North Central London
Joint Formulary Committee

Insulin for Adults with Type 2 Diabetes

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Document management

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Contents

1. Target audience

Secondary and Primary care

2. Purpose

The guideline provides recommendation on the following areas of type 2 diabetes (T2DM) management:

- Clinical monitoring of blood glucose control: HbA1c, self-monitoring blood glucose
- Insulin regimens
- Choice of insulins

This guideline does not cover:

- Oral hypoglycaemic agents (OHAs) and GLP-1 receptor agonists (GLP-1 RA) in insulin naïve patients with T2DM
- OHAs and GLP-1RAs as adjuvant to insulin in patients with T2DM
- Children and young people with T2DM
- People with type 1 or other types of diabetes
- Preconception care in women with type 2 diabetes and diabetes in pregnancy
- Management of microvascular and microvascular diabetic complications
- Broader management of patients with T2DM e.g. diagnosis, educational programs

3. Abbreviations

BMI	Body Mass Index
GLP-1 RA	Glucagon-like peptide-1 (GLP-1) receptor agonists
LAIA	Long-acting insulin analogue
NICE	National Institute for Health and Care Excellence
NPH	Neutral Protamine Hagedorn (human insulin)
OHA	Oral hypoglycaemic agents
T2DM	Type 2 diabetes mellitus

4. Introduction to insulin treatment in type 2 diabetes

In people with type 2 diabetes (T2DM) there is a steady decline in beta cell function that leads to progressive hyperglycaemia, despite continued therapy with OHAs or GLP-1 RAs. Consequently, many people with T2DM will ultimately need insulin therapy. The role of insulin is to lower blood glucose to prevent hyperglycaemia and its associated complications, such as cardiovascular disease, retinopathy and neuropathy (1). The targets for glycaemic control should be individualized to meet each person's particular needs, priorities, and risk of disabling hypoglycaemia.

5. Insulin for people with Type 2 Diabetes

Consider triple OHA therapy *or* insulin-based treatment for adults with T2DM if:

- Dual therapy with metformin and another OHA has not continued to control HbA1c to below the person's individually agreed threshold for intensification

Insulin-based treatment is recommended for adults with T2DM if:

- Triple therapy with metformin has not continued to control HbA1c to below the person's individually agreed threshold for intensification
- Dual therapy, where metformin is contraindicated or not tolerated, has not continued to control HbA1c to below the person's individually agreed threshold for intensification
- Oral hypoglycaemic treatment or non-insulin therapies are not tolerated or are contra-indicated

- The individual is symptomatic e.g. rapid weight loss, polyuria, nocturia, recurrent fungal infections (especially genital thrush) or bacterial infections (especially urine infections)
- The individual expresses a preference for insulin treatment to achieve early / sustained optimal glycaemic control

6. Personalised HbA1c targets

Involve adults with type 2 diabetes in decisions about their individual HbA1c target.

Encourage them to achieve the target and maintain it unless any resulting adverse effects (including hypoglycaemia), or their efforts to achieve their target, impair their quality of life.

