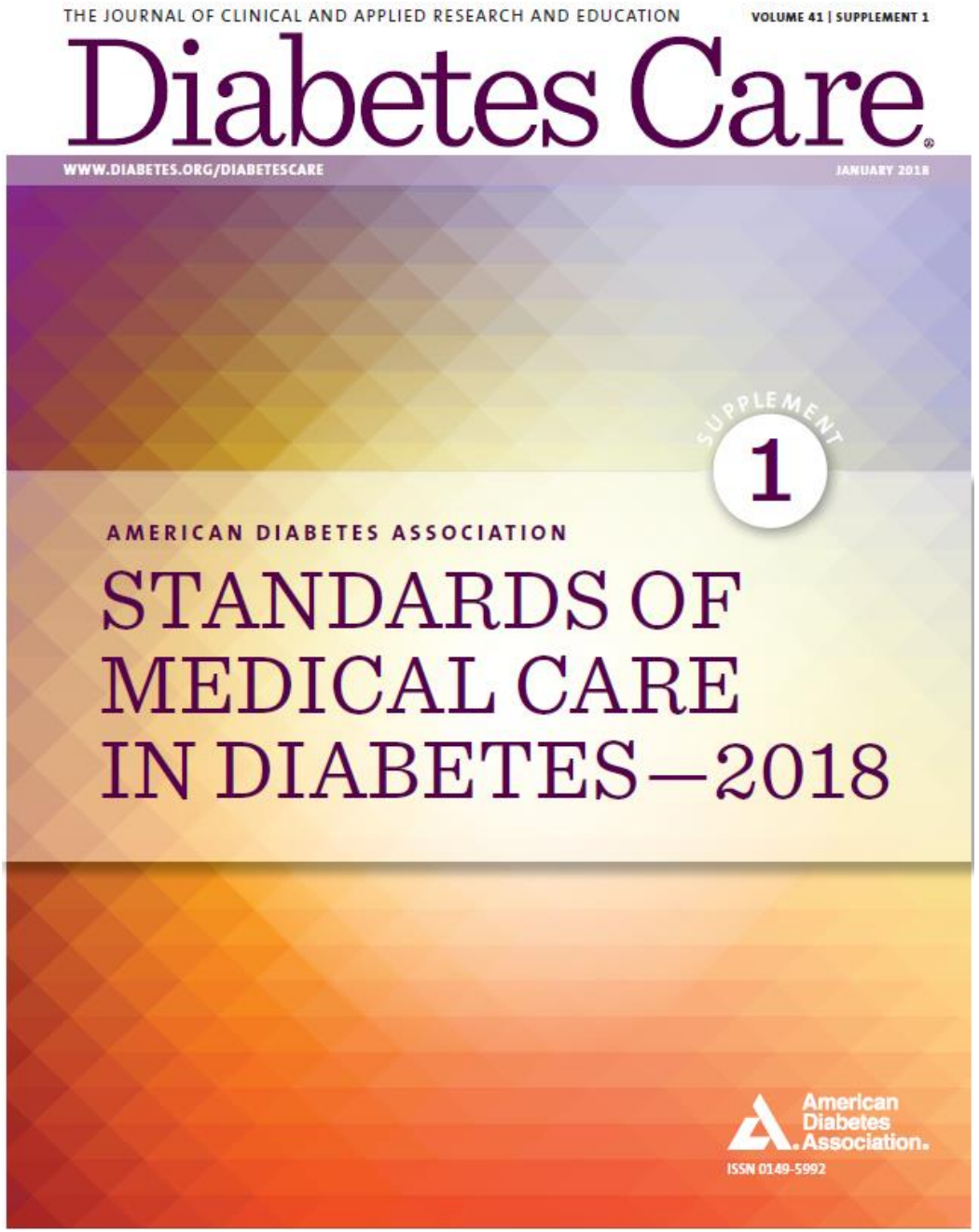


Standards of Medical Care in Diabetes - 2018

Management of Hyperglycemia in Type 2 Diabetes, 2018.

Report by the
American Diabetes Association
(ADA) and the European Association
for the Study of Diabetes (EASD),

published online October 4, 2018

- Despite over 200 years of research on lifestyle management of diabetes and more than 50 years of comparative effectiveness research in diabetes, in numerable un anaswerecd questions regarding the management of type 2 diabetes remain

- The 2012 and 2015 editions accepted as a starting point.

