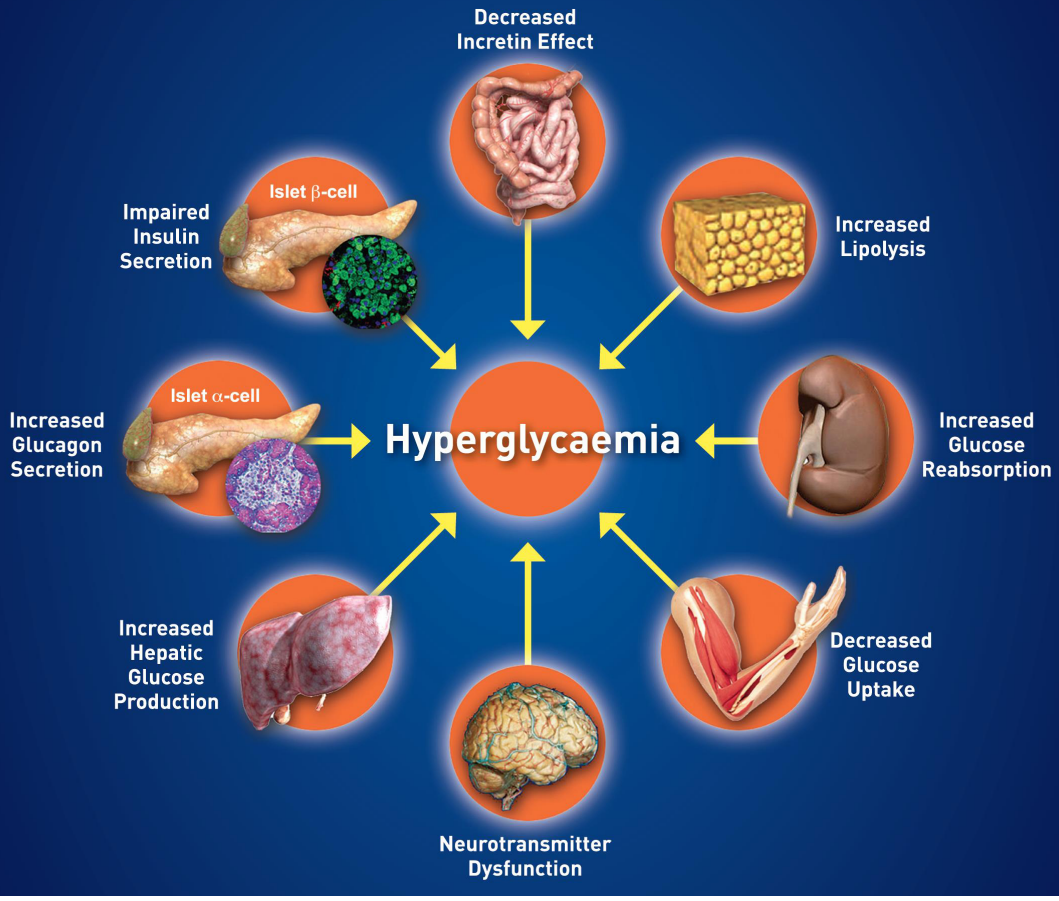
2016 MOH/P/PAK/303.15 (GU)

CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF TYPE 2 DIABETES MELLITUS

5TH EDITION



QUICK REFERENCE GUIDE
FOR HEALTHCARE PROFESSIONALS

MALAYSIAN ENDOCRINE & METABOLIC SOCIETY
MINISTRY OF HEALTH MALAYSIA
ACADEMY OF MEDICINE MALAYSIA
DIABETES MALAYSIA
FAMILY MEDICINE SPECIALISTS ASSOCIATION OF MALAYSIA

This Quick Reference Guide provides key messages and summary of the main recommendations in the Clinical Practice Guidelines (CPG) for the Management of Type 2 Diabetes Mellitus, 5th Edition.