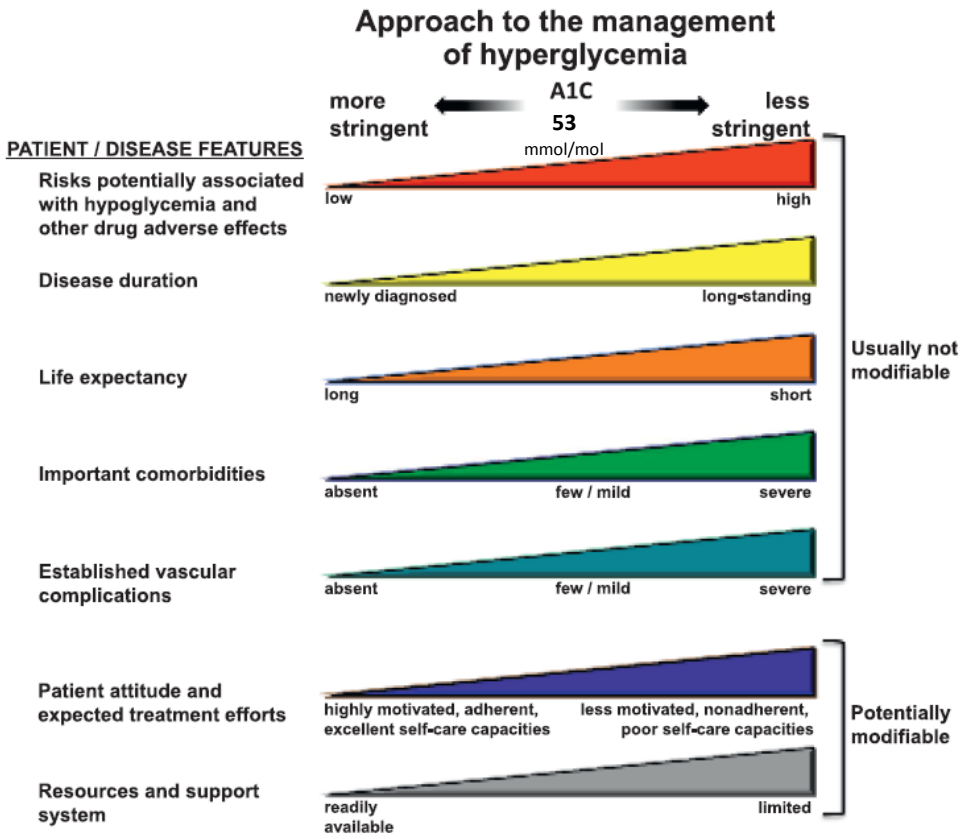
Offer dietary advice (see NICE NG28, section 1.3) and drug treatment to support adults with type 2 diabetes to achieve and maintain their HbA1c target.

In adults with type 2 diabetes, measure HbA1c levels at:

- 3–6-monthly intervals (tailored to individual needs), until the HbA1c is stable on unchanging therapy
- 6-monthly intervals once the HbA1c level and blood glucose lowering therapy are stable

Patients group	**Target HbA1c presumption (this must be individualised)**
Patients managed by lifestyle and diet	< 48 mmol/mol (6.5%)
If **all** the following apply: • Younger patients < 60 years within 10 years of diagnosis • Without established macrovascular disease (IHD, CVA, PVD) • Taking a ***single oral agent*** which is not associated with risk of hypoglycaemia (metformin, gliptin, SGLT2-i, pioglitazone)	48 mmol/mol (6.5%)
If **all** the following apply: • Younger patients < 60 years within 10 years of diagnosis • Without established macrovascular disease (IHD, CVA, PVD) • Without CKD on dialysis • Low risk for serious consequences of hypoglycaemia • Taking SU/repaglinide/insulin/GLP-1RA ***OR*** on more than one oral agent • Without significant comorbidities	53 mmol/mol (7.0%)
If life-expectancy > 10 years and **any** of the following apply: • Age > 60 years or duration diabetes > 10 years • Established macrovascular disease (IHD, CVA, PVD) • CKD on dialysis • Tight control poses a high risk of the consequences of hypoglycaemia (e.g. risk of falling, impaired awareness of hypoglycaemia, people who drive or operate machinery as part of their job) • Experiences recurrent hypoglycaemia on SU/insulin • Significant comorbidities	58 mmol/mol (7.5%)
Patients who are frail and elderly (>80 years), dementia and/or life-expectancy < 10 years	69 mmol/mol (8.5%)

Figure 1: Approach to the management of hyperglycaemia (adapted from ADA 'Standards of Care' 2015)



7. Choice of insulin regimens

There are three main insulin regimes:

