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About the Agency

The Agency for Care Effectiveness (ACE) is the national health technology assessment agency in Singapore residing within the Ministry of Health (MOH). ACE develops evidence-based "Appropriate Care Guides" or ACGs to guide a specific area of clinical practice. ACGs are aimed at complementing MOH Clinical Practice Guidelines when these are available, by providing additions and updates as reflected in the evidence at the time of development, and incorporating cost-effectiveness considerations where relevant. The ACGs are not exhaustive of the subject matter. When using the ACGs, the responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional. This ACG will be reviewed 3 years after publication, or earlier, if new evidence emerges that requires substantive changes to the recommendations.

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Practical advice for patients



Insulin administration and storage

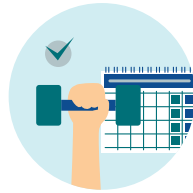
Advise patients to:

- Inspect insulin to ensure that it looks as it should (cloudy versus clear). Do not use if clumping, frosting, precipitation, or changes in colour and appearances occur.
- Inject insulin subcutaneously into the abdomen, arms, thighs or buttocks. Note that absorption rates of insulin vary from site to site. Be consistent and do not massage injection sites.
- Avoid areas with bruises, scar tissue and areas near joints, the groin and the navel.
- Rotate injection sites regularly within one area to avoid the development of lipohypertrophy.
- Store unopened insulin in the fridge between 2°C and 8°C. Do not freeze.
- Once insulin is in use, do not store in the fridge but keep in a cool area below 30°C for up to 4 or 6 weeks (refer to manufacturer's guidelines).
- Discard used syringes and pen needles in a puncture-resistant container (hard plastic/metal/sharps container) with a secured lid. Do not reuse them.



Diet

- Advise patients regarding healthy eating habits. Skipping or delaying meals, or changing the amount or type of food can affect their blood glucose levels.
- Advise patients who are on fixed insulin doses that they need consistent patterns of carbohydrate intake.
- Refer patients to a dietitian if available.



Fasting and exercise

- Encourage patients to discuss any changes in diet (including religious fasting) and physical activities as their insulin requirements may change.
- Before patients start fasting (e.g. during Ramadan):
 - » Assess their suitability to fast.
 - » Discuss risks associated with fasting and address any problems encountered during previous fasts.
 - » Reinforce SMBG and how to prevent and manage hypoglycaemia.
 - » Advise them to maintain a healthy and balanced diet when they break their fast.



Sick days

- Blood glucose levels usually rise when a patient is ill. Advise patients to continue their insulin and monitor their blood glucose more regularly.
- Encourage patients not to skip meals but to take smaller, more frequent meals or to drink sweetened juices or liquid supplements if their appetite decreases.



Travel

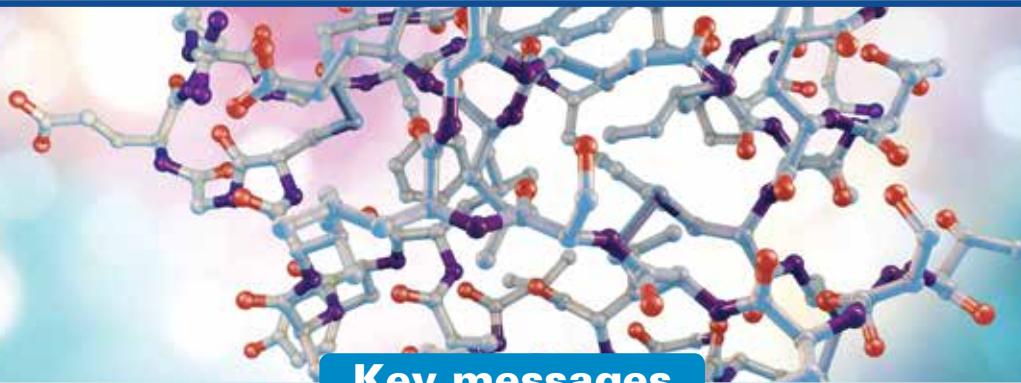
- Remind patients to bring sufficient insulin, syringes or pen needles, and to keep them in carry-on baggage.
- Remind them to carry some sweets or biscuits in case of hypoglycaemia.
- Encourage them to obtain a doctor's letter certifying that they need their insulin and needles at all times.



