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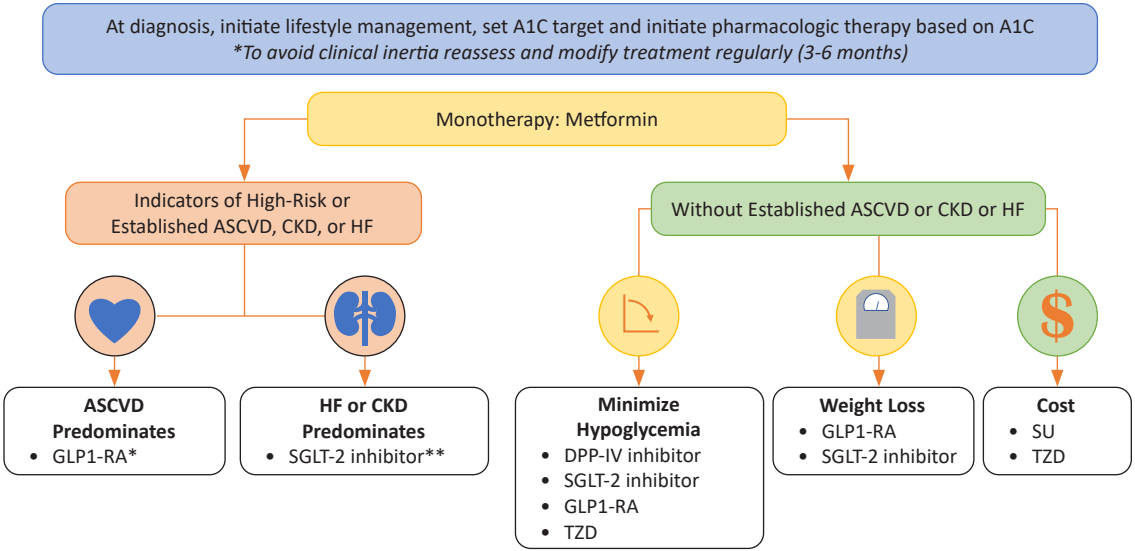
ADA Algorithm for Pharmacological Treatment in Adults with Type 2 Diabetes*

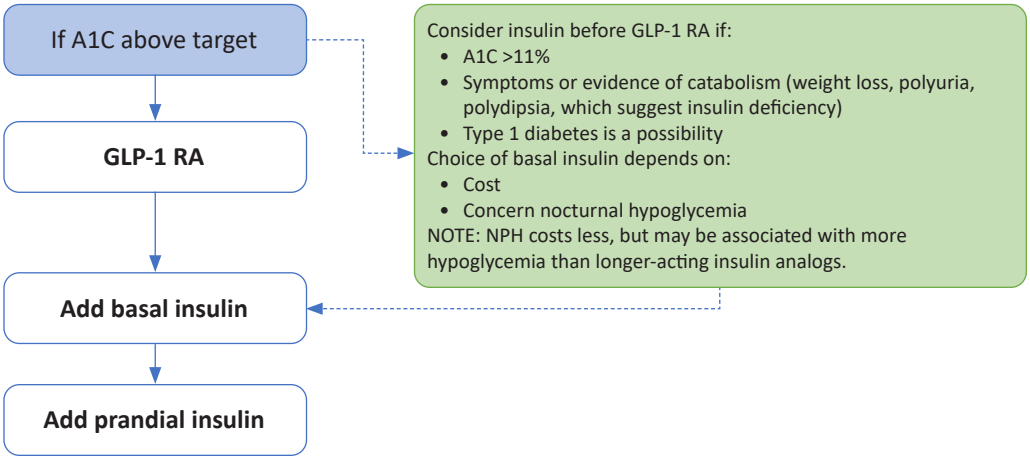


Adapted from Figure 9.1 in American Diabetes Association. Diabetes Care 2020; 43(Supplement 1): S98-S110.