12 Key Messages

1	Individuals with risk factors for diabetes should be screened annually as more than half of adults with the disease are unaware of their diagnosis.
2	An A1c ≥ 6.3% performed using NGSP-certified method and standardised to DCCT assay is diagnostic of diabetes mellitus in Malaysian adults.
3	Patients with pre-diabetes (IFG & IGT) are 2 to 3 times at risk of developing cardiovascular diseases and diabetes.
4	Framingham Risk Score should be calculated for patients with pre-diabetes and diabetes to determine the risk of developing cardiovascular disease.
5	A1c, BP and Cholesterol should be monitored 3-6 monthly with annual fundoscopy, feet examination, urine dipstick, renal and liver function tests.
6	A1c ≤ 6.5% is recommended to reduce complications. However, it should be individualised to minimise the risk of hypoglycaemia.
7	Serious attention must be given to patient's glycaemic control as only a quarter of patients in primary care clinics and one-eighth in tertiary care hospitals are able to control their diabetes.
8	Patients who upon diagnosis control their diabetes will continue to benefit from the reduced risk of cardiovascular diseases even if their control deteriorate later in life (Metabolic Memory)
9	Newer anti-diabetic agents and insulins have not been shown to be more effective than older ones. However, they cause less hypoglycaemia and weight gain.
10	Universal screening should be performed on all pregnant women between week 24 to 28 using mOGTT wherever feasible. Those with risk factors should be screened at booking and repeated 4-6 weeks later if normal.
11	Muslims with diabetes can fast safely in Ramadan provided they exercise caution and make appropriate adjustments to their therapy in consultation with their healthcare providers.
12	In those at risk of developing diabetes, the use of metformin can be considered after 6 months of failed lifestyle intervention.

Published by
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Values For Diagnosis *

(A) Diagnostic Value for T2DM Based on Venous Plasma Glucose

Fasting	Random
≥7.0 mmol/L	≥11.1 mmol/L

(B) Diagnostic Values for Pre-diabetes and T2DM Based on A1c

Normal	Pre-diabetes	Diabetes
<5.6% (38 mmol/mol)	5.6-6.2% (38-44 mmol/mol)	≥6.3% (45 mmol/mol)

(C) Diagnostic Values for Glucose Intolerance and T2DM Based on OGTT

OGTT Plasma Glucose Values (mmol/L)		
Category	**0-hour**	**2-hour**
Normal	<6.1	<7.8
IFG	6.1–6.9	
IGT	-	7.8–11.0
DM	≥7.0	≥11.1

OGTT: Oral glucose tolerance test; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; DM: Diabetes mellitus
* In asymptomatic patients, the blood test has to be repeated on another day to confirm the diagnosis of Diabetes Mellitus

Management Of Type 2 Diabetes Mellitus

1. At diagnosis, a detailed history, full physical examination and baseline investigations must bedone to assess the cardiovascular disease risk factors and complications arising from diabetes.
2. Management should be based on the initial clinical assessment and baseline investigations.
3. It involves lifestyle modification, medications and patient education to promote *self-care and empowerment.*
4. Prior to increasing the dose or adding a new oral medication or insulin, *compliance* to therapy has to be determined satisfactorily.

Clinical Monitoring Schedule (√= must do, + = optional, - = omit)

Test	Initial Visit	3-monthly Visit	Annual Visit
Weight √		√	√
Waist circumference	√	√	√
BMI	√	-	√
Blood Pressure	√	√	√
Eye: Visual acuity	√	-	√
Fundoscopy	√	-	√
Feet: Pulses	√	√	√
Neuropathy	√	√	√
Dental Check-up	√	√ (6-monthly)	√
Blood Glucose	√	√	√
A1c	√	√	√
Cholesterol/HDL cholesterol	√	+	√
Triglycerides	√	+	√
Creatinine/BUSE	√	+	√
Liver function test	√	-	√
Urine microscopy	√	-	√
Albuminuria	√	+	√
ECG	√	+	√

