CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF TYPE 2 DIABETES MELLITUS

(6th Edition)

Quick Reference Guide for Healthcare Professionals

Malaysia 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 CPG for the Management of Type 2 Diabetes Mellitus, 6th edition

KEY MESSAGES

Risk-based screening for pre- and/or T2DM in adults should be performed in individuals >30 years of age and repeated annually, as ~50% of people with diabetes are undiagnosed.

HbA_{1c} ≥6.3% (IFCC ≥ 45 mmol/mol) performed by an NGSP-certified method, standardised to DCCT assay is diagnostic of diabetes.

In asymptomatic individuals, 2 abnormal values (e.g. plasma glucose and HbA_{1c}) from the same blood sample is adequate for diagnosis of T2DM.

Pre-DM (IFG and/or IGT) predisposes these individuals to progression to overt T2DM as well as increased CV risk. Lifestyle modification with weight loss is the mainstay; but failing this, metformin can be initiated.

Remission of T2DM may be possible in some individuals with short duration of disease, following significant and sustained weight loss by either caloric restriction or bariatric surgery.

T2DM is a CVD defining disease, and patients should have their other CVD risk factors, e.g. blood pressure, lipids treated aggressively and closely monitored.

Target HbA_{1c} is individualised; ≤6.5% for those young, uncomplicated, with short duration of disease; while <7.0% would be appropriate for most other adult T2DM individuals.

Achieving HbA_{1c} target early, from diagnosis and maintaining glucose control for as long as possible, will result in persistent benefits and reduction of complications in the long-term (Metabolic memory).

Metabolic associated fatty liver disease (MAFLD)* is a new proposed nomenclature to replace NAFLD as it includes a key driver of this disease which, is presence of metabolic dysfunction. NAFLD is increasingly recognised as a co-morbidity associated with T2DM. If left unchecked, it can lead to liver cirrhosis and hepatocellular carcinoma. NAFLD is also associated with higher CV risk and aggressive management of CV risk, including statin therapy is indicated.

Recent CVOTs have proven that 2 classes of glucose-lowering agents (GLDs) significantly reduce MACE outcomes, in people with established ASCVD or are at high-CV risk, beyond their glucose-lowering effects; GLP1-RAs and SGLT2-i. The data from these trials have resulted in paradigm shifts in recommendations for choice of therapeutic agents.

SGLT2-i have also been proven to be reno-protective, delaying progression to end-stage renal failure, >40% reduction in eGFR or renal death. This is the 2nd class of therapy proven to be reno-protective, apart from RAS-blockers.

The newer therapeutic agents are expensive, and may not be affordable to many. In these people, achieving HbA_{1c} remains an important goal.

**NAFLD will be used in this edition of the T2DM CPG instead of MAFLD.*
For expansion of abbreviations, refer to the main CPG document.

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 HbA_{1c}

Normal	Pre-DM	DM
<5.7 % (<39 mmol/mol)	5.7-<6.3% (39-44 mmol/mol)	≥6.3% (≥45 mmol/mol)

(C) Diagnostic values for glucose intolerance and T2DM based on OGTT

Category	0 hr	2 hr
Normal	<6.1	<7.8
IFG	6.1-6.9	-
IGT	-	7.8-11.0
DM	≥7.0	≥11.1

** In asymptomatic patients, a repeat blood test on another day or 2 abnormal values (1 glucose + HbA_{1c} in the same sample) is required to confirm diagnosis.*

Management of T2DM

- At diagnosis of T2DM the following should be performed:
  - › detailed history and physical examination, focusing on key issues which will affect treatment decision
  - › baseline investigations to assess ASCVD risk factors and complications of T2DM
- Management is based on the results of the above.
- Management involves lifestyle modification, medications and patient education encouraging self-care and empowerment.

Test	Initial visit	3-monthly OR Every follow-up visit	At annual visit
Physical examination			
Weight	√	√	√
Waist circumference	√	√	√
BMI	√		√
BP	√	√	√
Eye			
Visual acuity	√		√
Fundoscopy/Fundus camera	√		√
Feet			
Pulses/ABI	√	√	√
Neuropathy	√	√	√
Dental check-up	√		√
ECG	√		√
Laboratory investigations			
Plasma glucose	√	√	√
HbA_{1c}	√	√	√
Lipid profile	√		√
Creatinine/BUSE + eGFR	√		√
LFT (AST, ALT)	√		√
Urine microscopy	√		√
Urine albumin/microalbumin/ spot morning urinary ACR	√		√

√: conduct test ■ *conduct test if abnormal on initial visit or symptomatic* ■ *no test is required*

Note: refer to main CPG for important notations.