* Preferably GLP1-RA with proven CVD benefit OR SLGT-2 inhibitor with proven CVD benefit if eGFR adequate

** Preferably SGLT-2 inhibitor with evidence of reducing HF and/or CKD progression if eGFR adequate

Combination Injectable Therapy*



Adapted from Figure 7. Davies MJ, D'Alessio DA, Fradkin J, et al. Diabetes Care 2018;41:2669–2701.
Adapted from Figure 9.2 in American Diabetes Association. Diabetes Care 2020; 43(Supplement 1): S98-S110.

Glucose-Lowering Agents[2,3,4]

Drug (Brand name)	*First-Generation Sulfonylureas*—Stimulate insulin release*		
	Tolbutamide (Orinase®, Generics)	**Tolazamide (Tolinase®, Generics)**	**Chlorpropamide (Diabinese®, Generics)**
Recommended dose	0.25 to 3 g divided doses	100 to 1000 mg in 1–2 divided doses	100 to 500 mg daily
Maximum dose	2 to 3 g/day	750 to 1000 mg/day	500 mg/day
Half-life, hours	5 to 7	7	24 to 48
Onset, hours	1	4 to 6	1
Duration, hours	6 to 12	10 to 14	72
Metabolism	Hepatic via CYP2C9 with active metabolites	Hepatic with active metabolites	Hepatic via CYP2C9 with active metabolites
Excretion	Urine (75–85%), Feces	Urine (85%), Feces	Urine
Precautions	Hepatic and kidney impairment may require a decreased dose	Hepatic and kidney impairment may require a decreased dose	Hepatic and kidney impairment may require a decreased dose
Adverse Events	Hypoglycemia, epigastric fullness, nausea, Disulfiram-like reaction, weight gain	Hypoglycemia, epigastric fullness, nausea, Disulfiram-like reaction, weight gain	Hypoglycemia, nausea, Disulfiram-like reaction, weight gain
Comments	Divided doses may improve GI tolerance.	Doses >500 mg/day should be given in 2 divided doses.	Longest duration of action of first-generation sulfonylureas.

*First-generation sulfonylureas are rarely used due to the superior potency and side effect profile of second-generation agents.

Drug (Brand name) Webpage	*Second-Generation Sulfonylureas—Stimulate insulin release*		
	Glyburide (DiaBeta®, Micronase®, Glynase PresTabs®, Generics) www.pfizer.com	**Glipizide (Glucotrol®/Glucotrol XL®, Generics) www.pfizer.com**	**Glimepiride (Amaryl®, Generics)**
Recommended dose	1.25 to 10 mg in 1–2 divided doses; 0.75 to 12 mg daily (Glynase)	2.5 to 20 mg in 1–2 divided doses; single dose for extended release (XL)	1 to 4 mg daily
Maximum dose	20 mg/day; 12 mg/day (Glynase)	40 mg/day; 20 mg/day (XL)	8 mg/day
Half-life, hours	Biphasic 3.2 + 10	3.5 to 6	2.5 ± 1.2
Onset, hours	1.5	1	2 to 3
Duration, hours	24	12 to 16	24
Metabolism	Hepatic to weakly active metabolites	Hepatic via CYP2C9 to inactive metabolites	Hepatic via CYP2C9 to M1 (active) and M2 (inactive) metabolites
Excretion	Feces (50%), Urine (50%)	Urine (90%), Feces	Urine (60%), Feces (40%)
Precautions	Hepatic and kidney impairment may require a decreased dose	Hepatic and kidney impairment may require a decreased dose	Hepatic and kidney impairment may require a decreased dose
Adverse Events	Hypoglycemia, weight gain	Hypoglycemia, weight gain	Hypoglycemia, weight gain
Comments	Administer once daily doses with breakfast or first main meal. Give doses >10 mg/day as 2 divided doses.	Administer once daily doses 30 minutes before breakfast. Give doses >15 mg/day (non-XL) as 2 divided doses.	Administer with breakfast or first main meal.