Targets for Control of Type 2 Diabetes Mellitus

Parameters		Levels
Glycaemic control	Fasting or pre-prandial	4.4–7.0 mmol/L
	Post-prandial	4.4–8.5 mmol/L
	A1c	≤6.5%
Lipids	Triglycerides	≤1.7 mmol/L
	HDL-cholesterol	>1.0 mmol/L (male) >1.2 mmol/L (female)
	LDL-cholesterol	≤2.6 mmol/L
Blood pressure		≤135/75 mm Hg
Exercise		150 minutes/week
Body weight	If overweight or obese, aim for 5-10% weight loss in 6 months	

Individualised A1c Targets and Patients' Profile

Tight (6.0–6.5%)	6.6–7.0%	Less tight (7.1–8.0%)
• Newly diagnosed • Relatively younger age • Healthier (long life expectancy, no CVD or its complications) • Low risk of hypoglycaemia	• All others	• Comorbidities (coronary artery disease, heart failure, renal failure, liver dysfunction) • Short life expectancy • Prone to hypoglycaemia

Principal Recommendations for Dietary & Lifestyle Modification

1. A modest albeit realistic weight loss of 5-10 % of initial body weight over a 6-month period is beneficial for all overweight or obese patients who have or at risk for diabetes as it improves significantly their cardiovascular disease risk factors.
2. Patients should monitor and limit their total caloric, carbohydrate & fat intake during each meal.
3. Carbohydrate counting and meal planning may help patients to control their blood glucose levels.
4. Low glycaemic index foods should be encouraged at mealtimes as they reduce post-prandial blood glucose levels.
5. Exercise of moderate-intensity should be encouraged for at least 150 minutes per week
   (Just 30 minutes every alternate day)

Recommendations for Self-Monitoring of Blood Glucose

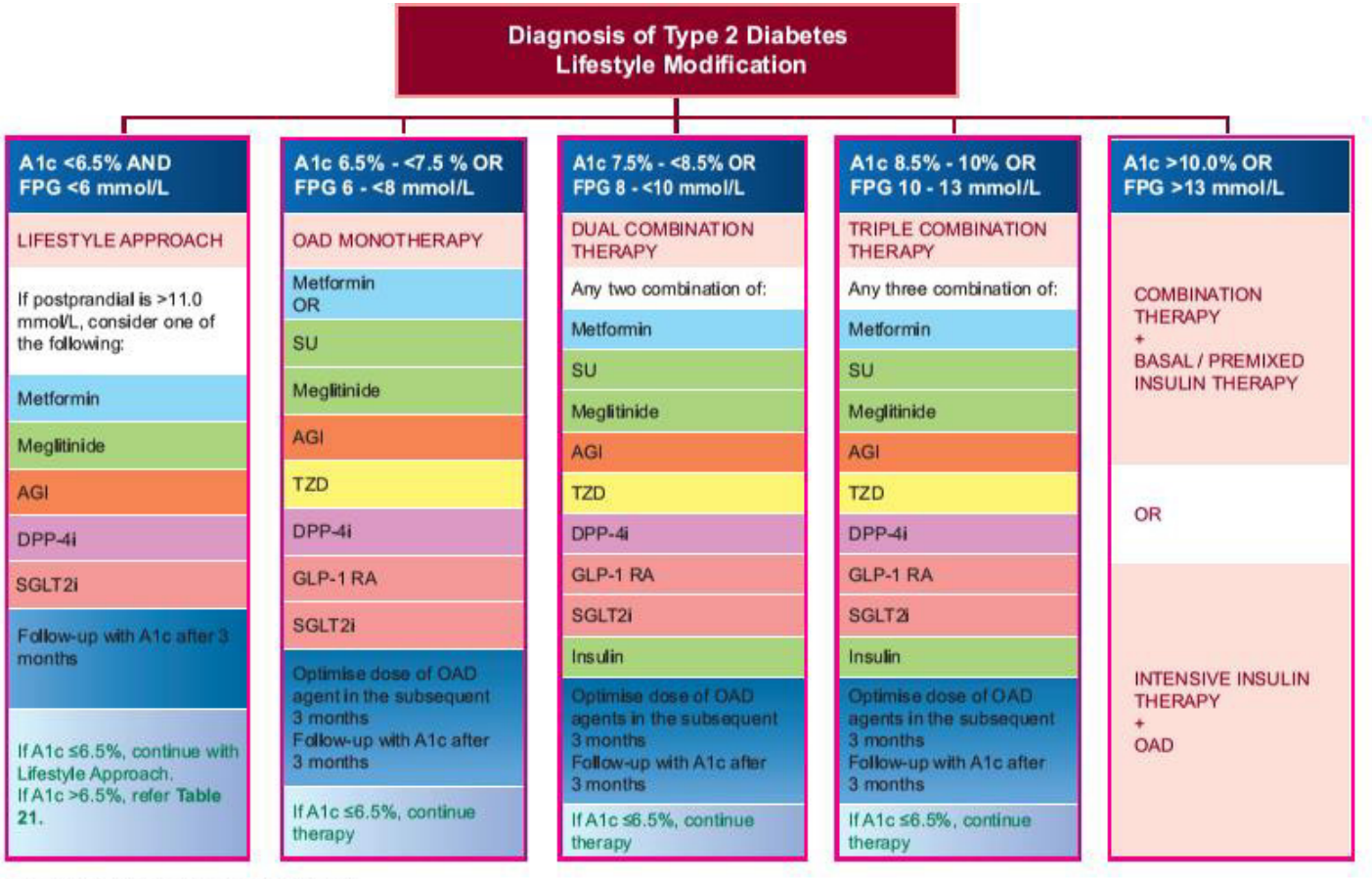
Mode of Treatment	Breakfast		Lunch		Dinner	
	Pre	Post	Pre	Post	Pre	Post/Pre-bed
Diet only	√	√		√		√
Oral anti-diabetic agents	√	√		√		√
Insulin	√	√	√	√	√	√

