Appropriate Care Guide (ACG)

Initiating basal insulin in type 2 diabetes mellitus

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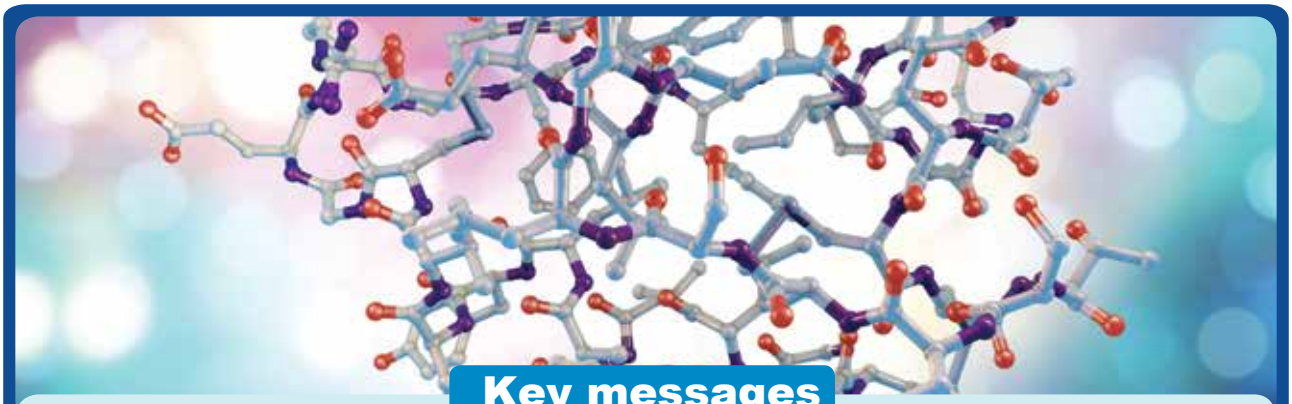

Key messages

1. Start insulin therapy if glycaemic targets are not met on non-insulin glucose-lowering agents alone.
2. Insulin therapy is usually started by initiating basal insulin (intermediate- or long-acting insulin).
3. When starting insulin therapy, review concomitant glucose-lowering agents and continue them as appropriate.
4. Educate patients and their caregivers about prevention and management of hypoglycaemia.

When to start insulin therapy

Approximately 1 in 3 Singaporeans with diabetes mellitus have poor glycaemic control and hence are at increased risk of diabetes-related complications.[1-4] For patients with type 2 diabetes mellitus (T2DM), non-insulin glucose-lowering agents are usually successful in achieving initial glycaemic control but may not be able to do so in the long term. Insulin therapy should be started when patients with T2DM are unable to reach their glycaemic targets despite optimal treatment with non-insulin agents alone or for those with symptomatic hyperglycaemia.[5]

Many patients and clinicians are reluctant to start insulin therapy in T2DM. It is often delayed for up to five years for patients with poor glycaemic control, even in the presence of diabetes-related complications.[6] Barriers to insulin therapy include stigma and perceived failure, fear of injection and pain, concerns about weight gain, and hypoglycaemia.[7] Regular patient education can help address these barriers.[8]

ACE agency for care effectiveness

MINISTRY OF HEALTH SINGAPORE

Academy of Medicine, Singapore
Chapter of Endocrinologists, CPS
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How to initiate basal insulin

A common approach to starting insulin therapy in T2DM is to initiate basal insulin. Basal insulin is used to control fasting blood glucose and can be categorised into intermediate- or long-acting according to the time-action profile (Table 1).

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 events, especially nocturnal hypoglycaemia, but are more expensive than insulin NPH.[9]

The various LAIAs registered in Singapore (insulin detemir, insulin glargine, insulin degludec) are comparable in efficacy and safety. However, to achieve the same glycaemic control, insulin degludec and insulin glargine are usually injected once daily, while a twice-daily dose of insulin detemir may be needed.[10,11] With a longer duration of action, insulin degludec results in less nocturnal hypoglycaemia than insulin detemir and insulin glargine.[11-14] Include cost considerations in weighing up the choices of basal insulin.

Table 1. Types and profiles of basal insulin

Registered compounds (Brand)	Dosage form	Onset	Peak	Duration	Dosing
Intermediate-acting					
Isophane/NPH (Humulin N or Insulatard)	**U-100 vial** **U-100 cartridge**	1–4 h	8–12 h	12–20 h	Once to twice daily
Long-acting (analogues)					
Detemir (Levemir)	**U-100 prefilled pen** U-100 cartridge	1–4 h	No peak	18–24 h	Once to twice daily
Glargine (Lantus)	**U-100 vial** **U-100 prefilled pen**	1–4 h	No peak	24 h	Once daily*
Glargine biosimilar (Basalog One)	U-100 prefilled pen	1–4 h	No peak	24 h	
Glargine biosimilar (Semglee)	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
Degludec (Tresiba)	U-100 prefilled pen U-200 prefilled pen	1–4 h	No peak	42 h	Once daily

NPH, neutral protamine Hagedorn

*Dosage forms in **bold** denote availability on government subsidy list.*

** Patients requiring high doses may need twice-daily dosing.*

† U-300 glargine has a longer duration of action than U-100 glargine due to the lower injection volume needed for the same insulin dose (as U-300 is more concentrated than U-100), and the smaller precipitate surface area leads to more sustained release.