1) **Basal insulin** (usually once-daily)
   - Used for insulin naïve patients with HbA1c <9% (75mmol/mol)
   - Treatment involves once daily basal insulin, increasing to twice daily in some patients.
2) **Biphasic or pre-mixed insulin** (usually twice-daily)
   - Used for insulin naïve patients with a very high HbA1c (≥9% [75mmol/mol]) and in patients who are failing to achieve adequate HbA1c levels with basal insulin.
   - Biphasic insulin is a pre-mixed suspension of short/fast-acting and intermediate-acting insulin.
   - Treatment may involve one to three daily injections of biphasic insulin before meals.
3) **Basal-bolus insulin** (multiple daily injection regimen)
   - Basal-bolus insulin is not commonly used in T2DM however may be useful in patients who have flexible lifestyles, are very sensitive to insulin, or in patients who develop significant postprandial hyperglycaemia.
   - Treatment involves once-daily basal insulin with separate rapid-acting bolus insulin before at least one main meal.

Continuous subcutaneous insulin infusion (insulin pump therapy) is not recommended for patients with T2DM (2).

See Appendix 1 for the insulin regimen flow diagram. See Appendix 2 for a summary of the properties of available insulins.

7.1. Basal insulin

Recommendation

- Once-daily NPH insulin in the evening is the 1st choice insulin regimen for insulin naïve adults with HbA1c <9% (<75mmol/mol)
  - Insuman Basal SoloStar will be suitable for most patients
  - Consider Insulatard Innolet for patients with dexterity or visual impairment
- Consider biosimilar insulin glargine (Abasaglar) if a patient
  - Experiences problematic hypoglycaemia with NPH insulin
  - Would require twice-daily NPH insulin
  - Has significant co-morbidities, or who are at risk of falling, or have impaired awareness of hypoglycaemia
- Patients prescribed insulin glargine (Lantus) should consider transition to biosimilar insulin glargine (Abasaglar) following counselling at a routine diabetes appointment
- Once- and twice-daily insulin detemir (Levemir) is **not recommended**

Further information

Once-daily NPH insulin is the first-line basal insulin and should usually be initiated in the evening. NICE does not recommend a specific NPH insulin and there is little evidence for preference of one NPH inulin over another therefore choice should be based on device preference, clinical experience and acquisition cost. Insuman Basal is available as a SoloStar pre-filled pen device and is the lowest cost NPH insulin therefore should be considered first for most patients, if the clinician feels appropriate. Insulatard is available as an Innolet pre-filled device and is preferred for patients with visual impairment or dexterity issues.

Once-daily biosimilar insulin glargine 100iU/mL (Abasaglar) should only be considered for patients already prescribed once-daily NPH insulin who experience:

- Problematic hypoglycaemic, defined as frequent unpleasant minor hypoglycaemia (patient can self-treat) where dose titration following assessment as not worked, or 1 episode of severe hypoglycaemia (requiring third party assistance), or 1 episode associated with impaired awareness of hypoglycaemia, extreme glycaemic liability, or major fear and maladaptive behavior (1,3)
- Would require dose escalation to twice-daily NPH insulin (1,3)

If a patient is being transitioned from insulin glargine 100iU/mL (Lantus) to biosimilar insulin glargine 100iU/mL (Abasaglar) this should be discussed during a patient consultation with a demonstration of the new device. Direct 'script-switches' without patient agreement are likely to cause confusion and are not recommended.

Patients with significant co-morbidities, or who are at risk of falling, or have impaired awareness of hypoglycaemia should be considered for a relaxed HbA1c target (>7.5%, [58 mmol/mol]) and 1st line basal analogue insulin.

Once-daily insulin detemir is not recommended as the shorter duration of action compared to insulin glargine (16hrs vs 24hrs) is unlikely to provide adequate insulin cover. Furthermore a recent systematic literature review identified a 26-wk study which found once-daily insulin detemir to be inferior to once-daily insulin glargine at reducing HbA1c and required a larger total daily dose (4).