- PubMed search for randomized clinical trials (RCTs), systematic reviews, and meta-analyses:
- Published in English between 1 January 2014 and 28 February 2018.

Lifestyle interventions, including MNT and physical activity:

Effective and safe

for improving glucose control in type 2 diabetes

Low-carbohydrate diets (26% of total energy)
produce
substantial reductions in HbA1c at 3months and 6months .

The most effective

nonsurgical strategies for weight reduction

food substitution and intensive, sustained counseling

(e.g., 12–26 individual counseling sessions over 6–12 months).

Among adults with type 2 diabetes,

meal replacement

(825–853 kcal/day formula diet for 3–5 months)

resulted in 9-kg placebo-adjusted weight loss at 1 year

and high rates of diabetes remission compared with best usual practice .

Physical Activity

Aerobic exercise, resistance training, and the combination of

the two are effective in reducing HbA1c by about 0.6%.

Special considerations are required for individuals with

CVD, uncontrolled retinopathy or nephropathy, and severe neuropathy.

In general,

supervision of exercise and motivational strategies,

such as monitoring using a step counter, can improve the effect of exercise on HbA1c compared with advice alone .

Immunization: Recommendations

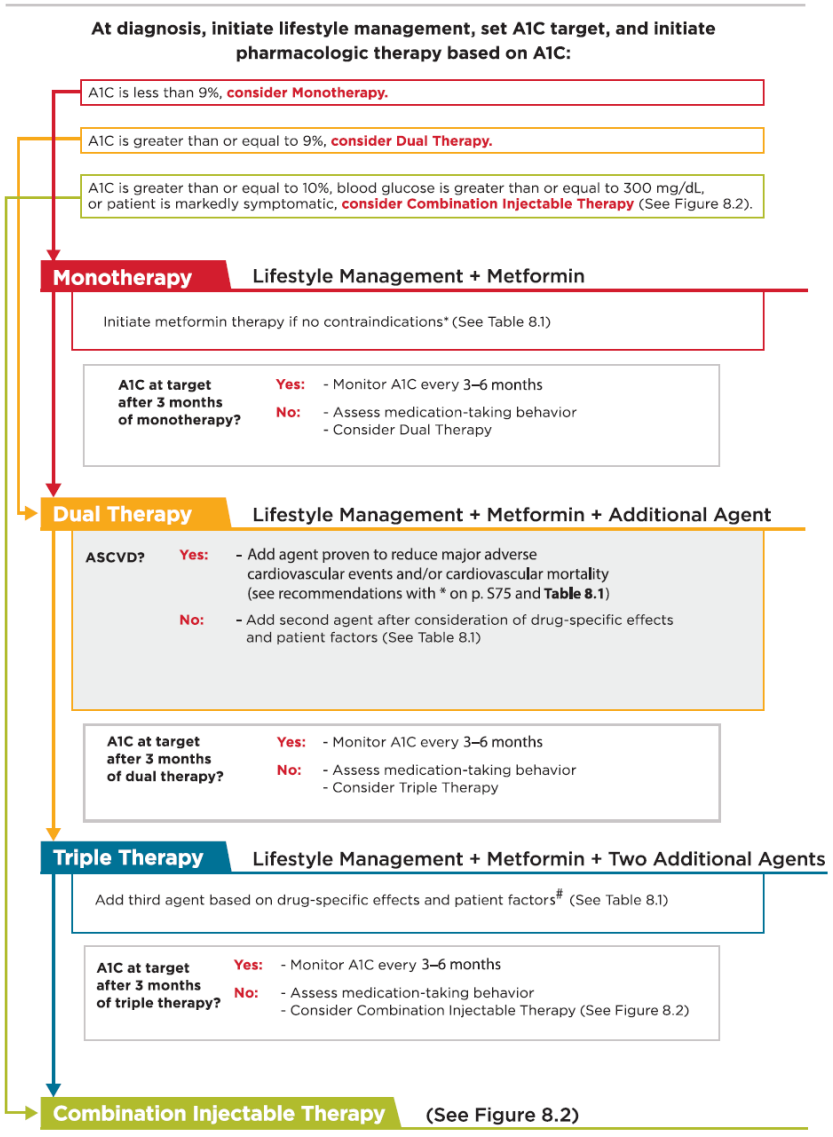
- Provide routinely recommended vaccinations for children and adults with diabetes by age. C
- Annual vaccination against influenza is recommended for all people ≥6 months of age, including those with diabetes. C
- Administer 3-dose series of hepatitis B vaccine to unvaccinated adults with diabetes aged 19-59 years. C

