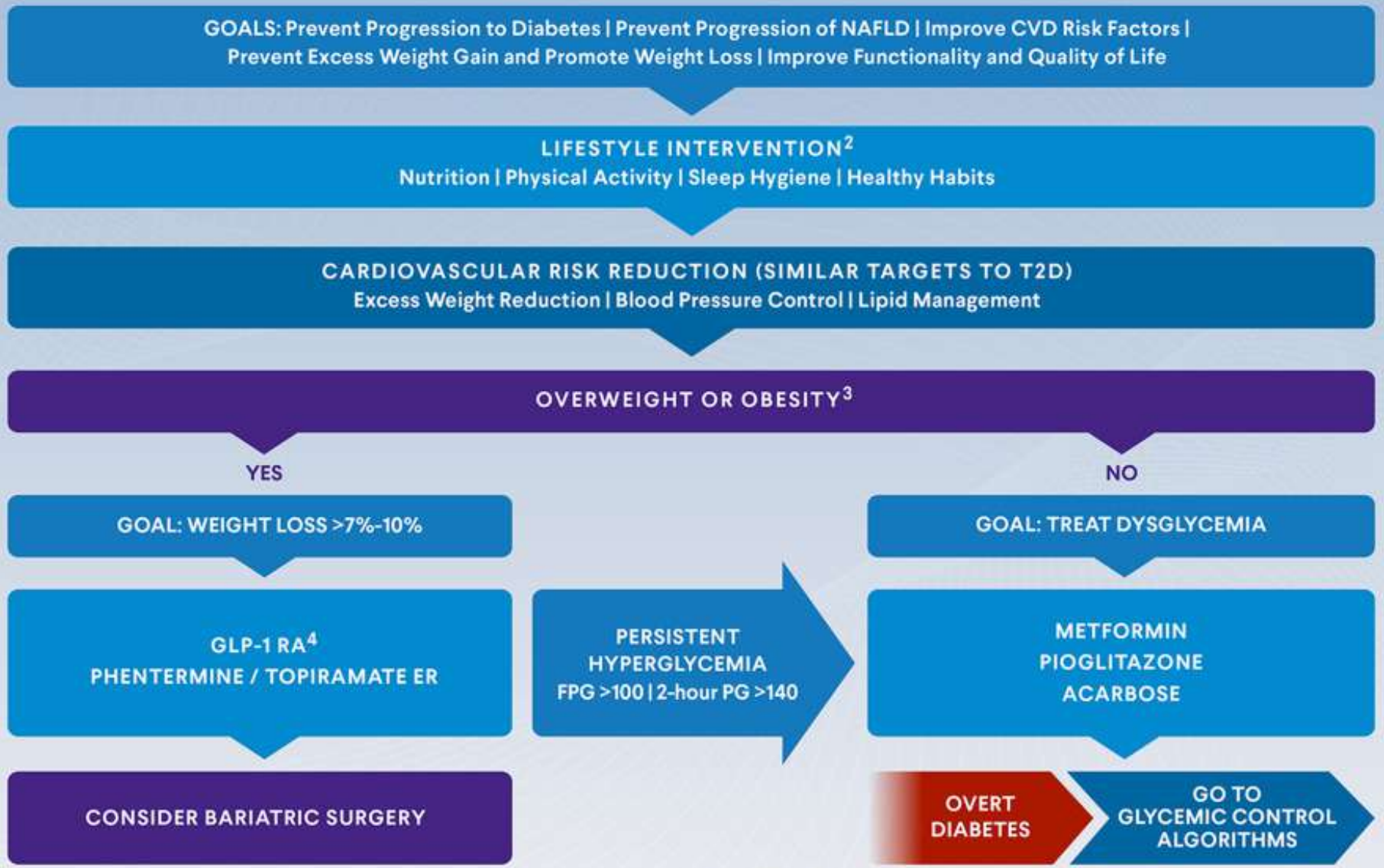
PREDIABETES ALGORITHM

IFG (100-125 mg/dL) | IGT (140-199 mg/dL) | A1C (5.7%-6.4%) | METABOLIC SYNDROME[1]



[1]NCEP ATP III Criteria. [2]See COMPLICATIONS-CENTRIC MODEL FOR THE CARE OF PERSONS WITH OVERWEIGHT/OBESITY. [3]If no overweight or obesity, consider T1D antibody testing for LADA. [4]Indications for weight-loss medications are obesity or overweight BMI >27 kg/m^2 with ABCD complication(s) including prediabetes. Choose GLP-1 RA for approved for weight loss. Also consider other approved weight-loss medications (phentermine [short term], orlistat, naltrexone-ER/bupropion-ER). See also PROFILES OF WEIGHT-LOSS MEDICATIONS table.

