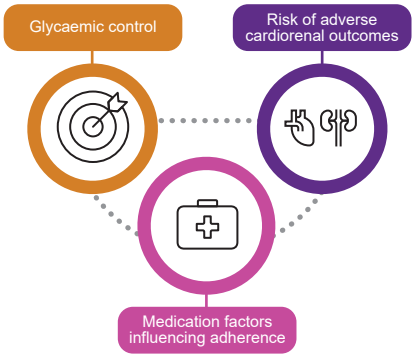
Type 2 diabetes mellitus

Personalising management with non-insulin diabetes medications

Appropriate treatment is integral to reducing the risk of complications and improving quality of life for patients with type 2 diabetes mellitus (T2DM). This resource focuses on personalising selection of non-insulin diabetes medications. Metformin remains a good treatment foundation for most patients with T2DM, given its established efficacy, safety profile, availability and cost. Choice of other medications should be individualised and include consideration of the three factors shown on the right and discussed below.



Glycaemic control

Treatment targets may differ based on patient circumstances. Set individual HbA1c target, monitor response to treatment and progress against goals, and adjust treatment accordingly.

Medication factors influencing adherence

Patient adherence is critical to treatment success. Consider the patient's preferences, needs and values, and involve them in discussions regarding choice of medication(s).

Side effect and safety profile

Assess and review **individual risk and tolerability** of side effects, and consider the overall medication safety profile.

Weight changes

Decrease weight: SGLT2i, GLP-1 RA, dual GIP/GLP-1 RA

Weight neutral: DPP-4i, acarbose

Increase weight: SU, TZD, meglitinide

Safety considerations: hypoglycaemia

Increased risk: SU, meglitinide

Safety considerations: others

Check individual product inserts for contraindications and precautions before prescribing (see reverse for summary).

Cost

Consider **long-term patient affordability**. Medications from newer classes are usually more costly than medications with generic options. See reverse for link to list of medications on government subsidy list.

Route and frequency of administration

Choose a dosing regimen that patients can accept and commit to, based on **individual preferences** (see reverse for available formulations).

Route

Oral: all non-insulin diabetes medications (semaglutide only for GLP-1 RA)

Subcutaneous: all GLP-1 RA, dual GIP/GLP-1 RA

Frequency

Oral: options from one to four doses per day

Subcutaneous: options of one dose per day or one dose per week

Risk of adverse cardiorenal outcomes

Patients with T2DM who need to reduce their risk of adverse cardiorenal outcomes may benefit from newer diabetes medications that have been shown to reduce these risks.[a] Consider prescribing these medications to reduce the risk of adverse cardiorenal outcomes[b] (see below).

Reducing risk of major adverse cardiovascular events (MACE)

SGLT2i

Medication with proven benefit	Studied in T2DM population[a] with
Canagliflozin	ASCVD, CV risk
Empagliflozin	ASCVD

GLP-1 RA

Medication with proven benefit	Studied in T2DM population[a] with
Dulaglutide	ASCVD, CV risk
Liraglutide	ASCVD, CV risk
Semaglutide SC	ASCVD, CV risk

While trials included both patients with ASCVD and patients with multiple cardiovascular (CV) risk factors (no ASCVD), **evidence for reduction of MACE (CV death, non-fatal myocardial infarction and non-fatal stroke) with SGLT2i and GLP-1 RA is more certain for patients with established ASCVD.**

Reducing risk of hospitalisation for heart failure

SGLT2i

Medication with proven benefit	Studied in T2DM population[a] with
Canagliflozin	ASCVD, HF, CV risk
Dapagliflozin	ASCVD, HF*, CV risk
Empagliflozin	ASCVD, HF*
Ertugliflozin	ASCVD, HF

* Separately studied in trials involving patients with heart failure, with or without T2DM.

Reducing risk of adverse renal outcomes[c]

SGLT2i‡

Medication with proven benefit	Studied in T2DM population[a] with
Canagliflozin	ASCVD, Renal†, CV risk
Dapagliflozin	ASCVD, Renal†, CV risk
Empagliflozin	ASCVD, Renal†

GLP-1 RA

Medication with proven benefit	Studied in T2DM population[a] with
Dulaglutide	ASCVD, Renal, CV risk
Liraglutide	ASCVD, Renal, CV risk
Semaglutide SC	ASCVD, Renal, CV risk

† Separately studied in trials involving patients with albuminuric kidney disease, with T2DM (canagliflozin, dapagliflozin, empagliflozin) or without T2DM (dapagliflozin, empagliflozin).

‡ In renal impairment, dose adjustment(s) may be required, with eGFR cut-offs varying between medications and indications. See reverse for summary, and check individual product inserts for full details.

ASCVD	Atherosclerotic cardiovascular disease	CV risk	Multiple cardiovascular risk factors, e.g., hypertension, dyslipidaemia, obesity and smoking	HF	Heart failure	Renal	Kidney damage or reduced kidney function (definition differed between trials)[c]

Cardiovascular and renal outcome trials included patients with T2DM with the above conditions. Conditions may coexist, except for ASCVD and CV risk.