Comparison of A1c with average blood glucose levels

A1c (%)	4-6	6.5	8	9	10	11	12	13	14	15
Average Blood Glucose (mmol/l)	4-7	8	10	12	13	15	17	19	21	23

OAD Formulations and Dosage

Drugs	Formulation	Minimum Dose	Maximum Dose
Biguanides			
Metformin	500 mg	Initial dose 500 mg OD Usual dose 1500 mg OD	1000 mg TDS
Metformin SR	850 mg	Usual dose 850 mg BD	850 mg TDS
Metformin XR	500 mg, 750 mg	Initial dose 500 mg OD Usual dose 2000 mg OD	2000 mg OD
Sulphonylureas (SU)			
Glibenclamide	5 mg	2.5 mg OD	10 mg BD
Gliclazide	80 mg	40 mg OM	160 mg BD
Gliclazide MR	60 mg	30 mg OM	120 mg OM
Glipizide	5 mg	2.5 mg OM	10 mg BD
Glimepiride	2 mg, 3 mg	1 mg OM	6 mg OM
Meglitinides			
Repaglinide	0.5 mg, 1 mg, 2 mg	0.5 mg with main meals	4 mg with main meals (not exceeding 16 mg daily)
Nateglinide	120 mg	60 mg with main meals	120 mg with main meals (not exceeding 360 mg daily)
Alpha-glucosidase Inhibitors (AGI)			
Acarbose	50 mg, 100 mg	Initial dose 50 mg OD	100 mg TDS
		Usual dose 50–100 mg during main meals	
Thiazolidinediones (TZD)			
Rosiglitazone	4 mg, 8 mg	4 mg OD	8 mg OD
Pioglitazone	15 mg, 30 mg	15 mg OD	45 mg OD
Dipeptidyl Peptidase-4 Inhibitors (DPP-4i)			
Sitagliptin	25 mg, 50 mg, 100 mg	25 mg OD	100 mg OD
Vildagliptin	50 mg	25 mg BD	50 mg BD
Saxagliptin	2.5 mg, 5 mg	2.5 mg OD	5 mg OD
Linagliptin	5 mg	5 mg OD	5 mg OD
Alogliptin	6.25 mg, 12.5 mg, 25 mg	6.25 mg OD	25 mg OD
Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i)			
Dapagliflozin	5 mg, 10 mg	5 mg OD	10 mg OD
Canagliflozin	100 mg, 300 mg	100 mg OD	300 mg OD
Empagliflozin	10 mg, 25 mg	10 mg OD	25 mg OD
Glucagon-like Peptide-1 Receptor Agonists (GLP-1 RA)			
Exenatide IR	5 µg/20 µL, 10 µg/40 µL	5 µg BD	10 µg BD
Exenatide XR	2 mg	2 mg weekly	2 mg weekly
Dulaglutide	0.75 mg, 1.5 mg	0.75 mg weekly	1.5 mg weekly
Liraglutide	6 mg/mL	0.6 mg OD	1.8 mg OD
Lixisenatide	50 µg/mL, 100 µg/mL	10 µg OD	20 µg OD



