Drug therapy for Diabetes Mellitus: Clinical Practice Guidelines

Initial presentation with T2DM BOX1

- Patient has severe hyperglycemia:(symptoms of severe hyperglycemia (polyuria,polydipsia, weight loss, ketosis)
- Is blood glucose levels ›300 mg/dL or A1C ›10% at initial presentation

NO → Initiate Metformin in combination with life style
If metformin is contraindicated or not tolerated, consider a drug from another class

Yes →
- Consider insulin
- As glucose toxicity resolves consider shifting to oral treatment
- Consider combination therapy if HbA1C is 1.5% above target.

HbA1c target achieved after 3 months Box2 → Yes → Review twice a year

NO →
- Does the patients have established CVD, CKD or HF ? OR
- Is the patient at high risk of CVD (age ›55 years with coronary or peripheral vascular disease, left ventricular hypertrophy)

Yes → An SGLT-2 inhibitor or GLP-1RA with demonstrated CVD benefit is recommended independent of A1C and in consideration of patient-specific factors Table1

NO → Adding a second agent to metformin is based on avoidance of side effects mainly (hypoglycemia and weight gain), cost, and patient preferences Tabel1

HbA1c target achieved after 3 months → Yes → Review twice a year

NO →
- Stepwise addition of 3rd medication to achieve A1C at target is based on the patients have established ASCVD, CKD or HF and avoidance of side effects(hypoglycemia, weight gain), cost, patient preferences.
- Treatment regimens need to be continuously reviewed for efficacy, side effects, and patient response .
- Discontinue agents in non responders after 6 months of use . Table 1

HbA1c target achieved after 3 months → Yes → Review twice a year

NO →
Consider GLP-1RA UNLESS Table 1
- Already on GLP-1RA or GLP-1RA not appropriate OR
- insulin preferred by patient OR
- HbA1c target NOT achieved after 3 months of GLP-1RA use

Add basal insulin or bedtime NPH insulin
INITIATION:10 IU a day or 0.1-0.2IU /kg a day TITRATION: 2-4 units every 3 days to reach target FPG
For Hypoglycemia determine cause and if not clear then lower dose by 10-20%.

HbA1c target not achieved despite adequate titration of insulin OR basal dose › 0.5IU/kg OR FPG at target

If on basal insulin Add prandial insulin with the largest meal
INITIATION: 4IU or 10% of basal dose TITRATION: increase by 1-2 IU twice weekly
If on NPH convert to twice daily 80% of current bedtime dose give 2/3 before breakfast and 1/3 before dinner
For Hypoglycemia determine cause and if not clear then lower dose by 10-20%.

If HbA1c target not met consider:
- Stepwise additional injections of prandial insulin , two then three injections
- Split insulin regimen
- Premix insulin regimen Table 1

Comprehensive lifestyle changes

BOX1: Diagnosis of diabetes
In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.
- A1C ≥6.5% **OR**
- FPG ≥126 mg/dL **OR**
- 2-h PG ≥200 mg/dL during an OGTT **OR**
- in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL

Box2:HbA1c target
- ≤ 7% : individuals with recent onset DM, intact hypoglycaemia awareness and no concurrent illnesses
- 7--8% :a more relaxed individualized target based on age , co-morbidities, duration of DM, risk of hypoglycaemia , patient motivation ,adherence and life expectancy.
- check every 3 months until target achieved then every 3-6 months

Reference :
ADA- Standards Of Medical Care Diabetes Care 2021 Jan; 44(Supplement 1): S1-S2.

Table 1 : drug- specific and patients factors to consider when selecting antihyperglycemic treatment