T2DM: Targets for control

Parameters		Levels
Glycaemic control	Fasting or pre-prandial	4.4 mmol/L-7.0 mmol/L
	Post-prandial	4.4 mmol/L-8.5 mmol/L
	HbA_{1c}	<7.0% (for most) ≤6.5 %***
Lipids	Triglycerides	≤1.7 mmol/L
	HDL-C	Male: >1.0 mmol/L Female: >1.2 mmol/L
	LDL-C⁺	≤2.6 mmol/L
BP		130-139/70-79 mmHg
Exercise		150 minutes/week
Body weight	If overweight or obese, aim for up to 10% weight loss in 6 months	

****Young, healthy, short duration of T2D, no/minimal risk of hypoglycaemia, ⁺ Depending on risk category, i.e., moderate (<2.6 mmol/L), high (<1.8 mmol/L) and very high (<1.4 mmol/L).*

Relationships between NGSP, IFCC HbA_{1c} and estimated average glucose (eAG)

NGSP HbA_{1c} (%)	IFCC HbA_{1c} (mmol/mol)	eAG (mmol/L) (95% CI)
5.0	31	5.4 (4.2-6.7)
6.0	42	7.0 (5.5-8.5)
7.0	53	8.6 (6.8-10.3)
8.0	64	10.2 (8.1-12.1)
9.0	75	11.8 (9.4-13.9)
10.0	86	13.4 (10.7-15.7)
11.0	97	14.9 (12.0-17.5)
12.0	108	16.5 (13.3-19.3)

Individualised HbA_{1c} targets based on patient profile

≤6.5 % (Tight)	6.6%-7.0%	7.1%-8.0% (Less tight)
• Newly and recently diagnosed • Younger age • Healthier (no complications) • Low risk of hypoglycaemia	• All others	• Elderly patients • Presence of co-morbidities • High risk of severe hypoglycaemia; hypo unawareness • Short life expectancy

Principal recommendation: Medical nutrition therapy & lifestyle modification

- Weight loss of ≥7%-10% of initial body weight within 6 months has been proven to be effective for diabetes prevention.
- Proper diet is crucial at all stages of management of diabetes including those on medication.
- Meal plans that meet individualised caloric goals with a macronutrient distribution that is consistent with healthful eating pattern is recommended for long-term achievement of glycaemia, lipids and weight goals.
- Encourage foods with low GI in the Malaysian context because excessive rise in post-prandial glycaemia is frequently observed.
- Encourage moderate-intensity exercise, at least 150 mins/week or at least 75 mins/ week of vigorous aerobic

Recommendations for SMBG

Mode of Treatment	Breakfast		Lunch		Dinner	
	Pre	Post	Pre	Post	Pre	Post / Pre-bed
Diet only	√	√	-	√	-	√
OGLDs	√	√	-	√	-	√
Insulin	√	√	√	√	√	√

Glucose-lowering agents (oral & injectable)

Drugs	Formulation	Minimum dose	Maximum dose
Biguanides			
Metformin	500/1000 mg	Initial dose: 500 mg OD	Usual: 1000 mg BD *Exception: 1000 mg TDS
Metformin SR	850 mg	Usual dose: 850 mg BD	850 mg TDS
Metformin XR	500/750/1000 mg	Initial dose: 500 mg OD Usual dose: 2000 mg OD	2000 mg OD
Sulphonylureas			
Glibenclamide	5 mg	2.5 mg OD	10 mg BD
Gliclazide	80 mg	40 mg OM	160 mg BD
Gliclazide MR	60/30 mg	30 mg OM	120 mg OM
Glipizide	5 mg	2.5 mg OM	10 mg BD
Glimepiride	2/3 mg	1 mg OM	6 mg OM
Meglitinides			
Repaglinide	0.5/1/2 mg	0.5 mg with main meal	4 mg with main meals (not exceeding 16 mg daily)
α-glucosidase inhibitor			
Acarbose	50/100 mg	Initial dose: 50 mg OD Usual dose: 50-100 mg take at 1st bite of main meals	100 mg TDS
Thiazolidinedione			
Rosiglitazone	4/8 mg	4 mg OD	8 mg OD
Pioglitazone	15/30 mg	15 mg OD	45 mg OD
DPP4-inhibitors			
Sitagliptin	25/50/100 mg	25 mg OD	100 mg OD
Vildagliptin	50 mg	50 mg OD	50 mg BD
Saxagliptin	2.5/5 mg	2.5 mg OD	5 mg OD
Linagliptin	5 mg	5 mg OD	5 mg OD
SGLT2-inhibitors			
Dapagliflozin	5/10 mg	5 mg OD	10 mg OD
Canagliflozin	100/300 mg	100 mg OD	300 mg OD
Empagliflozin	10/25 mg	10 mg OD	25 mg OD
Luseogliflozin	2.5/5 mg	2.5 mg OD	5 mg OD
Ertugliflozin	5/15 mg	5 mg OD	15 mg OD
GLP1-RA			
Exenatide IR	5 µg/20 µL; 10 µg/40 µL	5 µg BD	10 µg BD
Exenatide ER	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
Semaglutide	0.25/0.5 mg	0.25 weekly	1.0 mg weekly