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Algorithm Figure 3-Prediabetes

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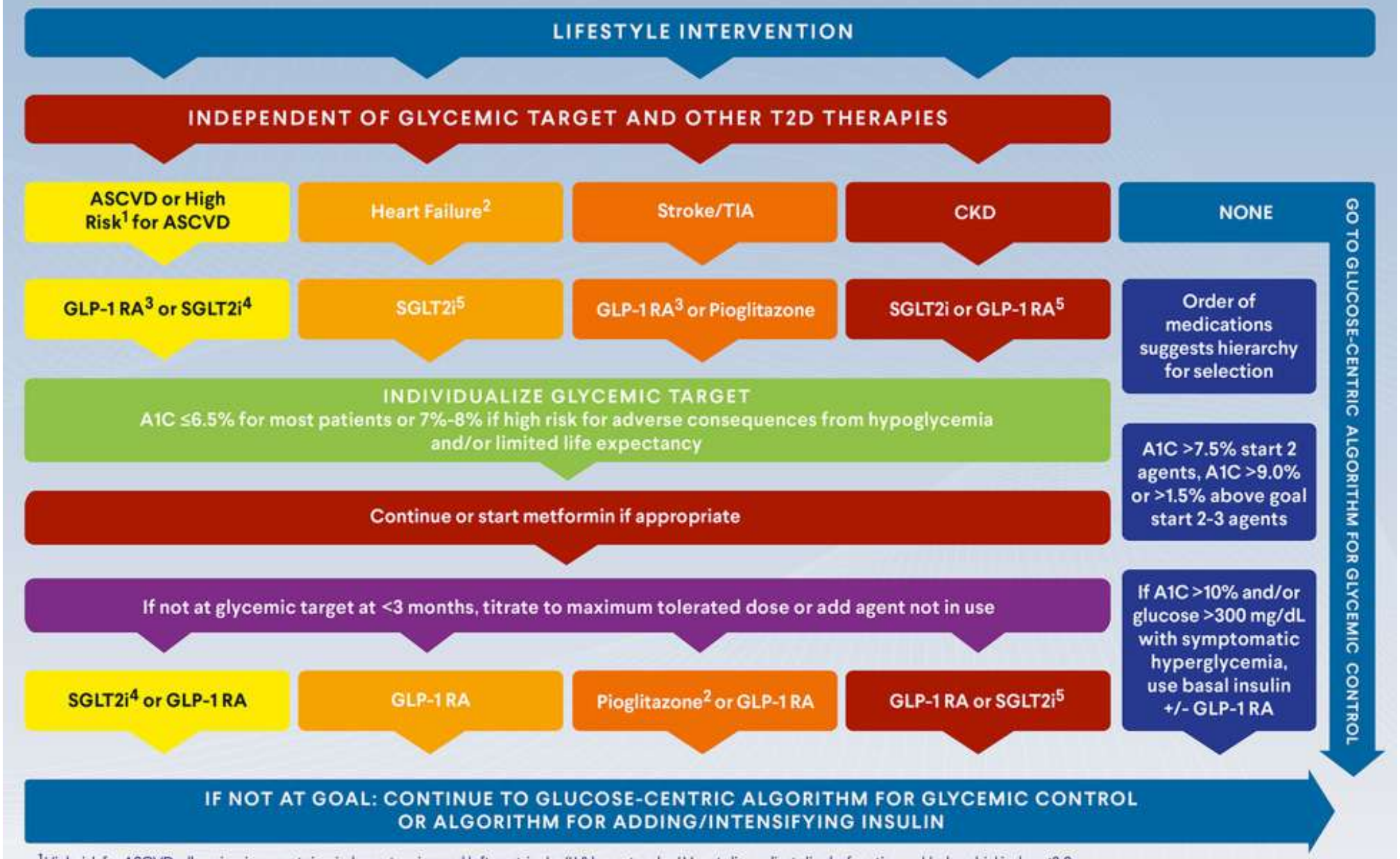
COMPLICATIONS-CENTRIC ALGORITHM FOR GLYCEMIC CONTROL



[1]High risk for ASCVD: albuminuria or proteinuria, hypertension and left ventricular (LV) hypertrophy, LV systolic or diastolic dysfunction, ankle-brachial index <0.9.
[2]TZDs are contraindicated in NYHA Class III/IV HF. [3]ASCVD: liraglutide/semaglutide/dulaglutide or Stroke: semaglutide/dulaglutide.
[4]canagliflozin/empagliflozin. [5]Use SGLT2i or GLP-1 RA with proven benefit.