Initiating basal insulin in type 2 diabetes mellitus

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Key messages

- 1 Start insulin therapy if glycaemic goals are not met on oral glucose-lowering agents alone.
- 2 Initiate with basal insulin, such as intermediate- or long-acting insulin.
- 3 When initiating insulin, review concomitant oral glucose-lowering agents. Continue metformin +/- SGLT-2 inhibitors where appropriate.
- 4 Educate patients and their caregivers about taking preventative measures for hypoglycaemia.

When to initiate insulin

One in three Singaporeans with diabetes has poor glycaemic control, increasing the risk of diabetes-related complications.¹ In patients with type 2 diabetes mellitus (T2DM), oral glucose-lowering agents are usually successful in achieving initial glycaemic control but are often unable to do so in the long term. Among available agents, insulin has the greatest glucose-lowering potential. It should be initiated when patients are unable to reach their glycaemic goals on oral agents alone or in those with symptomatic hyperglycaemia.

Many patients and clinicians are reluctant to initiate insulin. It is often delayed for up to 5 years in patients with poor glycaemic control, even in the presence of diabetes-related complications.² Barriers to insulin therapy include stigma and perceived failure, fear of injection and pain, concerns about weight gain and hypoglycaemia.

How to initiate insulin

A common approach to initiating insulin is to start basal insulin once daily. Basal insulin is used to control fasting blood glucose.

Intermediate-acting insulin isophane, or neutral protamine Hagedorn (NPH), has traditionally been used. It is usually injected once daily at bedtime. Long-acting insulin analogues (LAIAs) are as effective as NPH in lowering fasting blood glucose. LAIAs are associated with fewer hypoglycaemic episodes, especially nocturnal hypoglycaemia, but are more expensive than insulin NPH.³

Among LAIAs, insulin glargine and insulin detemir are comparable in efficacy and safety. However, to achieve the same glycaemic control, insulin glargine is usually injected once daily, while a twice-daily dose of insulin detemir may be needed.⁴ Consider the cost of insulin in weighing up the choices.

Table 1: Types and profiles of basal insulins

Registered compounds (Brand)	Dosage form	Onset	Peak	Duration	Dosing
Intermediate-acting					
Isophane/NPH (Humulin N or Insulatard)	U-100 vial	1–4 h	8–12 h	12–20 h	Once to twice daily
	U-100 cartridge				
Long-acting (analogues)					
Glargine (Lantus)	U-100 vial	1–4 h	No peak	24 h	Once daily [†]
	U-100 cartridge				
	U-100 prefilled pen				
Glargine biosimilar (Basaglar)	U-100 cartridge U-100 prefilled pen	1–4 h	No peak	24 h	
Glargine (Toujeo)*	U-300 prefilled pen	6 h	No peak	24–36 h	Once daily
Detemir (Levemir)	U-100 prefilled pen	1–4 h	No peak	18–24 h	Once to twice daily

Dosage forms in **BOLD** denote availability on government subsidy and assistance list.

*U-300 glargine (Toujeo) is three times more concentrated than U-100 glargine per volume used. It has a longer duration of action and may be useful in patients who require larger doses of basal insulin.

[†]Patients with high doses may require twice-daily dosing.



Address the barriers

Reinforce the progressive nature of T2DM due to β -cell failure.

Assure patients the need for insulin is not a failure or punishment.

Educate patients regularly on:

- insulin administration and storage
- diet
- dose adjustments for fasting, exercise, sick days and travel
- self-monitoring of blood glucose and insulin dose titration
- hypoglycaemia prevention and management.