Immunization: Recommendations (2)

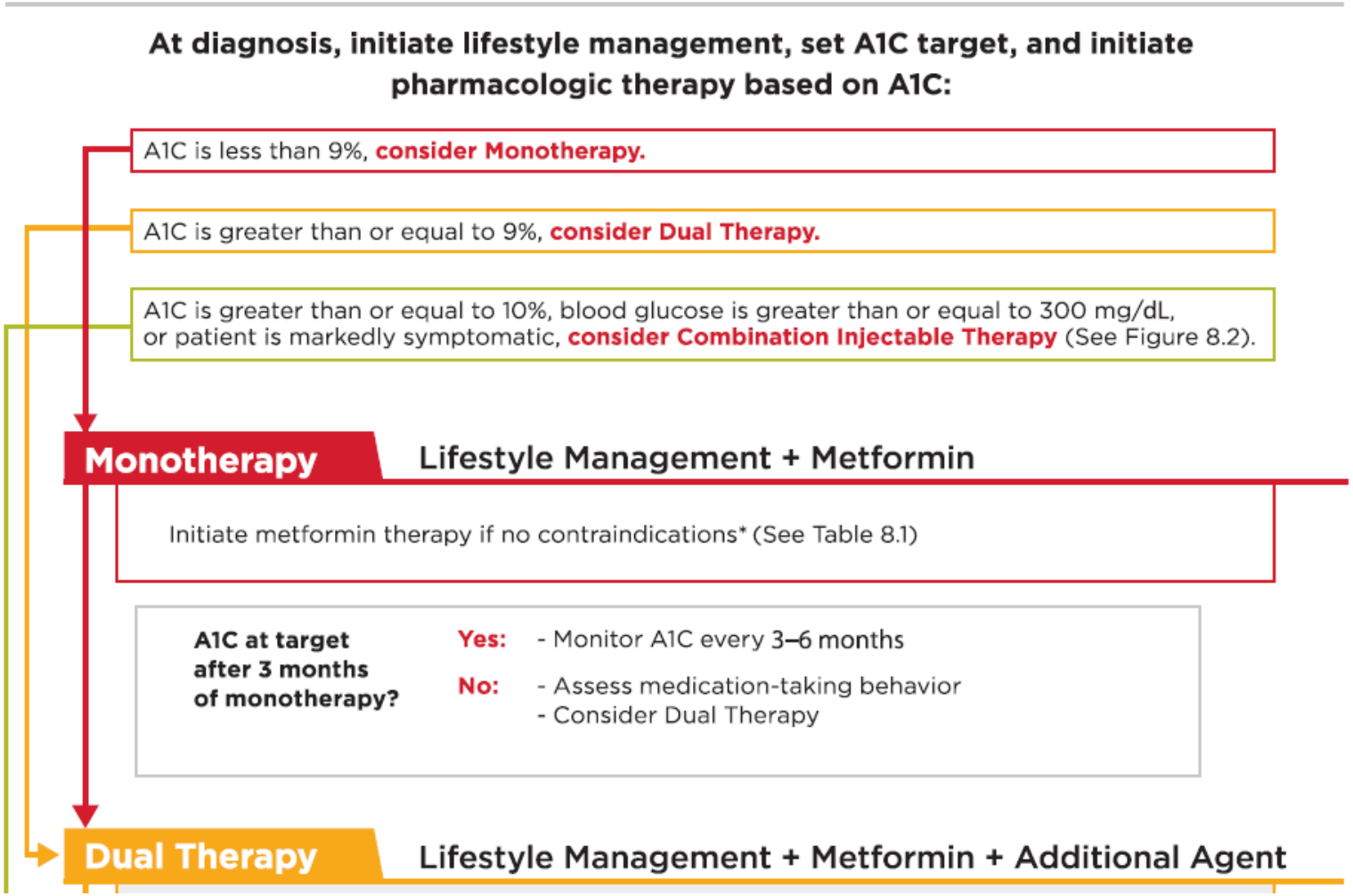
- Vaccination against pneumococcal disease, including pneumococcal pneumonia, with 13-valent pneumococcal conjugate vaccine (PCV13) is recommended for children before age 2 years.
- People with diabetes ages 2-64 years should also receive 23-valent pneumococcal polysaccharide vaccine (PPSV23).
- Ag age ≥65 years, regardless of vaccination history, additional PPSV23 vaccination is necessary. C