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Algorithm Figure 6-Complications-Centric Glycemic Control

ASCVD RISK REDUCTION ALGORITHM: DYSLIPIDEMIA

ASSESS LIPID PANEL (LDL-C, HDL-C, Non-HDL-C, TG, Apo B)[1]

LIFESTYLE INTERVENTION: increase ↑ dietary fiber | ↑ healthy fat | ↓ saturated fat | ↓ simple carbs | ↓ added sugars | ↑ physical activity | weight management

PREDIABETES OR T2D + RISK FACTORS: USE ASCVD 10-YEAR RISK CALCULATOR
Major ASCVD Risk Factors: Age >40 | HTN | CKD >3a | Smoking | Family History of Premature ASCVD | Low HDL-C | High Non-HDL-C

INITIATE STATIN THERAPY

		HIGH RISK <10% T2D <10 years <2 other risk factors No target organ damage	VERY HIGH RISK 10%-20% T2D >10 years Age >40 years No ASCVD No target organ damage ≥2 additional risk factors	EXTREME RISK >20% T2D & ASCVD Severe target organ damage: eGFR <45 mL/min/1.73 m^2, UACR >300, ABI <0.9, LV systolic/diastolic dysfunction
		Moderate-intensity statin	High-intensity statin	
GOAL	LDL-C (mg/dL) <100		<70	<55
	Non-HDL-C (mg/dL) <130		<100	<80
	TG (mg/dL) <150		<150	<150
	Apo B (mg/dL) <90		<80	<70

Monitor and titrate therapy every 3-6 months to achieve lipid targets according to risk[2]

Intensify statin and lifestyle & optimize glycemic control

Add ezetimibe

Consider additional therapy: bile acid sequestrant, bempedoic acid, PCSK9 inhibitor, inclisiran

HYPERTRIGLYCERIDEMIA MANAGEMENT:

TG 135-199 | TG 200-499[3] | TG ≥500 | TG >1000[4]

Intensify Lifestyle & Achieve Glycemic Targets

If TG >135: Consider addition of icosapent ethyl to statin if DM and CVD or ≥2 risk factors

Fibrate or/and Rx Grade Omega-3

TG target achieved: Continue lifestyle therapy, maximally tolerated statin and achieve glucose targets

+Niacin[5]

[1] Baseline LDL-C >190 mg/dL, consider familial hypercholesterolemia. [2] Statin intolerance: Use alternative statin with lower incidence of myopathy (pitavastatin, extended-release fluvastatin) or decrease dose/frequency, use non-statin Rx, check for Rx interactions, consider CoQ10. [3] If TG >200 and HDL <40, add fibrate/omega-2 to achieve apo B and non-HDL goals. [4] Elevated triglycerides >500 mg/dL to >1000 mg/dL can cause acute pancreatitis. Urgent intervention with dietary management and fibrate/omega 3 therapy is needed. Suspect familial chylomicronemia syndrome or lipodystrophy, refer to lipid specialist. [5] For severe hypertriglyceridemia >1000 refractory to previous interventions, consider niacin to reduce the risk of pancreatitis. Niacin may lower TG and Lp(a) but does not reduce ASCVD and can promote hyperglycemia.