Twice-daily insulin detemir is not recommended as insulin detemir is more costly than insulin glargine, and there is no evidence of superiority in terms of HbA1c control or hypoglycaemia (5,6). Twice-daily detemir has a short term non-clinically significant weight benefit (0.8kg) over once-daily glargine (5,6) however the incremental cost does not justify the small benefit. Data to suggest that insulin detemir is weight sparing in obese patients is inconclusive and is limited to a single-arm observational study of once-daily detemir used 1st line for OHA failure (7) and one study of twice-daily detemir which excluded patients with BMI ≥ 35kg/m^2 (8,9).

7.2. Biphasic or pre-mixed insulin

Recommendation

- Twice-daily biphasic human insulin is the 1st choice insulin regimen for insulin naïve adults with an HbA1c >9% (>75mmol/mol)
- Consider a twice-daily biphasic human insulin if the patient:
    - Experiences significant postprandial hyperglycaemia with NPH insulin
- Consider a twice-daily biphasic analogue insulin, rather biphasic human insulin if the patient:
    - Prefers to inject insulin with meals (rather than 30-45 minutes before meals)
    - Experiences problematic hypoglycaemia with biphasic human insulin
    - Experiences significant postprandial hyperglycaemia with biphasic human insulin
    - Has significant co-morbidities, or who are at risk of falling, or have impaired awareness of hypoglycaemia
    - Fails to achieve adequate control on once-daily biosimilar glargine (Abasaglar)
- A once-daily and three-times daily regimes may useful however this is dependent on the individual patient's preference, convenience and insulin resistance

Insuman Comb 25 (25% soluble, 75% isophane) will be suitable for most patients requiring biphasic human insulin.

Humalog Mix 25 KwikPen (25% lispro, 75% lispro protamine) will be suitable for most patients requiring biphasic analogue insulin.

Further information

Twice-daily biphasic human insulin is the 1st line insulin for patients with an HbA1c ≥9% (75mmol/mol). Biphasic human insulin should be taken 30-45 minutes before a meal (10,11). NICE does not recommend one specific biphasic human insulin over another therefore choice should be based on device preference, clinical experience and acquisition cost. The Insuman Comb range is available in a Solostar device and includes Insuman Comb 25 (25% soluble, 75% isophane) and Insuman Comb 50 (50% soluble, 50% isophane). Patients frequently need to increase the ratio of prandial insulin above 25-30% and the Insuman Comb range is the only range that includes a 50% soluble biphasic human insulin, therefore Insuman Comb should be considered first for most patients..

Twice-daily biphasic analogue insulins have a faster onset of action and can be injected with meals therefore should be reserved for patients who prefer to inject with meals or who have significant postprandial hyperglycaemia with biphasic human insulin. Biphasic analogue insulin should also be considered who patients who experience significant hypoglycaemia with biphasic human. NICE does not recommend one specific biphasic analogue insulin over another therefore choice should be based on device preference, clinical experience and acquisition cost. The Humalog Mix range is available in a KwikPen device and includes Humalog Mix25 (25% soluble, 75% lispro protamine) and Humalog Mix50 (50% lispro, 50% lispro protamine). The Humalog Mix range is the only range that includes 50% rapid acting biphasic insulin therefore should be considered first for most patients.

Patients with significant co-morbidities, or who are at risk of falling, or have impaired awareness of hypoglycaemia should be considered for a relaxed HbA1c target (>7.5% [58 mmol/mol]) and 1st line biphasic analogue insulin.