Medications for Lowering Glucose

Antihyperglycemic Therapy in Adults with T2DM



Antihyperglycemic Therapy in Adults with T2DM



Antihyperglycemic Therapy in Adults with T2DM

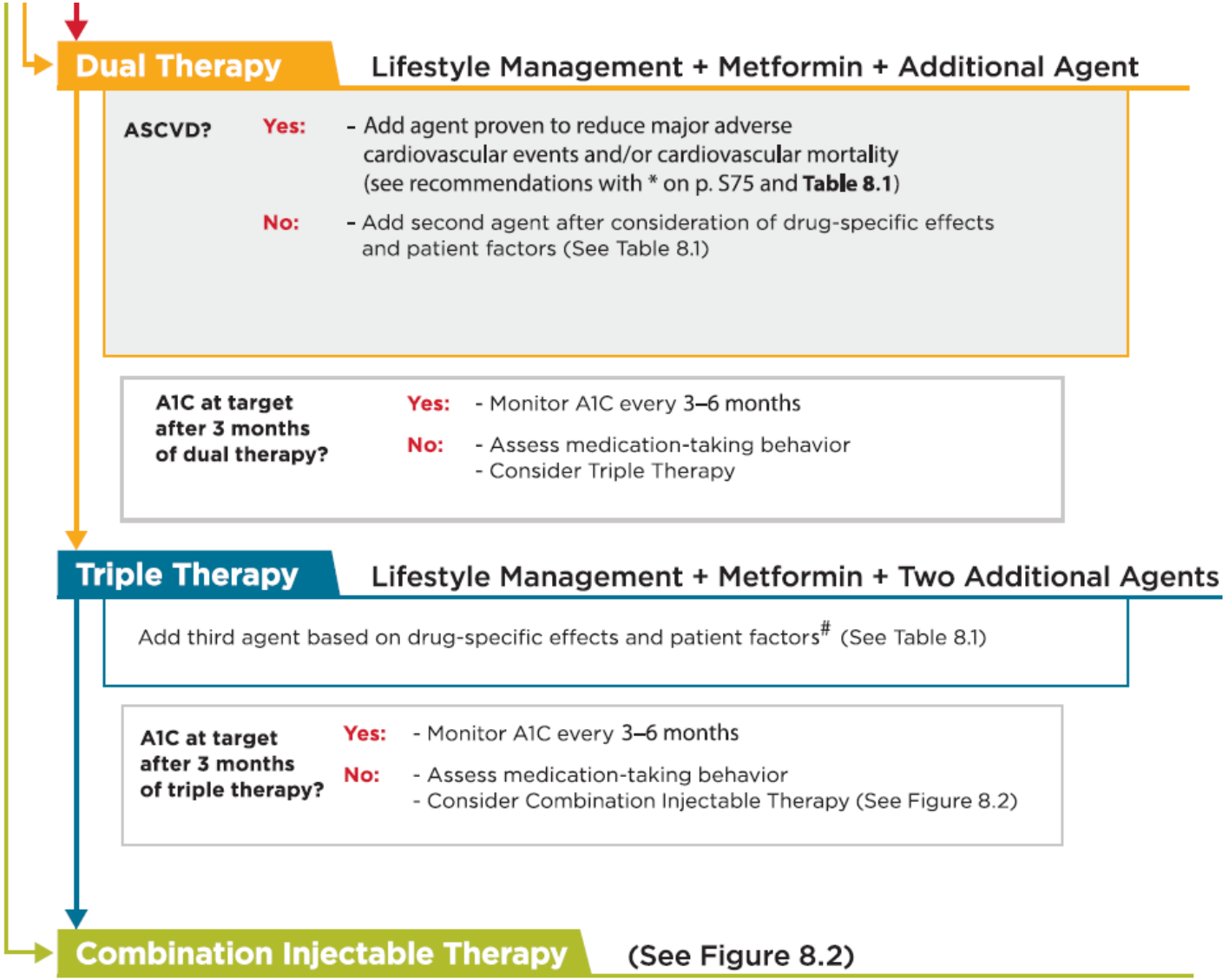
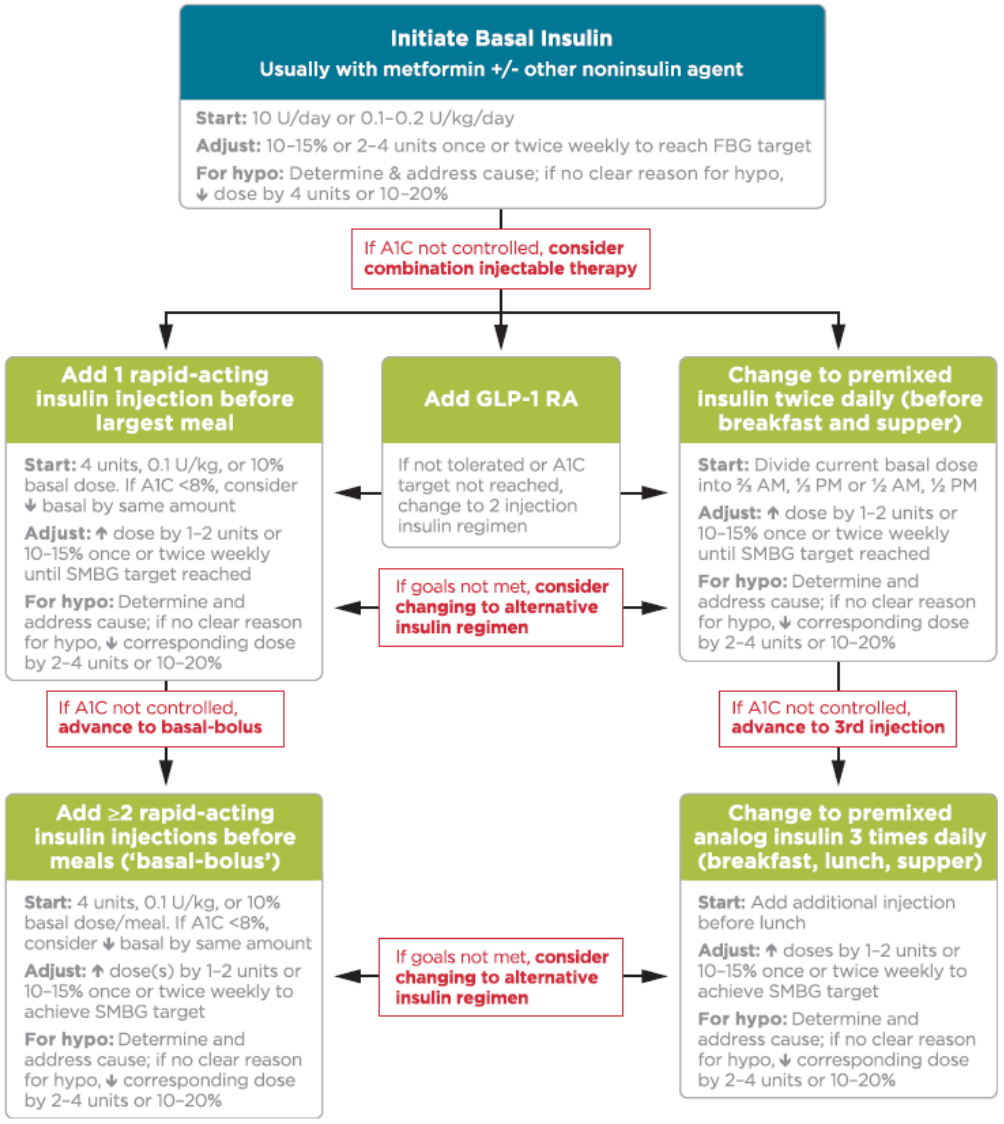