A note about insulin: Commence insulin without delay for patients with T2DM when clinically indicated, e.g., for symptomatic hyperglycaemia, or to maintain glycaemic control when optimal treatment with other T2DM medications is not enough.

Scan the QR code for ACE Clinical Guidance on *Initiating basal insulin in T2DM*

[a] Based on placebo-controlled cardiovascular or renal outcome trials in T2DM patients; most patients enrolled were on metformin at baseline. [b] Outcomes discussed do not take into consideration subgroup analyses, unless stated. [c] Definitions of adverse renal outcomes differed between trials; most used a composite of renal endpoints (e.g., doubling of serum creatinine level, new-onset macroalbuminuria, ≥40% decrease in eGFR, end-stage kidney disease, or death from renal causes).

CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; SC, subcutaneous; SGLT2i, sodium-glucose co-transporter 2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione

ACE agency for care effectiveness
MINISTRY OF HEALTH SINGAPORE

Non-insulin type 2 diabetes medications in Singapore

ACECUES CLINICAL UPDATE SERVICE

Medication*	Dosage and route (oral unless specified)	Dose adjustments in renal impairment	Common side effects	Additional considerations
Alpha-glucosidase inhibitor	**Inhibits intestinal α-glucosidase, slowing absorption of carbohydrates**			
Acarbose	Initial: 50mg TDS Max: 100–200mg TDS	CrCl ≥25: not required CrCl <25: contraindicated	GI effects (flatulence, diarrhoea, abdominal pain)	**Contraindications:** Chronic intestinal disorders **Monitoring:** Liver function test
Biguanide	**Decreases hepatic glucose production**			
Metformin	**IR:** Initial: 500–850mg BD–TDS Max: 850–1000mg TDS **XR:** Initial: 500mg OD Max: 2g OD or 1g BD	GFR 30–59: review risk of lactic acidosis and reduce starting and maximum dose (based on GFR) GFR <30: contraindicated	GI effects (nausea, vomiting, diarrhoea, abdominal pain), loss of appetite, taste disturbance	**Contraindications:** Hepatic insufficiency; acute metabolic acidosis; acute conditions that can alter renal function; diseases which may cause tissue hypoxia (e.g., decompensated renal failure, recent myocardial infarction) **Monitoring:** Signs and symptoms of lactic acidosis, vitamin B12
DPP-4 inhibitor	**Prolongs incretin action, enhancing glucose-dependent insulin production and suppressing glucagon secretion**			
Linagliptin (Trajenta)	5mg OD	Not required	Nasopharyngitis, URTI, cough, headache, dizziness	**Precautions:** Reports of acute pancreatitis, severe arthralgia, severe skin reactions e.g., bullous pemphigoid; saxagliptin – possible increased risk of heart failure; vildagliptin – not recommended in hepatic impairment
Saxagliptin (Onglyza)	2.5–5mg OD	eGFR <45 or HD: 2.5mg OD		
Sitagliptin (Januvia)	100mg OD	eGFR 30–45: 50mg OD eGFR <30 or HD/PD: 25mg OD		
Vildagliptin (Galvus)	50mg OD–BD	CrCl <50 or HD: 50mg OD		
Dual GIP/GLP-1 receptor agonist	**Enhances first- and second-phase insulin secretion, and reduces glucagon levels, both in a glucose-dependent manner**			
Tirzepatide (Mounjaro)	**SC:** Initial: 2.5mg once weekly Max: 15mg once weekly	Not required	GI effects (nausea, diarrhoea, decreased appetite, vomiting)	**Contraindications:** MEN 2, personal or family history of MTC **Precautions:** pancreatitis, risk of thyroid C-cell tumours, acute kidney injury and gallbladder disease, worsening of diabetic retinopathy, severe GI reactions **Impact on weight:** Associated with weight loss
GLP-1 receptor agonist†	**Enhances glucose-dependent insulin production, suppresses glucose-dependent glucagon secretion, slows gastric emptying, suppresses appetite**			
Dulaglutide (Trulicity)	**SC:** Initial: 0.75mg once weekly Max: 1.5mg once weekly	Not required. Not recommended in ESKD (eGFR <15)	GI effects (nausea, diarrhoea, vomiting, constipation, abdominal pain, dyspepsia), headache, fatigue, nasopharyngitis, injection site reactions (SC route)	**Precautions:** Not recommended in severe hepatic impairment; possible risk of acute pancreatitis and dehydration (may lead to acute renal failure or worsening renal impairment); semaglutide SC – exercise caution in patients with history of diabetic retinopathy or treated with insulin **Impact on weight:** Associated with weight loss
Liraglutide (Victoza)	**SC:** Initial: 0.6mg OD Max: 1.8mg OD			
Semaglutide (Ozempic – SC, Rybelsus – PO)	**SC:** Initial: 0.25mg once weekly Max: 1mg once weekly **PO:** Initial: 3mg OD Max: 14mg OD			
Meglitinide	**Increases insulin secretion**			