Drug (Brand name) Webpage	*Nonsulfonylurea-Secretagogues (Glinides)—Stimulate insulin release*		*Biguanides—Inhibit hepatic glucose output*	
	Repaglinide (Prandin®) www.prandin.com	**Nateglinide (Starlix®) www.starlix.com**	**Metformin (Glucophage®, Generics) www.bms.com**	**Metformin Extended Release (Glucophage XR®) www.bms.com**
Recommended dose	0.5 to 4.0 mg before meals	120 mg before meals	500 to 850 mg 3 times daily, or 1000 mg 2 times daily	500 to 2000 mg once daily with evening meal, or 1000 mg 2 times daily
Maximum dose	16 mg/day	120 mg before meals	2550 mg/day	2000 mg/day
Half-life, hours	1	1.5	6	1.5 to 4.9
Onset, hours	0.25 to 0.5	Within 20 minutes	Not related to dose	Not related to dose
Duration, hours	2 to 3	2 to 3	~6	Up to 24
Metabolism	Hepatic via CYP2C8 and CYP3A4 to inactive metabolites	Hepatic via CYP2C9 and CYP3A4	N/A	N/A
Excretion	Feces (~90%), Urine	Urine (83%; ~16% unchanged), Feces	Urine (as unchanged drug)	Urine (as unchanged drug)
Precautions	Poor kidney and hepatic function	Poor kidney and hepatic function	Renal impairment*, CHF, liver disease, alcohol abuse	Renal impairment*, CHF, liver disease, alcohol abuse
Adverse Events	Hypoglycemia	Hypoglycemia	Diarrhea (self-limiting 7–10 days), lactic acidosis	Diarrhea (self-limiting 7–10 days), lactic acidosis

Drug (Brand name) Webpage	*Nonsulfonylurea-Secretagogues (Glinides)—Stimulate insulin release*		*Biguanides—Inhibit hepatic glucose output*	
	Repaglinide (Prandin®) www.prandin.com	**Nateglinide (Starlix®) www.starlix.com**	**Metformin (Glucophage®, Generics) www.bms.com**	**Metformin Extended Release (Glucophage XR®) www.bms.com**
Comments	Administer 15 to 30 minutes before each meal.	Administer 15 to 30 minutes before each meal.	Maximum effective dose is 2000 mg daily. Preferred initial agent for type 2 diabetes.	May have better GI tolerance compared to immediate release.

*Metformin is contraindicated in male PWDs with a serum creatinine >1.5 mg/dL (female >1.4 mg/dL), and should be discontinued if eGFR <30 mL/min.

	Thiazolidinediones (Glitazones, TZD's)—Enhance insulin sensitivity	*Alpha-Glucosidase Inhibitors—Delay carbohydrate absorption*	
Drug (Brand name) Webpage	**Pioglitazone (Actos®) www.actos.com**	**Acarbose (Precose®)**	**Miglitol (Glyset®) www.pfizer.com**
Recommended dose	15 to 45 mg daily	25 to 100 mg 3 times daily	25 to 100 mg 3 times daily
Maximum dose	45 mg/day	300 mg/day	100 mg 3 times daily
Half-life, hours	16 to 24	2	2 to 3
Onset	Days (4–6 weeks for max effect)	Immediate	Rapid
Duration, hours	N/A	~6	Short
Metabolism	Hepatic via CYP2C8 and CYP3A4 to metabolites	GI tract by intestinal bacteria and digestive enzymes	N/A
Excretion	Urine (15–30%), Feces	Urine (~34%), Feces	Urine (unchanged)
Precautions	Hepatic impairment, CHF*, bladder cancer[+]	Bowel/digestion disorders	Bowel/digestion disorders
Adverse Events	Edema (especially if used with insulin), weight gain	Dose-related diarrhea, abdominal pain, flatulence	Dose-related diarrhea, abdominal pain, flatulence
Comments	Monitor liver function tests.	Take with first bite of meal. Must use oral glucose if hypoglycemia occurs. Titrate slowly over weeks to decrease GI effects.	Take with first bite of meal. Must use oral glucose if hypoglycemia occurs. Titrate slowly over weeks to decrease GI effects.

*FDA labeling includes a black box warning that thiazolidinediones may cause or exacerbate heart failure. These agents are also contraindicated in PWDs with NYHA class III or IV heart failure. Although some meta-analyses suggested an increased risk of myocardial infarction with rosiglitazone, the FDA later determined that no increased risk existed. The REMS program for rosiglitazone-containing products was eliminated entirely December 2015 but the use remains limited.