Table 8.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

		Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
					ASCVD	CHF			Progression of DKD	Dosing/Use considerations	
Metformin		High	No	Neutral (Potential for Modest Loss)	Potential Benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 Inhibitors		Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	▪ Canagliflozin: not recommended with eGFR <45 ▪ Dapagliflozin: not recommended with eGFR <60; contraindicated with eGFR <30 ▪ Empagliflozin: contraindicated with eGFR <30	▪ **FDA Black Box:** Risk of amputation (**canagliflozin**) ▪ Risk of bone fractures (canagliflozin) ▪ DKA risk (all agents, rare in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol
GLP-1 RAs		High	No	Loss	Neutral: lixisenatide, exenatide extended release Benefit: liraglutide†	Neutral	High	SQ	Benefit: liraglutide	▪ Exenatide: not indicated with eGFR <30 ▪ Lixisenatide: caution with eGFR <30 ▪ Increased risk of side effects in patients with renal impairment	▪ **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) ▪ Gastrointestinal side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ ?Acute pancreatitis risk
DPP-4 Inhibitors		Intermediate	No	Neutral	Neutral	Potential Risk: saxagliptin, alogliptin	High	Oral	Neutral	▪ Renal dose adjustment required; can be used in renal impairment	▪ Potential risk of acute pancreatitis ▪ Joint pain
Thiazolidinediones		High	No	Gain	Potential Benefit: pioglitazone	Increased Risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure (**pioglitazone, rosiglitazone**) ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd Generation)		High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide & glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin	**Human Insulin**	Highest	Yes	Gain	Neutral	Neutral	Low	SQ	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
	Analogs						High	SQ			

*See ref. 31 for description of efficacy. †FDA approved for CVD benefit. CVD, cardiovascular disease; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; NASH, nonalcoholic steatohepatitis; RAs, receptor agonists; SQ, subcutaneous; T2DM, type 2 diabetes.

Combination Injectable Therapy in T2DM



Pharmacologic Interventions for Prevention: Recommendations

- Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI ≥35 kg/m^2, those aged <60 years, and women with prior GDM. A

Metformin

Dosages of

immediate release metformin

start at 500 mg once or twice a day with meals

and

should be increased as tolerated to a target dosage of 1,000 mg twice a day.

- The doses above 2,000 mg are generally associated with little additional efficacy and poorer tolerability.

- Gastrointestinal symptoms are common and dose dependent, and may improve over time or with dose reduction.

Metformin should not be used
in patients with
an GFR<30
and dose reduction
when the GFR is 45 mL min.

Rare cases of lactic acidosis

have been reported,

usually in the setting of severe illness or acute kidney injury.

Therefore, metformin should be omitted in the setting of severe illness, vomiting, or dehydration.

Metformin may result in lower serum vitamin B12 concentration;

therefore, periodic monitoring and supplementation is generally recommended if levels are deficient, particularly in those with anemia or neuropathy .

Because of its high efficacy in lowering HbA1c, good safety profile, and low cost,

metformin

remains the

first-line medication for management of type 2 diabetes.

•

Choice of Glucose-Lowering Medication
After Metformin

The selection of medication added to metformin is based on:

Patient preference

and

Clinical characteristics.

Important clinical characteristics include

the presence of established
comorbidities such as ASCVD, HF or CKD
; the risk for specific adverse medication effects,
particularly hypoglycemia and weight gain;
as well as
safety,
tolerability,
cost.

- The early introduction of basal insulin

when HbA1c levels are very high in particular

when symptoms of hyperglycemia are present, or there is evidence of ongoing catabolism (e.g.weight loss).

This constellation of symptoms can occur in type 2 diabetes with insulin deficiency and raise the possibility of autoimmune (type 1) or pancreatogenic diabetes .

SGLT2 inhibitors

and GLP-1 receptor agonists

have demonstrated efficacy in patients with HbA1c exceeding 9%,

with the additional benefits of

weight reduction

and

reduced risk of hypoglycemia.

SGLT2 Inhibitors

SGLT2 inhibitors are oral medications that reduce plasma glucose by enhancing urinary excretion of glucose .

The glucose-lowering efficacy of these medications is dependent on renal function.

Not approved for use by at an GFR below 45

All SGLT2 inhibitors are associated with a

reduction

in weight and blood pressure.

Alone or with metformin, they do not increase the risk for hypoglycemia.

Empagliflozin and canagliflozin have
cardiac and renal benefits
in patients with
established or at high risk of CVD.

The class is associated with increased risk for mycotic genital infections (mostly vaginitis in women, balanitis in men).

Case reports of diabetic ketoacidosis with SGLT2 inhibitors in type 2 diabetes ?