Address the barriers

Explain to patients the progressive nature of T2DM due to ß-cell failure.

Assure patients that the need for insulin is no one's fault and is not a 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

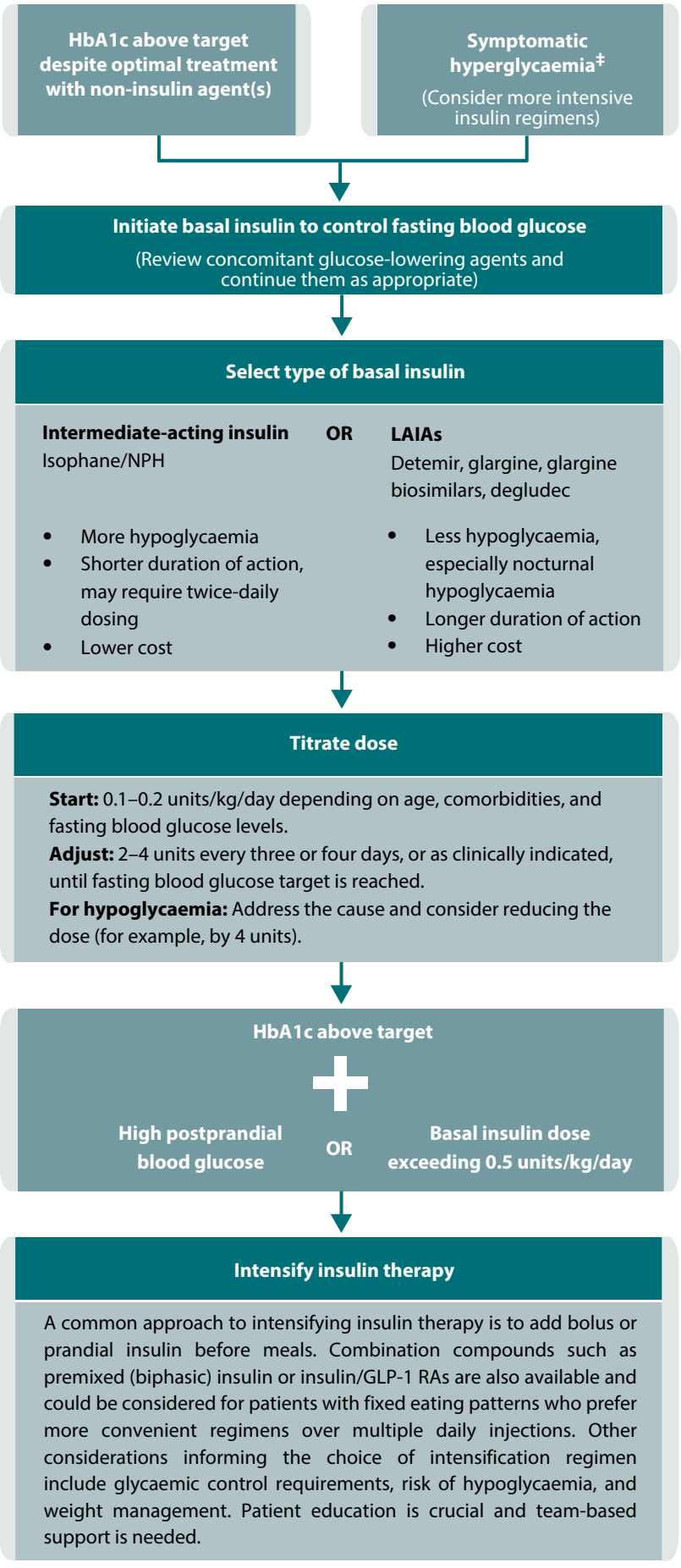
Notes on insulin prescribing

Different insulin compounds (Table 1), even within the same time-action category, are not identical and the decision to switch between products should be evaluated by the clinician. Include brand names when prescribing to distinguish between products and minimise errors.

Biosimilars are biological products with physicochemical characteristics, biological activity, safety, and efficacy similar to their originator reference products.[15] They offer cost savings, although generally smaller in magnitude compared to generics.