	Efficacy	Hypoglycemia	weight	CV effect		Renal Effect		Side effects & precautions
				ASCVD	HF	CKD progression	Dosing adjustment	
Metformin	High	No	Loss	Possible Benefit	Neutral	Neutral	review dose if CrCl ‹45 stop if CrCl drops below 30	nausea, anorexia, GI upset ,transient diarrhea, taste disturbance, lactic acidosis, potential for B12 deficiency. suspend prior to tests requiring intravenous iodine- containing contrast and elective surgery , restart 48 hours after procedure providing renal function returned to base line
Dose: start 500mg with breakfast titrate over weeks up to 2g daily in divided doses						**Ramadan**: advice 2/3 of daily dose with Iftar and 1/3 with Suhur		
SGLT-2 inhibitor Empagloflozin Canagliflozin Dapaglifozin Ertuglifozin	Intermediate	No	Loss	Benefit: Empagloflozin canagliflozin	Benefit	Benefit	Required renal dose adjustment for all SGLT-2 inhibitors	volume depletion(gastrointestinal infections , use of diuretics, age of above 75, avoid in liver impairment . Risk of DKA . Increase LDL , risk of Fournier's gangrene & long bone fracture **FDA black Box**-Risk of amputation with canagliflozin.
GLP-1 RA Exenetide Liraglutide **Dulaglutide** **Semaglutide (weekly)** semaglutide (oral)	High	No	Loss	Benefit Liraglutide Dulaglutide Semaglutide	Neutral	Benefit Liraglutide Dulaglutide Semaglutide	Required :Exenetide	gastrointestinal (discomfort, and dry mouth, burping, constipation, diarrhea, nausea, altered taste, toothache and gall bladder disorder, decreased appetite), headaches, dizziness, skin reactions, increased risk of infections, Avoid in severe impairment. **FDA black Box**-Risk of thyroid C-cell tumor with Liraglutide, dulaglutide, exenatide extended release
DPP-4 inhibitor Linagliptin Sitagliptin Vildagliptin Saxagliptin	Intermediate	No	Neutral	Neutral	Risk saxagliptin	Neutral	Required for all except linagliptin	uremia , nasopharyngitis ,cough, increased serum lipase ,urtricaria, GI disturbances, peripheral edema, URI, dry mouth, headache, rash Risk of pancreatitis
TZD Pioglitazone	High	No	Gain	Benefit: pioglitazone	Risk	Neutral	Not required, generally not recommended in renal impairment as potential risk of fluid overload.	anemia, headache, vertigo, sweating ,visual disturbances, impotence, fatigue, insomnia, caution: increase risk of fractures , bladder cancer ,undiagnosed hematuria Benefit in NASH. **FDA black Box**-Risk of heart failure.
Sulfonylurea Gliclazide Glibenclamide Glimepride Glipazide	High	Yes	Gain	Neutral	Neutral	Neutral	Glipizide and Glimepiride initiate conservatively to avoid hypoglycaemia	usually well tolerated ,nausea ,vomiting , diarrhea, constipation, hypersensitivity reactions.
Insulin	Highest	Yes	gain	Neutral	Neutral	Neutral	Required	Injection site reactions
Basal Insulin	Glargine Galrgine follow-on Detemir Degludec	initiate 10 IU a day OR 0.1-0.2IU/kg a day . Titrate by increase 2 unites (4 units if FPG ›180 mg /dl) every 3 days to reach FPG target without hypoglycemia OR dose ›0.5 IU/KG On initiation of basal insulin : **metformin** : continue **SU**: option to continue, reduce or stop **TZD**: stop **GLP-1RA** continue **DPP4** continue (stop if combined injections) **SGLT2** continue						
	NPH	initiate 10 IU a day OR 0.1-0.2IU/kg a day at night . Titrate by increase 2 unites every 3 days to reach FPG target without hypoglycemia. For Twice daily regimen : Total dose 80% of current bedtime dose give 2/3 am and 1/3 bedtime						
Prandial insulin	Short acting	Human regular	Short acting(give 30-45 minutes before meal). Initiate 4 IU (or 10% of basal dose) with the largest meal . Titrate by increasing dose by 1-2 IU twice weekly					
	Rapid acting	Aspart lispro Glulisine	Rapid acting (give immediately to 15 mins before meal). Initiate 4 IU (or 10% of basal dose) with the largest meal . Titrate by increasing dose by 1-2 IU twice weekly.					
Premixed insulin	Lispro 50/50 Lispro 75/25 Aspart 70/30 NPH70/30	give immediately before meal. initial total insulin dose: 0.1-0.3 units/kg/day . Usual maintenance range: 0.5-1 units/kg/day in divided doses. Existing basal(unit-to-unit conversion) Existing basal-bolus (reduce TDD by 20-30%) Titrate1-2 units,1-2xweekly,unitl goal						

Combination of medications can be prescribed based on evidence and patient preferences