7.3. Basal-bolus insulin

Recommendation

Consider basal-bolus insulin analogue regimens if:

- The patient has a lower body weight and is very sensitive to insulin
- Twice-daily biphasic insulin is failing to adequately control HbA1c and the patient is experiencing

significant postprandial hyperglycaemia after snacks and lunch

- Basal insulin is failing to adequately control HbA1c and the patient is suitable for a basal-bolus regimen
- Individuals who lead unpredictable lifestyles or would prefer to carbohydrate count and adjust prandial insulin doses to accommodate varying meal sizes / dieting / exercise

Further information

Peak activity for rapid-acting insulin analogues is between 1 – 2 hours compared to 2 – 4 hours for soluble human insulins. Rapid-acting insulin analogues therefore avoid post-prandial hyperglycaemia, related to the delayed onset and peak of action of human soluble insulins. There is no evidence that any rapid-acting insulin analogue has superiority over another. The two most commonly used rapid-acting insulin analogues are insulin lispro (Humalog®) and insulin aspart (NovoRapid®).

Due to the rapid-acting profile of analogues, these insulins allow flexibility with lifestyle and the timing of meals which can become more important with periods of fasting and sleep (during religious fasts or with shift-work).

7.4. Insulin management for patients receiving long-term district nursing

Adult patients with T2DM who require long-term district nurse care may require a different treatment pathway to allow flexibility in insulin timing. When considering a meal-time insulin, discuss the feasibility of co-ordinating meal times and insulin administration with the patient and district nursing team.

- Regimens should only be changed where this is clinically appropriate and in the best interests of the patient
- Establish whether the patient would prefer morning or evening administration of basal insulin (there is usually more staff during the day service than at night service)
- Consider once-daily biosimilar glargine in place of twice-daily NPH insulin for patients who would otherwise be suitable for once-daily district nurse visits
- Consider twice-daily NPH insulin (which will provide some peak) in place of twice-daily biphasic insulin where administration cannot be guaranteed around meal times which might otherwise increase the risks of hyperglycaemia, hypoglycaemia and snacking related weight gain
- Should the requirement for long-term district nursing care be no longer required, consider reverting to the original insulin regimen if not well controlled on current regimen

7.5. Longer acting basal insulin analogues

Recommendation

- Toujeo (insulin glargine 300iU/mL) is **not recommended**
- Tresiba (insulin degludec) is **not recommended**

Further information

Toujeo (insulin glargine 300iU/mL) and Tresiba (insulin degludec) are both more expensive than Abasaglar (biosimilar insulin glargine) and only offer a small reduction in the risk of nocturnal hypoglycaemia. This marginal benefit is not considered sufficient to justify the additional cost.

Toujeo (insulin glargine 300iU/mL) is limited to injecting 80iU insulin therefore offers no benefit to patients who need to inject large volumes of glargine as multiple injections are still required.

8. Self-monitoring blood glucose target

Agree individual targets with the patient and where possible aim for:

- Pre-breakfast or fasting glucose level of 4-6mmol/l and pre-prandial levels at other times of the day at 4-7mmol/l
- Post-prandial (i.e. 2 hours after a main meal) <9mmol/l but this will depend on the individual (e.g. in the elderly or end of life care these targets may not be appropriate)

See Section 6 on setting patient specific HbA1c thresholds for intensification.

9. Associated documents

Guideline for Antihyperglycaemic agents for Type 2 diabetes V1.0 link
GP Fact Sheet for liraglutide and dulaglutide for Type 2 diabetes V1.0 link