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Algorithm Figure 4-Dyslipidemia

ASCVD RISK REDUCTION ALGORITHM: HYPERTENSION

GOAL: <130 SYSTOLIC/<80 DIASTOLIC mmHg[1]

<120 Systolic/<70 Diastolic mmHg considered for Micro/Macroalbuminuria | Moderate-to-High Risk or Established ASCVD | PVD | Retinopathy
Goal BP may be higher for Autonomic Neuropathy | Orthostatic Hypotension | Acute Coronary Syndrome | Frailty | Medication Intolerance

LIFESTYLE INTERVENTION:

Decrease Sodium Intake | Diet (DASH, Mediterranean) | Physical Activity | Achieve Optimal Weight

ARB OR ACEi[2]

For initial blood pressure >150/100 mmHg, consider starting DUAL THERAPY combined with another agent below

TITRATE MEDICATION DOSE OR ADD ON THERAPY EVERY 2-3 MONTHS TO REACH GOAL

THIAZIDE[3] | CALCIUM CHANNEL BLOCKER[4]

COMBINED α-β BLOCKER[5] | β1 SELECTIVE BLOCKER[6] | MINERALOCORTICOID RA[7]

ADDITIONAL ANTIHYPERTENSIVE AGENTS[8]: CENTRAL α2 AGONIST | PERIPHERAL α1-BLOCKER | HYDRALAZINE

[1]Consider patient-specific characteristics DKD, retinopathy, ASCVD, post-MI, CHF, age, and race. [2]ACEi and ARB reduce progression of DKD. Use as first line for UACR >30 mg/g. Thiazide or CCB may also be appropriate as first line in absence of albuminuria. ACEi and ARB should not be used concomitantly. Rule out pregnancy. [3]Chlorthalidone, indapamide, hydrochlorothiazide. [4]Non-dihydropyridine amlodipine or nifedipine unless indication for dihydropyridine. [5]Carvedilol, labetalol, dilevalol. [6]Nebivolol, betaxolol. [7]Resistant hypertension with >140/90 mmHg if on ≥3 agents including maximum dose diuretic; laboratory evaluation for hyperaldosteronism is indicated. Increase laboratory monitoring for combination of ACEi or ARB with MRA due to risk of hyperkalemia or AKI. Finerenone is recommended for persons with CKD associated with diabetes and eGFR ≥25 mL/min/1.73m^2 and UACR ≥30 mg/g. [8]Initiation of SGLT2i or GLP-1 RA also may mildly lower BP.

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Algorithm Figure 5-Hypertension

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VACCINE RECOMMENDATIONS FOR PERSONS WITH DIABETES MELLITUS

CDC IMMUNIZATION RECOMMENDATIONS FOR PERSONS WITH DIABETES MELLITUS[1]

VACCINE	RECOMMENDATION
Age-appropriate vaccines	All persons should receive according to the CDC/ACIP immunization schedules.
COVID-19	Primary series and booster per current CDC recommendations and FDA approvals
Flu	Annually
HepB	All adults ≤59 years Based on risk and quality of immune response for adults ≥60 years
PCV	Adults with DM ages ≥19 years 1 dose PCV15 followed by PPSV23 at ≥1 year (or ≥8 weeks for adults who are immunocompromised) OR 1 dose PCV20 See also current CDC recommendations for details.
RZV	All adults ≥50 years
Tdap	Every 10 years following completion of the primary series

ACIP = Advisory Committee on Immunization Practices; **CDC** = Centers for Disease Control and Prevention; **COVID-19** = coronavirus disease 2019; **DM** = diabetes mellitus; **FDA** = Food and Drug Administration; **HepB** = hepatitis B; **PCV** = pneumococcal conjugate vaccine; **PPSV23** = pneumococcal polysaccharide vaccine; **RZV** = recombinant zoster vaccine; **TDAP** = tetanus, diphtheria, acellular pertussis

[1]https://www.cdc.gov/vaccines/schedules/index.html

For child/adolescent specific recommendations, see https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html

CDC STANDARDS FOR ADULT IMMUNIZATION PRACTICE

ASSESS	Assess immunization status of all individuals at every encounter. • Incorporate into workflow. • Stay up to date on the latest recommendations of the CDC Advisory Committee on Immunization Practices. Updated immunization schedules are released annually.
RECOMMEND	**STRONGLY** recommend vaccines based on age/risk factors. • Address questions and concerns. • Highlight positive experiences and benefits of vaccines.
ADMINISTER/ REFER	Administer or refer patients for immunization. • Stock routine vaccines or know your local vaccine providers for referral.
DOCUMENT	Document receipt of vaccine in state immunization registry and electronic health record. https://www.cdc.gov/vaccines/hcp/adults/for-practice/standards/index.html

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Algorithm Figure 11-Vaccine Recommendations for Persons with DM

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