Repaglinide (Novonorm)	Initial: 0.5–1mg per dose Max: 4mg QDS	Not required, but titrate with caution	Hypoglycaemia, GI effects (abdominal pain, diarrhoea)	**Contraindications:** Severe hepatic function disorder; diabetic ketoacidosis; concomitant gemfibrozil **Precautions:** Impaired liver function, may increase incidence of acute coronary syndrome
SGLT2 inhibitor	**Prevents glucose reabsorption from urine in the proximal tubules**			
Canagliflozin (Invokana)	Initial: 100mg OD Max: 300mg OD	eGFR 45–60: max 100mg OD‡ eGFR <45: discontinue/ do not initiate‡	Genital mycotic infections, urinary tract infection, pollakiuria and polyuria	**Precautions:** Not recommended for use in severe hepatic impairment; reports of (euglycaemic) diabetic ketoacidosis, necrotising fasciitis of the perineum (Fournier's gangrene), symptomatic hypotension (especially in elderly and those on diuretics) **Monitoring:** Canagliflozin – patients with a higher risk for amputation events **Impact on weight:** Associated with weight loss ‡ The listed eGFR cut-offs are based on use for glycaemic control. When using for other benefits where indicated (e.g., reducing risk of ESKD or risk of hospitalisation for heart failure), the eGFR cut-off may be lower. Check individual product inserts for further details before prescribing.
Dapagliflozin (Forxiga)	10mg OD	eGFR <45: reduced efficacy‡ eGFR <25: initiation not recommended‡		
Empagliflozin (Jardiance)	Initial: 10mg OD Max: 25mg OD	eGFR <45: discontinue/ do not initiate‡		
Ertugliflozin (Steglatro)	Initial: 5mg OD Max: 15mg OD	eGFR <60: do not initiate‡ eGFR 45–60: consider discontinuation‡ eGFR <45: discontinue‡		
Sulphonylurea	**Increases insulin secretion**			
Glibenclamide	Initial: 2.5–5mg/day in 1–2 doses Max: 20mg/day	Contraindicated in severe renal insufficiency	Hypoglycaemia, GI effects (abdominal pain, nausea, vomiting, dyspepsia, diarrhoea, constipation), weight gain	**Contraindications:** Severe hepatic insufficiency; diabetic ketoacidosis; diabetic coma **Precautions:** Patients with G6PD deficiency; conditions that increase risk of developing hypoglycaemia (e.g., excessive exercise, alcohol consumption, malnutrition, use of more than one diabetes medication, renal impairment); glibenclamide – avoid in elderly and those with renal impairment due to increased risk of severe and recurrent hypoglycaemia
Gliclazide	**IR:** Initial: 80mg OD Max: 160mg BD **MR:** 30mg to 120mg OD			
Glimepiride (Amaryl)	Initial: 1mg OD Max: 6mg OD			
Glipizide	Initial: 2.5–5mg OD Max: 20mg/day in 2 doses			
Tolbutamide	Initial: 1–2 g/day in 2–3 doses Max: 3g/day			
Thiazolidinedione	**Increases insulin sensitivity**			
Pioglitazone (Actos)	Initial: 15–30mg OD Max: 45mg OD	Not required, but avoid in dialysis patients due to lack of information	URTI, headache, sinusitis, myalgia, weight gain	**Contraindications:** Cardiac failure or history of cardiac failure; hepatic impairment; active or history of bladder cancer; uninvestigated macroscopic haematuria **Monitoring:** Signs and symptoms of bladder cancer or liver injury, fractures, fluid retention and heart failure

Click here or scan the QR code for list of medications on government subsidy list.

Information is referenced from local product inserts or consolidated product monographs; refer to product inserts for full details before prescribing. Information from other references (e.g., international guidelines) may differ. This table is not exhaustive of the subject matter. Clinical judgement should be exercised at all times when making decisions for an individual patient.

*Includes medications with single active ingredient registered in Singapore. For fixed-dose combination products, refer to information on individual components.
†Lixisenatide is not listed as it is only available as a combination product with insulin glargine.

BD, twice a day; CrCl, creatinine clearance in mL/min; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate in mL/min/1.73m^2; ESKD, end stage kidney disease; G6PD, glucose-6-phosphate dehydrogenase; GFR, glomerular filtration rate in mL/min/1.73m^2; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HD, haemodialysis; IR, immediate release; max, maximum; MEN 2, multiple endocrine neoplasia syndrome type 2; MR, modified release; MTC, medullary thyroid carcinoma; OD, once daily; PD, peritoneal dialysis; PO, oral; QDS, four times a day; SC, subcutaneous; SGLT2, sodium-glucose co-transporter 2; TDS, three times a day; URTI, upper respiratory tract infection; XR, extended release

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