10. References

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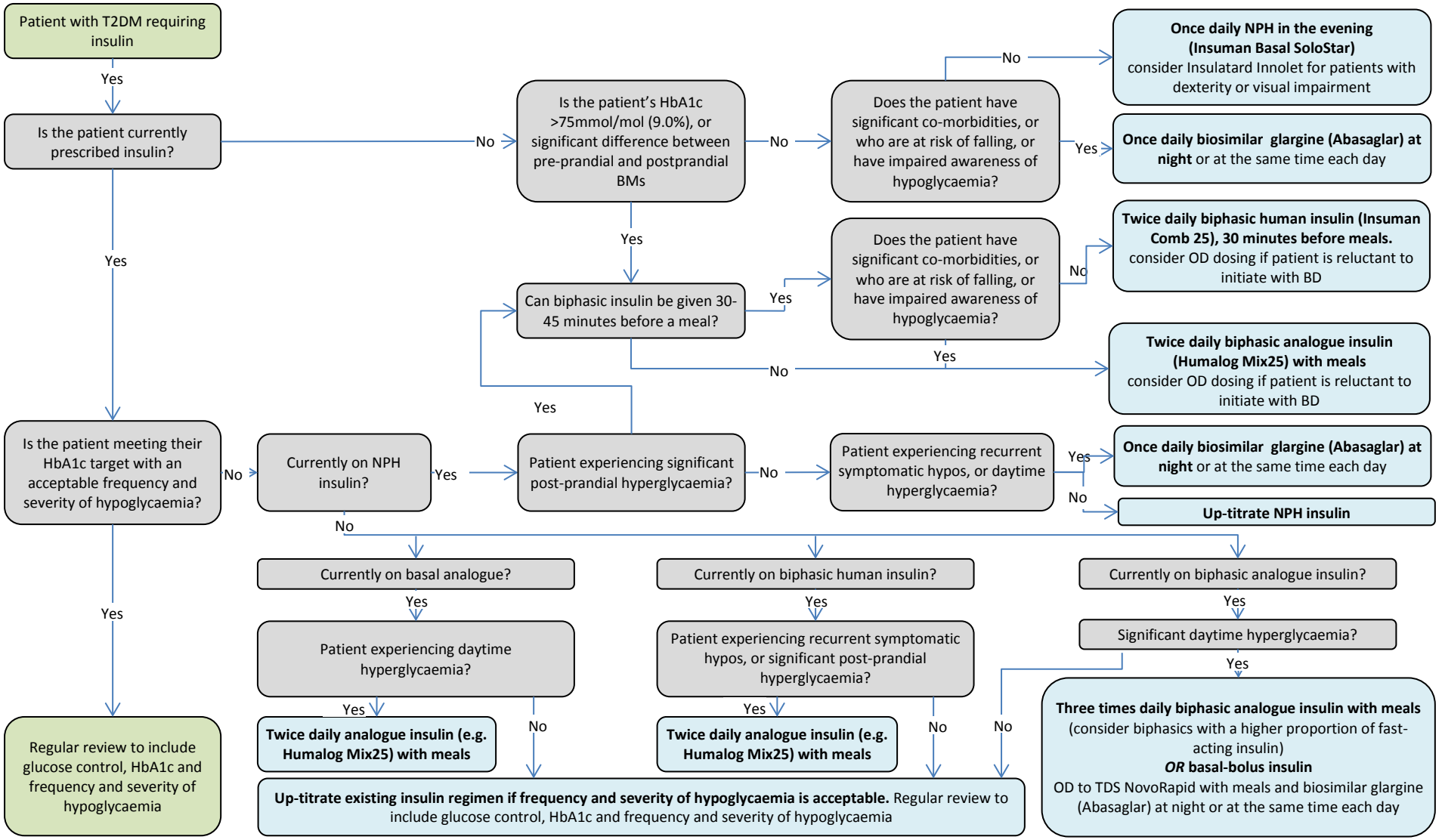
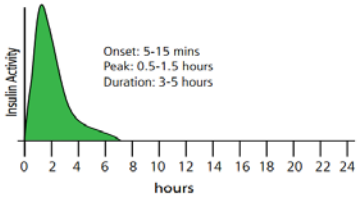
Appendix 1: Summary of treatment recommendations



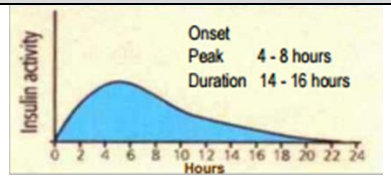
Appendix 2: Formulations of available insulin

(12–15)