*The agents above are based on historical order

Footnote:

Metformin	Efficacious, low risk of hypoglycaemia and weight neutral
SU, Glinides, Insulin	Efficacious, risk of hypoglycaemia and weight gain
DPP-4i	Moderate efficacy, low risk of hypoglycaemia and weight neutral
GLP-1 RA, SGLT-2i	Moderate efficacy, low risk of hypoglycaemia and weight loss
TZD	Moderate efficacy, low risk of hypoglycaemia and weight gain
AGI	Modest efficacy, low risk of hypoglycaemia and weight neutral

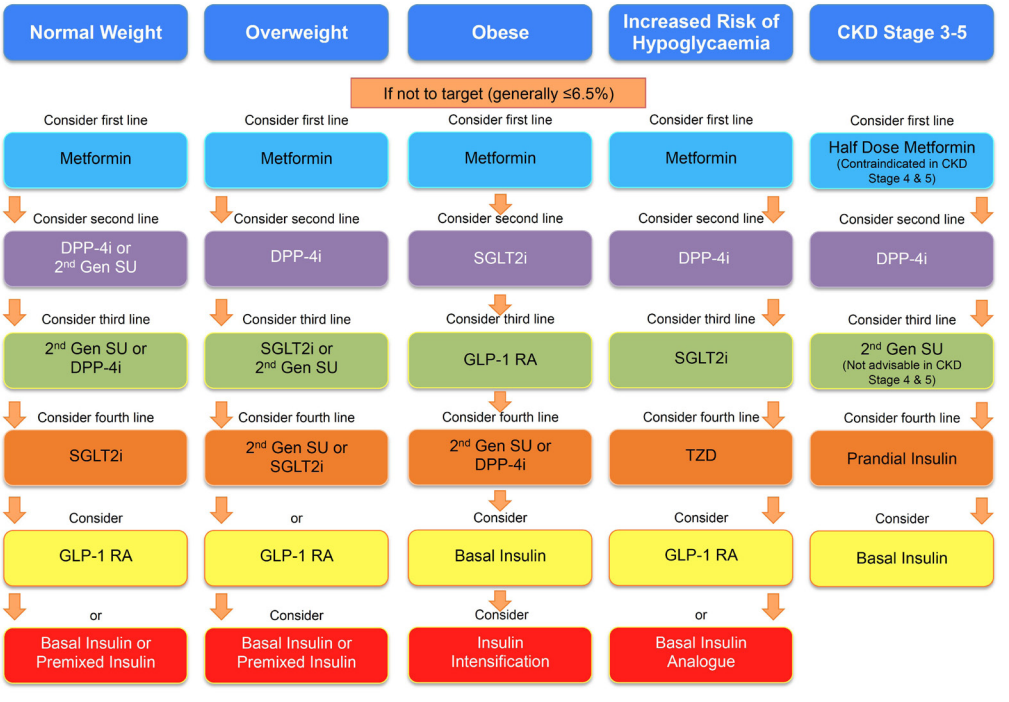
Treatment Recommendations for Patients on Clinic Follow-up