Note: Dose escalations will depend on tolerability and according to the PI.

Efficacy of various GLDs

	MET	SU	GLN	AGI	TZD	DPP4-i	SGLT2-i	GLP1-RA	Insulin
HbA_{1c} ↓ %	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	Both	PPG	PPG	FPG	Both	Both	Both	Both
Hypoglycaemia	↔	↑↑	↑	↔	↔	↔	↔	↔	↑↑
Weight change	↓	↑↑	↑	↔	↑↑	↔	↓–↓↓	↓↓	↑↑
GI symptoms	↑↑	↔	↔	↑↑	↔	↑	↔	↑↑	↔
CHF	↔	↔	↔	↔	↑	↔	↓↓	↔	↔
CVD	↓	↔	↔	↔	↔	↔	↓↓	↓↓	↔
Bone loss	↔	↔	↔	↔	↑	↔	↔	↔	↔
DKD	Avoid*	Hypo	Hypo	↔	Fluid ret'n	Dose adjustment	↓↓[a]	↓[†]	Hypo

** Avoid if eGFR < 30ml/min/1.73m²; † avoid if eGFR < 15 ml/min/1.73m²; [a]SGLT2-i can be used until dialysis is initiated and has proven reno-protection although glucose-lowering efficacy is reduced.*

Increased risk *Mild-mod risk* *Neutral* *Possible benefit* *Beneficial*

Note: refer to main CPG for important notations

Treatment algorithm: Newly diagnosed T2DM

Diagnosis of T2DM

Lifestyle modification[a]

HbA_{1c} <6.5% AND FPG <6.0 mmol/L	HbA_{1c} 6.5-7.4% OR FPG 6.0-7.9 mmol/L	HbA_{1c} 7.5-8.4% OR FPG 8.0-9.9 mmol/L	HbA_{1c} 8.5-10.0% OR FPG 10.0-13.0 mmol/L	HbA_{1c} >10.0% OR FPG >13.0 mmol/L[f]
Consider metformin monotherapy[b]	Mono- or dual-therapy[c] with	Dual combination therapy[e] with any combination of:	Triple combination therapy[e] with any combination of:	Basal/premixed insulin therapy + Combination therapy OR Intensive insulin therapy + OGLD
If post prandial is >11.0 mmol/L and/or metformin is not tolerated, consider one of the following:	Metformin[d] OR	Metformin	Metformin	
Meglitinide	SU	SU	SU	
AGI	DPP4-i	Meglitinide	Meglitinide	
DPP4-i	GLP1-RA	AGI	AGI	
• Follow-up with HbA_{1c} after 3-6 months	SGLT2-i	TZD	TZD	
• If HbA_{1c} ≤6.5%, continue with lifestyle modification. • If HbA_{1c} >6.5%[c]	• Optimise dose of GLD agent in subsequent 3-6 months. • Follow-up with HbA_{1c} after 3-6 months • If HbA_{1c} ≤6.5%, continue therapy	DPP4-i GLP1-RA SGLT2-i Insulin • Optimise dose of GLD agent in subsequent 3-6 months. • Follow-up with HbA_{1c} after 3-6 months • If HbA_{1c} ≤6.5%, continue therapy	DPP4-i GLP1-RA SGLT2-i Insulin • Optimise dose of GLD agent in subsequent 3-6 months. • Follow-up with HbA_{1c} after 3-6 months • If HbA_{1c} ≤6.5%, continue therapy	