Therefore, the SGLT2 inhibitors should be used with caution for those with insulin deficiency.

SGLT2 inhibitors have been associated with an

increased risk of

acute kidney injury, dehydration, and orthostatic hypotension;

caution

should be taken when SGLT2 inhibitors are used in combination with diuretics and/or ACE inhibitors and angiotensin receptor blockers.

GLP-1 Receptor Agonists

GLP-1 receptor agonists are currently delivered by subcutaneous injection.

These medications stimulate insulin secretion and reduce glucagon secretion in a

glucose-dependent manner,

improve satiety, and promote weight loss.

Dulaglutide, exenatide extended-release, and semaglutide are administered

once weekly.

Liraglutide and lixisenatide are administered once daily,

and exenatide

twice-daily

- GLP-1 receptor agonists have high glucose-lowering efficacy, but with variation within the drug class.
- Evidence suggests that the effect may be greatest for semaglutide once weekly, followed by dulaglutide and liraglutide, closely followed by exenatide once weekly, and then exenatide twice daily and lixisenatide.
- The short acting medications exenatide twice daily and lixisenatide have greater postprandial effects, at least after the meals with which they are administered.

All GLP-1 receptor agonists reduce weight ;

the reduction ranges from about 1.5 kg to 6.0 kg over about 30 weeks of therapy .

Liraglutide and semaglutide have been shown to improve cardiovascular outcomes .

- The most common side effects of GLP-1 receptor agonists are nausea, vomiting, and diarrhea, though these tend to diminish over time.
- GLP-1 receptor agonists have minimal risk for hypoglycemia, but may increase the hypoglycemic potential of insulin and sulfonylureas when combined with those medications .

- Contrary to early signals, GLP-1 receptor agonists do not seem to substantially increase risk for pancreatitis, pancreatic cancer, or bone disease .

- They are associated with increased risk of gallbladder events .

DPP-4 Inhibitors

DPP-4 inhibitors are oral medications that increase insulin secretion and reduce glucagon secretion in a glucose-dependent manner.

They have moderate glucose lowering efficacy .

- DPP-4 inhibitors are well tolerated, have a neutral effect on weight, and have minimal risk of hypoglycemia when used as monotherapy.
- When added to sulfonylurea therapy, however, the risk for hypoglycemia is increased 50% compared with sulfonylurea therapy alone .

- The recommended dose for each DPP-4 inhibitor is determined and needs to be adjusted based on renal function; linagliptin is the exception as it has minimal renal excretion.
- Rare but increased rates of pancreatitis and musculoskeletal side effects have been reported .
- The cardiovascular safety but no cardiovascular benefit of three DPP-4 inhibitors (saxagliptin, alogliptin, and sitagliptin) .

Thiazolidinediones

- Thiazolidinediones (TZDs) (pioglitazone and rosiglitazone) are oral medications that increase insulin sensitivity and are of high glucose-lowering efficacy .
- TZDs increase HDL-cholesterol, and pioglitazone has been shown to reduce cardiovascular end points and hepatic steatohepatitis ,but without conclusive evidence for benefit.
- TZDs are associated with the best evidence among glucose lowering medications for glycemic durability.

- However, these notable benefits must be balanced with safety concerns regarding fluid retention and congestive heart failure weight gain , bone fracture , and, possibly, bladder cancer .
- Lower-dose therapy (e.g., pioglitazone 15–30 mg) mitigates weight gain and edema, but the broader benefits and harms of low-dose TZD therapy have not been evaluated.

Sulfonylureas

- Sulfonylureas are oral medications that lower glucose by stimulating insulin secretion from pancreatic b-cells. They are inexpensive, widely available, and have high glucose-lowering efficacy .

- Sulfonylureas are associated with weight gain and risk for hypoglycemia and down titration of dose to reduce the risk of hypoglycemia results in higher HbA1c. The
- weight gain associated with sulfonylureas is relatively modest in large cohort studies and the incidence of severe hypoglycemia is lower than with insulin

- Sulfonylureas are known to be associated with a lack of durable effect on glucose lowering .

- Important differences among sulfonylureas affect both safety and efficacy.
- Glibenclamide (known as glyburide in the U.S. and Canada) has a higher risk of hypoglycemia compared with other sulfonylureas . Glipizide, glimepiride, and gliclazide may have a lower risk for hypoglycemia compared with other sulfonylureas.