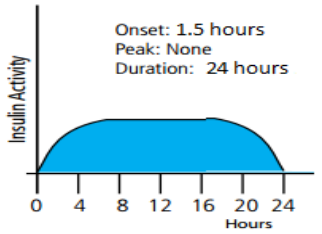
Bolus insulin

Brand name	Approved name	10mL vial	Prefilled device	3mL cartridge	Compatible pen/device with the cartridge	Approximate time action profile	Typical dosing schedule
NovoRapid (Novo Nordisk)	Insulin aspart 100iU/mL	✔	3mL FlexPen & FlexTouch pen	✔	NovoPens		Usually three times a day subcutaneously within 15 minutes before, or just after food 100iU/mL strength may be used in continuous subcutaneous insulin pumps
Humalog (Eli Lily)	Insulin lispro 100iU/mL	✔	3mL KwikPen	✔	HumaPens, Autopen Classic		
	Insulin lispro 200iU/mL		3mL KwikPen				
Apidra (Sanofi Aventis)	Insulin glulisine 100iU/mL	✔	3mL SoloStar	✔	Aventis Pens, Autopen 24		

Basal insulin – human isophane insulin (NPH)

Brand name	Approved name	10mL vial	Prefilled device	3mL cartridge	Compatible pen/device with the cartridge	Approximate time action profile	Typical dosing schedule
Insuman Basal (Sanofi)	Isophane insulin	✔	3mL SoloStar	✔	ClikSTAR, Autopen 24		Usually once-daily, can be twice-daily subcutaneously
Insulatard (Novo Nordisk)	Isophane insulin	✔	3mL Innolet	✔	NovoPen		
Humulin I (Eli Lily)	Isophane insulin	✔	3mL KwikPen	✔	HumaPens, Autopen Classic		

Basal insulin – analogue insulin

Brand name	Approved name	10mL vial	Prefilled device	3mL cartridge	Compatible pen/device with the cartridge	Approximate time action profile	Typical dosing schedule
Abasaglar (Eli Lily)	Biosimilar insulin glargine 100iU/mL		3mL KwikPen	✔	HumaPens, Autopen Classic		Usually once-daily subcutaneously
Lantus (Sanofi Aventis)	Insulin glargine 100iU/mL	✔	3mL SoloStar	✔	Aventis Pens, Autopen 24		
Toujeo (Sanofi Aventis)	Insulin glargine 300iU/mL		1.5mL SoloStar			Similar to above, duration up to 30hrs	Usually once-daily subcutaneously

Human biphasic (pre-mixed) insulin

Brand name	Approved name	10mL vial	Prefilled device	3mL cartridge	Compatible pen/device with the cartridge	Approximate time action profile	Typical dosing schedule
Insuman Comb 15 (Sanofi Aventis)	Soluble & isophane insulin			✔	Autopen 24		
Insuman Comb 25 (Sanofi Aventis)		5mL vial	3mL SoloStar	✔	Autopen 24		
Insuman Comb 50 (Sanofi Aventis)				✔	Autopen 24		
Humulin M3 (Eli Lily)	Soluble & isophane insulin	✔	3mL KwikPen	✔	HumaPens, Autopen Classic	Action profiles vary according to ratio of soluble and isophane insulin	Usually twice-daily subcutaneously; can be used three times daily. Note that these are cloudy insulins that need re-suspending before use

Data for Insuman Comb was not included in the Leeds Poster and was therefore taken from the BNF (15)

Analogue biphasic (pre-mixed) insulin

Brand name	Approved name	10mL vial	Prefilled device	3mL cartridge	Compatible pen/device with the cartridge	Approximate time action profile	Typical dosing schedule
Humalog Mix 25 (Eli Lily)	Biphasic insulin lispro	✔	3mL KwikPen	✔	HumaPens, Autopen Classic		
Humalog Mix 50 (Eli Lily)			3mL KwikPen				
NovoMix 30 (Eli Lily)	Biphasic insulin aspart		3mL FlexPen	✔	NovoPen	Action profiles vary according to ratio of rapid and intermediate acting insulin	Usually twice-daily subcutaneously; can be used three times daily. Note that these are cloudy insulins that need re-suspending before use