Glycaemic Control / Current Treatment	A1c 6.5–<7.5% or FPG 6–<8 mmol/L	A1c 7.5–<8.5% or FPG 8–<10 mmol/L	A1c 8.5–10.0% or FPG 10–13 mmol/L	A1c >10.0% or FPG >13 mmol/L
Lifestyle Treatment	Start metformin (if metformin not tolerated, use an agent from **Box 1**)	Start metformin and another agent from **Box 1** (dual therapy)	Start metformin and 2 other agents from **Box 1** (triple therapy)	Start metformin & another agent + insulin (basal or premixed od)
Monotherapy (Metformin preferred)	Add 1 agent from **Box 1** (dual therapy)	Add 2 agents from **Box 1** (triple therapy)	Add 2 agents from **Box 1** + insulin (basal or premixed od)	Initiate & intensify§ insulin (MDI) and continue metformin
Dual Therapy	Add 1 agent from **Box 1** (triple therapy)	Add 1 agent from **Box 1** or insulin (basal or premixed od)	Add 1 agent from **Box 1** + insulin (basal or premixed od)	Initiate & intensify§ insulin (MDI) and continue dual therapy (except SU/glinides)
Triple Therapy	Add 1 agent from **Box 1** (quadruple therapy)	Add 1 agent from **Box 1** or insulin (basal or premixed od)	Add insulin (basal or premixed od) and continue triple therapy	Initiate & intensify§ insulin (MDI) and continue triple therapy (except SU/glinides)

Box 1: Selection of Anti-diabetic Agents

SU, Meglitinide	Efficacious, risk of hypoglycaemia, weight gain
AGI	Modest efficacy, low risk of hypoglycaemia, weight neutral
TZD	Efficacious, low risk of hypoglycaemia, weight gain
DPP-4i	Moderate efficacy, low risk of hypoglycaemia, weight neutral
GLP-1 RA, SGLT2i	Moderate efficacy, low risk of hypoglycaemia, weight loss

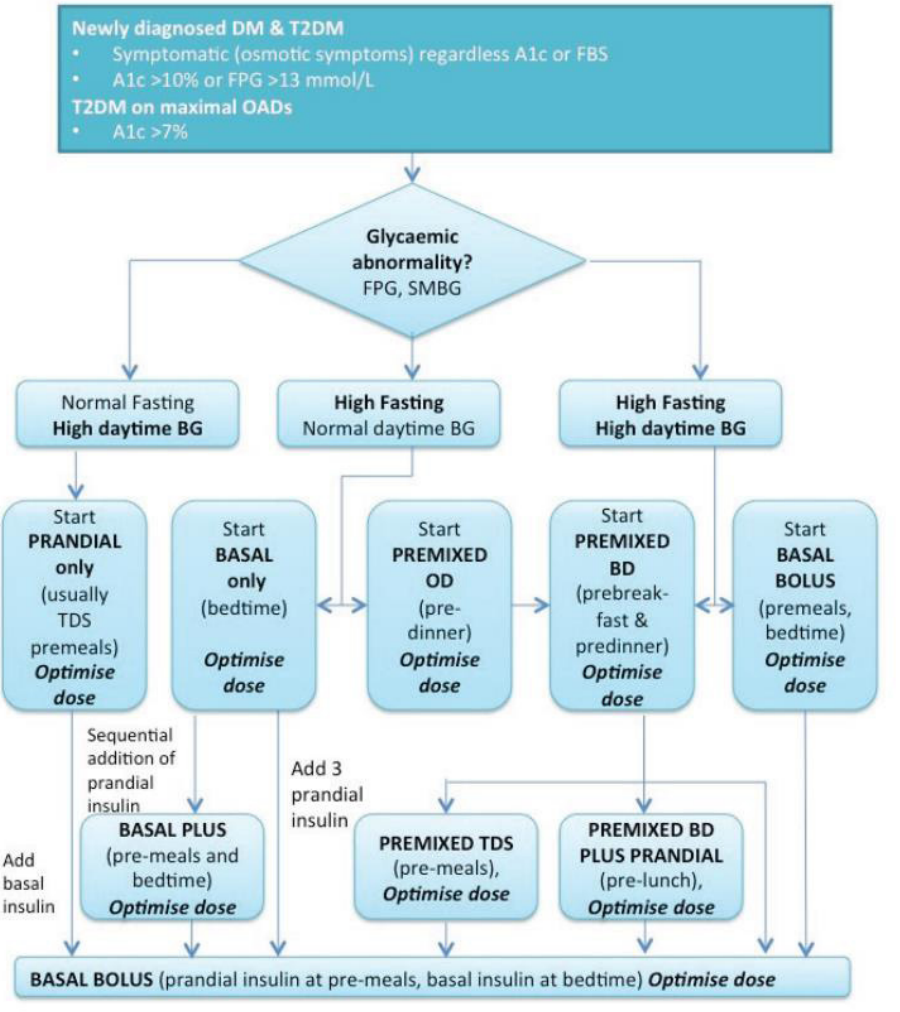
Suggested Treatment Approach for Specific Patient Profiles