- *Efficacious, low risk of hypoglycaemia and weight neutral*
- *Efficacious, risk of hypoglycaemia and weight gain*
- *Efficacious, low risk of hypoglycaemia and weight loss*
- *Moderate efficacy, low risk of hypoglycaemia and weight neutral*
- *Moderate efficacy, low risk of hypoglycaemia and weight gain*
- *Moderate efficacy, low risk of hypoglycaemia and weight loss*
- *Modest efficacy, low risk of hypoglycaemia and weight neutral*

c. Consider addition of DPP4-i (delays loss of glycaemic control) when initiated early.
Note: refer to main CPG for other important notations.

Treatment recommendations: Clinic follow-up

Lifestyle modification must be maintained at every juncture of T2DM treatment. It should include strategies to lose weight, correct diet and incorporate physical activities.[f]

3-6 months after initiation of therapy

HbA_{1c} above individualised target with lifestyle modification + existing therapy

0.5%-1% above target	1%-2% above target	>2% above target
Add **1 additional** GLD from different class OR Intensification of insulin (if already on insulin)[f]	Consider **2** GLDs from different classes* OR Intensification of insulin (if already on insulin)[f]	Initiation of insulin± GLP1-RA[f] OR Intensification of insulin[f]

Reassess HbA_{1c} after 3-6 months**

Note: refer to main CPG for important notations

Initiation and optimisation of insulin therapy

Newly diagnosed T2DM

- Symptomatic hyperglycaemia regardless of HbA_{1c} or FPG
- HbA_{1c} >10% or FPG >13.0 mmol/L
- T2DM on maximal OGLDs with HbA_{1c} >7% or, > individualised target

Pattern of hyperglycaemia FPG + PPG

Not adequately controlled on maximum OGLD ± GLP1-RA

- Add basal insulin 10 U OD OR 0.1-0.2 U/kg/day
- TITRATE based on FPG
- Choose evidence based titration algorithm
- If hypoglycaemia, reduce dose by 10-20%

- Premixed insulin OD/co-formulation OD at main meal

If HbA_{1c} above target despite adequate titration OR basal dose >0.5 U/kg OR FPG at target

If FPG at target but glucose high during the day, consider basal insulin analogue

- Co-formulation BD
- TITRATE based on individual need

Basal plus:
- Add prandial insulin 4 U/meal OR 10% of basal dose
- TITRATE prandial insulin by increasing 1-2 U OR 10-15% every 3 days
- If hypoglycaemia, reduce prandial insulin by 10-20%
- Stepwise addition of prandial insulin

- Premixed insulin BD
- TITRATE based on individual need

- Premixed analogue insulin TDS

- Basal bolus regimen

Suggested treatment approach for specific patient profiles

LIFESTYLE MODIFICATION + METFORMIN

(unless intolerant or contraindicated / ½ dose at DKD stage 3B, stop at DKD stages 4-5)

If HbA_{1c} not to individualised target

*Note: **Reaching HbA_{1c} is the priority (Targets individualised).** Cost of newer medications may render them inaccessible. Use therapies that have been shown to be efficacious and safe.*

Overweight / obese	Normal weight	Increased risk of hypoglycaemia	DKD Stage 3-5[a]	High risk CVD	ASCVD	Heart failure
Weight loss through lifestyle modification[e]	DPP4-i OR SU*	DPP4-i	SGLT2-i *(stop when initiating dialysis)*	GLP1-RA[k]	SGLT2-i / GLP1-RA	SGLT2-i
GLP1-RA/SGLT2-i	SU* *(if DPP4-i given)*	SGLT2-i	GLP1-RA[f] *(contraindicated at eGFR <15 ml/min/1.73m²)*	SGLT2-i	GLP1-RA *(if SGLT2-i given or vice-versa)*	GLP1-RA
GLP1-RA *(if SGLT2-i given or vice-versa)*	SGLT2-i	TZD	DPP4-i	DPP4-i[f] *(if not on GLP1-RA) OR SU*	DPP4-i[f] *(if not on GLP1-RA) OR SU**	DPP4-i[f] *(if not on GLP1-RA) OR SU**
DPP4-i *(if not on GLP1-RA)*	GLP1-RA[f]	GLP1-RA[f]	SU* *(not advisable in Stages 4-5)*	SU* *(if DPP4-i given)*	SU* *(if DPP4-i given)*	SU* *(if DPP4- given)*
SU*	Basal OR premixed insulin *(escalate to basal bolus/switch to analogues)*[g]	Low dose SU *(2nd generation)*	Basal OR premixed insulin *(escalate to basal bolus/switch to analogues)*[g]	TZD	TZD	Basal OR premixed insulin *(escalate to basal bolus/switch to analogues)*[g]
Basal OR premixed insulin *(escalate to basal bolus/switch to analogues)*[g]		Basal OR premixed OR basal/bolus insulin analogues		Basal OR premixed insulin *(escalate to basal bolus/switch to analogues)*[g]	Basal OR premixed insulin *(escalate to basal bolus/switch to analogues)*[g]	