[+]Clinical trial data suggest an increased risk of bladder cancer in PWDs exposed to pioglitazone, with an increasing risk possibly increased with duration of use. Avoid in active bladder cancer and consider risk versus benefit in PWDs with history of bladder cancer.

Drug (Brand name) Webpage	*Ergot Derivatives—Mechanism for glycemic control unknown*	*Amylin Analog—Effects similar to amylin*[+]	*Bile Acid Sequestrants—Block glucose absorption*
	Bromocriptine (Cycloset®) www.cycloset.com	**Pramlintide (Symlin®) www.symlin.com**	**Colesevelam (WelChol®) www.welchol.com**
Recommended dose	0.8 mg daily for 1 week, then increase to 1.6 mg daily	15 to 60 mcg 3 times daily (DM1); 60 to 120 mcg 3 times daily (DM2)	3750 mg daily (3 tablets twice daily or 6 tablets daily)
Maximum dose	4.8 mg daily	60 mcg 3 times daily (DM1); 120 mcg 3 times daily (DM2)	4375 mg daily
Half-life, hours	6	48	N/A
Onset, hours	1–2	0.5	~2 weeks
Duration, hours	N/A	3	24
Metabolism	Major hepatic via CYP3A4	Kidney	N/A
Excretion	Bile, Urine (2–6%)	Urine	Feces, Urine (0.05%)
Precautions	Orthostatic hypotension/ syncope, psychosis*, concomitant dopamine agonist/ antagonist use	Gastroparesis, hypoglycemia unawareness	GI motility disorders, triglycerides >300 mg/dL
Adverse Events	Somnolence, nausea, dizziness, headache	Nausea	Constipation
Comments	Should be taken within two hours after waking with food.	May be helpful in PWDs who can benefit from weight loss.	Cannot be used as monotherapy. See following table for lipid effects.

*May exacerbate psychotic disorders or reduce effectiveness of drugs that treat psychosis. Use in PWDs with severe psychotic disorders is not recommended.

[+]Amylin is co-secreted with insulin and has the effects of centrally promoting satiety, decreasing glucagon release, decreasing gastric secretions, and decreasing gastric emptying.

Drug (Brand name) Webpage	*Dipeptidyl Peptidase IV (DPP-4) Inhibitors—Restore GLP-1* levels*			
	Sitagliptin (Januvia™) www.januvia.com	**Saxagliptin (Onglyza™) www.onglyza.com**	**Linagliptin (Tradjenta™) www.tradjenta.com**	**Alogliptin (Nesina™) www.nesina.com**
Recommended dose	100 mg daily Cl_{cr} ≥30 to <50 mL/min: 50 mg daily Cl_{cr} <30 mL/min: 25 mg daily	2.5 to 5 mg daily Cl_{cr} <50 mL/min: 2.5 mg daily	5 mg daily with or without food	25 mg daily with or without food Cl_{cr} 30–59 mL/min: 12.5 mg daily Cl_{cr} 15–29 mL/min: 6.25 mg daily
Maximum dose	100 mg daily	5 mg daily	5 mg daily	25 mg daily
Half-life, hours	12	2.5–3	>100	21
Onset, hours	1–4	2–4	1.5	2–3
Duration, hours	24	24	24	24
Metabolism	Minor hepatic via CYP3A4 and 2C8	Major hepatic via CYP3A4/5; metabolite retains 50% activity	Minor, 90% excreted unchanged in urine	Minor hepatic via CYP2D6 and 3A4; N-demethylated alogliptin active metabolite
Excretion	Urine [87%; 79% (unchanged)], Feces	Urine (75%), Feces (22%)	Enterohepatic (85%), Urine (5%)	Renal (76%), Feces (13%)
Precautions	Pancreatitis+	Pancreatitis+, coadminstration with strong CYP3A4/5 inhibitors	Pancreatitis+	Pancreatitis+, hepatic failure
Adverse Events	Minor incidence of diarrhea, URTI	Headache, URTI	Nasopharyngitis, diarrhea, cough	Headache, nasopharyngitis, upper respiratory infection