2nd Gen SU: selected 2nd generation sulphonylurea (gliclazide); DPP-4i: dipeptidyl peptidase-4 inhibitor; SGLT2i: sodium-glucose cotransporter 2 inhibitor; GLP-1 RA: glucagon-like peptide-1 receptor agonist. DPP-4i should be stopped once GLP-1 RA is introduced.

- **Patients who are well-controlled on their existing drugs should continue with the treatment regime.**
- **Bariatric surgery may be considered in patients with BMI ≥32 kg/m2 and their diabetes not controlled by lifestyle changes and pharmacotherapy.**

Initiation and Optimisation of Insulin Therapy



Note:
1. Metformin should be continued while on insulin therapy unless contraindicated or intolerant
2. Sulphonylureas/Meglitinides should be withdrawn once prandial insulin is used regularly with meals
3. Insulin dose should be optimised prior to switching/intensifying regimens

Efficacy of Various Anti-diabetic Agents

	MET	SU	GLN	AGI	TZD	DPP4-i	SGLT2-i	GLP-1 RA	Insulin
A1c reduction, %	1.0-1.5	0.4-1.6	1.0-1.2	0.5-0.8	0.5-1.4	0.5-0.8	0.2-0.8	0.5-1.4	>1.5
FPG vs PPG	FPG	FPG	Both	PPG	FPG	Both	Both	Both	Both
Hypoglycaemia	↔	↑↑	↑	↔	↔	↔	↔	↔	↑↑
Weight change	↓	↑↑	↑	↔	↑↑	↔	↓↓	↓↓	↑↑
GI symptoms	↑↑	↔	↔	↑↑	↔	↑	↔	↑↑	↔
Congestive heart failure	↔	↔	↔	↔	↑	↔	↔	↔	↔
Cardiovascular disease	↓	↔?	↔	↔	↔	↔	↓?	↔	↔
Bone loss	↔	↔	↔	↔	↑	↔	↔	↔	↔
CKD	Avoid if GFR<30	Hypo-glycaemia	Hypo-glycaemia	↔	Fluid retention	Dose adjustment	Avoid if GFR<60	Avoid if GFR<30	Hypo-glycaemia
References	77 (Level I)	168,169 (Level I)	85 (Level I)	170 (Level I)	88-92 (Level I)	151-153 (Level I)	113-116 (Level I)	121 (Level I)	160,161,171, 172 (Level I)

MET = metformin; SU = sulphonylureas; GLN = glinides; GLP-1 RA = glucagon-like peptide-1 receptor agonists; DPP4-i = dipeptidyl peptidase-4 inhibitors; SGLT2-i = sodium-glucose co-transporter 2 inhibitors; AGI = α-glucosidase inhibitor; TZD = thiazolidinediones

The efficacy data for the above anti-diabetic agents were established with baseline A1c level below 10%. Efficacy of all OADs is dependent on the baseline A1c levels. The higher the A1c level, the more efficacious is the agent.

Beneficial | Possible benefit | Neutral | Minimal risk | Increased risk