- Adverse cardiovascular outcomes with sulfonylureas in some observational studies have raised concerns, although findings from recent systematic reviews have found no increase in all-cause mortality compared with other active treatments.
- As newer-generation sulfonylureas appear to confer a lower risk of hypoglycemia and have favorable cost, efficacy, and safety profiles, sulfonylureas remain a reasonable choice among glucose-lowering medications, particularly when cost is an important consideration.

- Greatest caution in this regard is warranted for people at high risk of hypoglycemia, such as older patients and those with CKD.

Insulin

Numerous formulations of insulin are available with differing durations of action.

Basal Insulin

- Basal insulin refers to longer-acting insulin that is meant to cover the body's basal metabolic insulin requirement (regulating hepatic glucose production), in contrast to bolus or prandial insulin, which is meant to reduce glycemic excursions after meals.

- Basal insulin is the preferred initial insulin formulation in patients with type 2 diabetes. Options include once- or twicedaily administration of intermediate acting NPH or detemir insulin and the once-daily administration of glargine (U100 or U300) or degludec (U100 or U200).
- Long-acting insulin analogs (degludec [U100 or U200], glargine [U100 and U300], detemir) have a modestly lower absolute risk for hypoglycemia compared with NPH insulin, but cost more.

- However, in real-world settings where patients are treated to conventional treatment targets, initiation of NPH compared with determir or glargine U100 did not increase hypoglycemia related emergency department visits or hospital admissions.
- When comparing human and analog insulins, cost differences can be large while differences in hypoglycemia risk are modest and differences in glycemic efficacy minimal.

Short- and rapid-acting insulin

- Short- and rapid-acting insulin formulations administered at mealtime are generally used to intensify basal insulin therapy in patients not meeting glycemic targets. Rapid-acting insulin analogs have a modestly lower risk for hypoglycemia compared with human regular insulin but at a higher cost.

Other Glucose-Lowering Medications

- Other oral glucose-lowering medications (i.e., meglitinides, a-glucosidase inhibitors, quick-release bromocriptine, pramlintide) are not used commonly in theU.S. and some are not licensed at all in Europe. No major new scientific information on these medications has emerged in recent years.

Metabolic Surgery

- Evidence supports gastrointestinal (GI) operations as effective treatments for overweight T2DM patients.
- Randomized controlled trials with postoperative follow-up ranging from 1 to 5 years have documented sustained diabetes remission in 30–63% of patients, though erosion of remission occurs in 35-50% or more.
- With or without diabetes relapse, the majority of patients who undergo surgery maintain substantial improvement of glycemic control for at least 5 to 15 years.

Metabolic Surgery: Recommendations

- Metabolic surgery *should be recommended* as an option to treat T2DM in appropriate surgical candidates with BMI ≥40 kg/m^2 (37.5*), regardless of the level of glycemic control or complexity of glucose-lowering regimens, and in adults with BMIs 35.0-39.9 kg/m^2 (32.5-37.4*) when hyperglycemia is inadequately controlled despite lifestyle and optimal medical therapy. A
- Metabolic surgery *should be considered* as an option for adults with T2DM and BMI 30-34.9 kg/m^2 (27.5-32.4*) if hyperglycemia is inadequately controlled despite optimal medical control by either oral or injectable medications (including insulin). B
- Metabolic surgery should be performed in high-volume centers with multidisciplinary teams that understand and are experienced in the management of diabetes and gastrointestinal surgery. C

Metabolic Surgery: Adverse Effects

- Costly
- Some associated risks
- Outcomes vary
- Patients undergoing metabolic surgery
  may be at higher risk for depression, substance abuse, and other psychosocial issues

Evidence Grading System

A	• Clear evidence from well-conducted, generalizable RCTs, that are adequately powered, including:
	  •Evidence from a well-conducted multicenter trial or meta-analysis that incorporated quality ratings in the analysis;
	  •Compelling nonexperimental evidence;
	  •Supportive evidence from well-conducted RCTs that are adequately powered

B	• Supportive evidence from a well-conducted cohort studies
	• Supportive evidence from a well-conducted case-control study
C	• Supportive evidence from poorly controlled or uncontrolled studies
	• Conflicting evidence with the weight of evidence supporting the recommendation
E	• Expert consensus or clinical experience