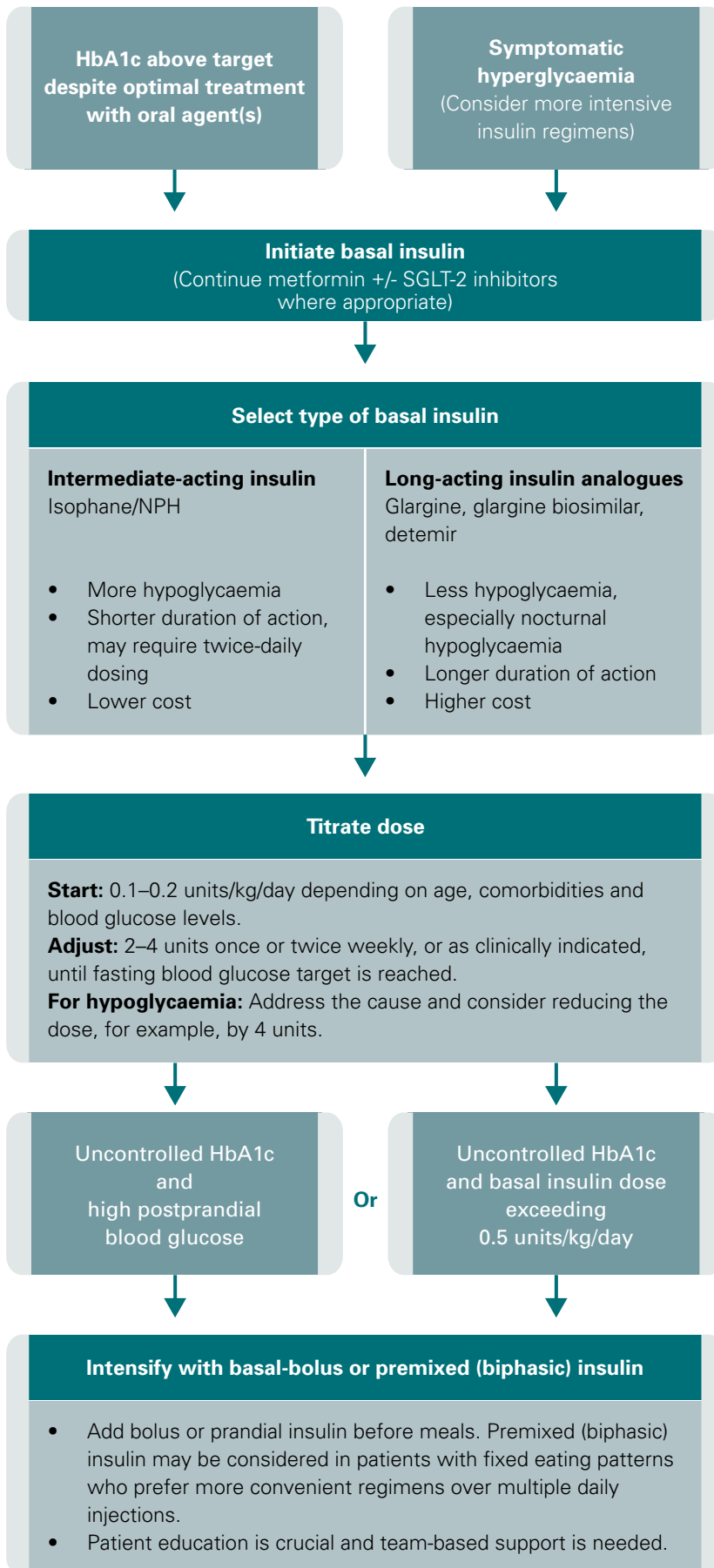


Insulin glargine biosimilars

Biosimilar insulin glargine has recently been registered in Singapore and is non-inferior to reference insulin glargine in efficacy and safety.⁵ Biosimilars are biological products with similar physicochemical characteristics, biological activity, safety and efficacy compared to their originator reference products.⁶ They offer cost savings although this is generally smaller in magnitude compared to generics.

Biosimilars are not identical and the decision to switch between products should be evaluated by the clinician. Cartridges for biosimilars cannot be used in devices for the originator reference product and vice versa. Include brand names when prescribing to distinguish between products and minimise errors.

