

Healthy eating, weight control, increased physical activity, and diabetes education

Mono-therapy

Efficacy [†]	high
Hypo risk	low risk
Weight	neutral / loss
Side effects	GI / lactic acidosis
Costs [‡]	low

Metformin

If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

Dual therapy[†]

	Metformin + Sulfonyleurea	Metformin + Thiazolidinedione	Metformin + DPP-4 inhibitor	Metformin + SGLT2 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + Insulin (basal)
Efficacy [†]	high	high	intermediate	intermediate	high	highest
Hypo risk	moderate risk	low risk	low risk	low risk	low risk	high risk
Weight	gain	gain	neutral	loss	loss	gain
Side effects	hypoglycemia	edema, HF, fxs	rare	GU, dehydration	GI	hypoglycemia
Costs [‡]	low	low	high	high	high	variable

If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

Triple therapy

	Metformin + Sulfonyleurea	Metformin + Thiazolidinedione	Metformin + DPP-4 inhibitor	Metformin + SGLT2 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + Insulin (basal)
	+ TZD	+ SU	+ SU	+ SU	+ SU	+ TZD
or	DPP-4-i	DPP-4-i	TZD	TZD	TZD	DPP-4-i
or	SGLT2-i	SGLT2-i	SGLT2-i	DPP-4-i	Insulin [§]	SGLT2-i
or	GLP-1-RA	GLP-1-RA	Insulin [§]	Insulin [§]		GLP-1-RA
or	Insulin [§]	Insulin [§]				

If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:

Combination injectable therapy[‡]

Metformin +	Basal insulin +	Mealtime insulin	or	GLP-1-RA
-------------	-----------------	------------------	----	----------