Insulin glargine biosimilars are non-inferior to reference insulin glargine in efficacy and safety.[16]

Figure 1. Algorithm for insulin therapy



GLP-1 RAs, glucagon-like peptide-1 receptor agonists; LAIAs, long-acting insulin analogues; NPH, neutral protamine Hagedorn

‡ *Symptoms of hyperglycaemia include polyuria, polydipsia, blurry vision, and weight loss.*

Review concomitant glucose-lowering agents

Other glucose-lowering agents can be used together with insulin therapy to improve glycaemic control over insulin alone, and this may reduce insulin requirements.[17-19] Some agents could be chosen for their positive effects beyond glycaemic control, such as a sodium-glucose cotransporter-2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor agonist for their cardiovascular or renal benefits, particularly for patients with relevant comorbidities.[20-22] Another example is that combining metformin or an SGLT-2 inhibitor with insulin may reduce weight gain associated with insulin therapy.[23,24]

Adverse effects of concomitant agents need to be considered as well. Notably, thiazolidinediones are usually discontinued upon starting insulin therapy due to increased risk of oedema and heart failure.[17] Using a sulfonylurea or meglitinide with insulin may increase the risk of hypoglycaemia and weight gain.[25]

Review the use of concomitant glucose-lowering agents regularly, including the patient's need for them, taking into account their benefits and risks.

Blood glucose monitoring (BGM)

BGM enables better assessment of the patient's insulin needs (including needs regarding control of fasting or postprandial blood glucose, and titration of insulin dose), response to therapy, and is useful to help detect hypoglycaemia. Continuous glucose monitoring devices are also available and could be considered for patients who need more frequent glucose monitoring.

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

Bolus and premixed (biphasic) insulin

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 events per month.[26] 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 not perceived or experienced by the patient, including lack of early warning symptoms. This is known as hypoglycaemia unawareness and can be detected through blood glucose monitoring.

Patients who are at 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
- Cognitive dysfunction

Practice points

- Educate patients and their caregivers about hypoglycaemia and its management (Table 2).
- Advise more vigilant monitoring for patients who are at increased risk of hypoglycaemia.
- Encourage patients to keep a record of each hypoglycaemic event (including possible causes), and review this at each clinic visit.
- Consider less stringent glycaemic targets for certain patients as appropriate (such as those with advanced age, renal impairment, or multiple comorbidities).
- Review insulin regimens (and concomitant glucose-lowering agents) as well as glycaemic targets for patients with hypoglycaemia unawareness or frequent hypoglycaemia.

Hypoglycaemia unawareness (HU)

HU or impaired awareness of hypoglycaemia significantly increases the risk of severe hypoglycaemia, and HU has been reported in 9 to 18% of patients with insulin-treated T2DM.[27]

Patients with HU do not experience or perceive typical early warning symptoms of hypoglycaemia (such as tremors, palpitations, sweating) when their blood glucose is low. This may occur in patients with repeated hypoglycaemic events or in those with concomitant autonomic neuropathy.

Advise patients with HU to raise their glycaemic targets for several weeks to months to avoid hypoglycaemia.[28-30]

Table 2. Hypoglycaemia and its management

	Typical symptoms and signs	Management
Mild to moderate hypoglycaemia (Self-management is possible)	Tremors, palpitations, sweating, excessive hunger, headaches, mood changes, confusion, irritability, decreased attentiveness, paraesthesias, or visual disturbances.	**15-15 rule** • **Glucose 15 g**[§] is preferred (for example, dextrose powder or 3 teaspoons of Glucolin), although any form of carbohydrate that contains glucose can be used (for example, 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 or signs do not improve or when blood glucose level remains < 4 mmol/L. • Once blood glucose level is ≥ 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.	• Call 995 for an ambulance and seek urgent medical assistance. • Do not administer anything orally.

[§] 30 g glucose is needed if blood glucose level < 2.8 mmol/L.

Practical advice for patients

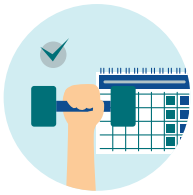
Insulin administration and storage

Advise patients to:

- Inspect insulin to ensure that it looks as it should. For example, NPH should look cloudy, while LAIAs should appear clear.
- Do not use if there is clumping, frosting, precipitation, change in colour, or if uncertain about the appearance.
- Inject insulin subcutaneously into the abdomen, arms, thighs, or buttocks. Note that absorption rates of insulin vary between body areas. Keep to one area and do not massage injection sites.
- Avoid areas with bruises, scar tissue, parts 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, keep in a cool area below 30°C for up to 4, 6, or 8 weeks depending on product characteristics (refer to product information leaflet).
- Discard used syringes and needles in a puncture-resistant container (hard plastic/metal/sharps container) with a secured lid. Do not reuse them.

Diet

- Advise patients regarding a healthy and balanced diet. 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 or another suitably trained healthcare professional for dietary advice, if available.



Fasting and physical activity

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

Sick days

- Blood glucose levels may 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 and injection/testing equipment, and to keep them in carry-on baggage.
- Remind them to carry glucose-containing sweets or biscuits in case of hypoglycaemia.
- Ensure that patients have a doctor's letter certifying that they need their insulin and injection/testing equipment at all times.

References

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