Figure 1. Algorithm for insulin therapy



Review concomitant oral agents

Using metformin with insulin reduces weight gain, HbA1c and insulin dose compared to insulin alone.⁷

Combining SGLT-2 inhibitors with insulin also reduces HbA1c and body weight.⁸

Using sulfonylureas or meglitinides with insulin can improve glycaemic control. However, they should be used with caution as they may also increase the risk of hypoglycaemia and weight gain.⁹

(Refer to the ACG on "Oral glucose-lowering agents in T2DM" for clinical considerations for each agent.)

Self-monitoring of blood glucose (SMBG)

SMBG allows patients to assess their response to therapy and is useful to help detect hypoglycaemia.

If basal insulin is given once daily at bedtime, once-daily SMBG pre-breakfast is useful to guide dose adjustment.

Bolus and premixed (biphasic) insulins

Bolus or prandial insulin has a short or rapid onset of action and is given before meals to control postprandial hyperglycaemia. Premixed (biphasic) insulin incorporates a short- or rapid-acting insulin with an intermediate-acting insulin to manage both prandial and basal insulin needs.

Preventing and managing hypoglycaemia

Hypoglycaemia (blood glucose level below 4 mmol/L) is a potentially serious adverse effect of insulin therapy. On average, a patient with insulin-treated T2DM may experience two hypoglycaemic episodes per month.¹⁰ Hypoglycaemia is, therefore, a major limiting factor in achieving good glycaemic control. Prevention and prompt management of hypoglycaemia are crucial.

Hypoglycaemia is associated with many symptoms (Table 2) but is sometimes asymptomatic. This is known as “hypoglycaemia unawareness” and may be detected through blood glucose monitoring.

Patients who are at an increased risk of hypoglycaemia include those with:

- advanced age
- renal impairment
- intensive or high dose insulin regimens
- poor oral intake or prolonged fasting with high activity levels
- concurrent illness such as infection or sepsis.

Practice points:

- Educate patients and their caregivers about hypoglycaemia and its management (Table 2).
- Advise more vigilant monitoring in patients who are at an increased risk of hypoglycaemia.
- Encourage patients to keep a record of each hypoglycaemic episode and review this at each clinic visit.
- Consider less stringent HbA1c targets in patients with advanced age, renal impairment or multiple comorbidities.
- Review insulin regimens and glycaemic targets in patients with hypoglycaemic unawareness or frequent episodes of severe hypoglycaemia.

“Hypoglycaemia unawareness (HU)”

HU or “impaired awareness of hypoglycaemia” significantly increases the risk of severe hypoglycaemia and this has been reported in 9 to 18% of patients with insulin-treated T2DM.¹¹

HU occurs when a patient does not experience the typical early warning symptoms of hypoglycaemia (tremors, palpitation, sweating) when their blood glucose is low. This may occur in patients with repeated hypoglycaemic episodes or in those with concomitant autonomic neuropathy.

Advise patients with HU to raise their glycaemic targets for several weeks to avoid hypoglycaemia.

Table 2. Hypoglycaemia and its management

	Signs and symptoms	Management
Mild to moderate hypoglycaemia (Self-treatment is possible)	Tremors, palpitations, sweating, excessive hunger, headaches, mood changes, irritability, decreased attentiveness, paraesthesias or visual disturbances.	15-15 rule <ul style="list-style-type: none"> • Glucose 15 g* is preferred (e.g. dextrose powder or 3 teaspoons of Glucolin) although any form of carbohydrate that contains glucose may be used (e.g. ½ cup juice or regular soda, 3–4 teaspoons of sugar). • Advise patients and their caregivers to re-check blood glucose levels after 15 minutes. Repeat treatment (glucose 15 g*) and seek medical advice when the patient's symptoms do not improve or when blood glucose level remains below 4 mmol/L. • Once blood glucose level is above 4 mmol/L, advise patients to consume a meal or snack to prevent the recurrence of hypoglycaemia.
Severe hypoglycaemia (Requires assistance)	Unresponsiveness, unconsciousness, seizures or coma.	<ul style="list-style-type: none"> • Call 995 for an ambulance and seek urgent medical assistance. • Do not administer anything orally.

*30 g glucose is needed if blood glucose level below 2.8 mmol/L.