Note: refer to main CPG for important notations.

Dosage of GLDs in renal failure

Generic Name	Usual dose*	Dose adjustment in renal failure		
		Mild (CKD 2) (GFR 60-89)	Moderate (CKD 3) (GFR 30-59)	Severe (CKD 4 & 5) (GFR <30)
Biguanide§				
Metformin	500-1000 mg BD	Continue	45-60: No dose adjustment <45: 50% dose reduction	Avoid
Sulphonylurea^				
Glibenclamide	5 mg OD-10 mg BD	Use with caution	Avoid	
Gliclazide	80 mg OD-160 mg BD	No dose adjustment		Caution
Gliclazide MR	30-120 mg OD	No dose adjustment		Caution
Glimepiride	1-6 mg OD	Initiate with 1 mg OD		≥15: Caution <15: Avoid
Glipizide	2.5 mg OD-10 mg BD	No dose adjustment		Caution
Meglitinides				
Repaglinide	0.5-4 mg TDS	No dose adjustment		Initiate at 0.5 mg with meals
Alpha-glucosidase Inhibitor				
Acarbose	25-100 mg TDS	50-100%		≥25: 50-100% <25: Avoid
Thiazolidinediones				
Pioglitazone	15-45 mg OD	No dose adjustment **(caution with fluid retention risk)**		
DPP4-i				
Sitagliptin	100 mg OD	No dose adjustment	≥50: No dose adjustment 30-<50: 50 mg OD	25 mg OD
Vildagliptin	50 mg OD-BD	No dose adjustment	≥50: No dose adjustment <50: 50 mg OD (limited data)	
Saxagliptin	2.5-5 mg OD	No dose adjustment	>50: No dose adjustment ≤50: 2.5 mg OD	
Linagliptin	2.5-5 mg OD	No dose adjustment		
GLP1-RAs				
Exenatide IR	5 µg/20 µL; 10 µg/40 µL	No dose adjustment	>50: No dose adjustment 30-50: Caution in initiating or escalating dose from 5 to 10 mcg	Avoid
Exenatide ER	2 mg weekly	No dose adjustment	>50: No dose adjustment 30-50: Use with caution	Avoid
Liraglutide	6 mg/mL	No dose adjustment	No dose adjustment	≥15: No dose adjustment <15: Avoid
	3 mg	No dose adjustment	No dose adjustment	Avoid
Lixisenatide	50 µg/mL; 100 µg/mL	No dose adjustment	No dose adjustment	Avoid
Dulaglutide	0.75-1.5 mg weekly	No dose adjustment	No dose adjustment	≥15: No dose adjustment <15: Avoid
Semaglutide	0.5-1.0 mg weekly	No dose adjustment	No dose adjustment	≥15: No dose adjustment <15: Avoid
SGLT2 Inhibitors¶				
Dapagliflozin	5-10 mg OD	No dose adjustment	45-60: No dose adjustment <45: Not recommended	Avoid
Canagliflozin	100-300 mg OD	No dose adjustment	45-60: 100 mg OD <45: Not recommended	Avoid
Empagliflozin	10-25 mg OD	No dose adjustment	No dose adjustment	Avoid
Ertugliflozin	5-15 mg OD	No dose adjustment	45-60: No initiation < 45: Not recommended	Avoid
Luseogliflozin	2.5-5 mg OD	No dose adjustment	<60: Not recommended	Avoid
Insulin				
Doses should be adjusted based on frequent monitoring to balance goals of glycaemic control with avoiding hypoglycaemia. Long-acting tends to accumulate longer than short-acting insulin.				

Dose escalation will depend on tolerability and according to the PI.
Note: refer to main CPG for important notations.