New insulins and newer insulin regimens: a review of their role in improving glycaemic control in patients with diabetes

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ABSTRACT

The legacy effect of early good glycaemic control in people with diabetes shows it is associated with reduction of microvascular and macrovascular complications. Insulin therapy is essential and lifesaving in individuals with type 1 diabetes and beneficial for those with type 2 diabetes who fail to achieve optimal glycaemic targets with other classes of glucose-lowering therapies. Since the introduction of insulin analogues, insulin management has changed. This follow-up review attempts to update our earlier publication from 2009 and discusses the role of new insulin analogues and newer insulin regimens. Recognising the advent of new quality and economic initiatives both in the UK and worldwide, this paper reviews current insulin prescribing and the pros and cons of prescribing analogues in comparison to the human insulins that are now gaining more acceptance in everyday clinical practice.

INTRODUCTION

Fuelled by the pandemic of obesity and an ageing population, global estimates indicate a rising incidence of diabetes of which nearly 90% of individuals are diagnosed with type 2 diabetes mellitus (T2DM).¹ Insulin is lifesaving in type 1 diabetes (T1DM), a condition characterised by complete lack of endogenous insulin. The disease trajectory of T2DM is not well defined. Insulin resistance is the hallmark of T2DM and over time results in diminishing beta-cell function and beta-cell failure. Although glycaemic control can often be achieved with other classes of glucose-lowering therapies following diagnosis, a significant proportion of individuals will still need insulin therapy to achieve optimal blood glucose targets.² Despite evidence-based consensus guidelines and documented benefits of good glycaemic control in reducing vascular complications, considerable clinical inertia exists with insulin initiation particularly in individuals with T2DM.³ Key factors impacting on insulin therapy include fear and risk of hypoglycaemia, weight gain, restricted lifestyle, reluctance to inject and difficulties in self-managing insulin therapy. Hence, there is a need for less restrictive insulin regimens with lower risk of hypoglycaemia.^{4,5}

Since our earlier publication in this journal on this subject,⁶ a second generation of new insulins, notably newer long-acting insulin analogues, have been introduced. Newer insulin regimens resulting from the addition of insulin analogues to a host of glucose-lowering therapies including the incretin-based therapies and sodium glucose co-transporter-2 (SGLT-2) inhibitors are now gaining acceptance.

However, the escalating cost of diabetes care and the advent of new quality and economic initiatives both in the UK and worldwide have favoured resurgence in the use of human insulins. Nonetheless, newer insulin analogues as well as newer insulin regimens may be appropriate in a defined group of patients with diabetes.

HUMAN INSULIN

Human insulin is synthetic insulin manufactured from recombinant DNA technology and is identical to insulin produced by the human pancreas. Animal insulins used since inception until the advent of human insulin in the 1980s are now only minimally used. Human insulin is available as short-acting (regular) and intermediate-acting (neutral protamine hagedorn (NPH)) insulin. Both regular (prandial) human insulin (onset of action 30 min; peak 2–4 h; duration 6–8 h) and ‘basal’ human insulin (variable onset of action; peak 4–10 h; duration <24 h) have features that are less physiological since they can promote weight gain as a result of snacking and are undesirable for use owing to increased risk of hypoglycaemia for some individuals with diabetes.⁷

Human insulin at higher concentrations is available as human regular U-500 (U-500R) insulin and is considered for individuals who often need insulin in excess of 3 units/kg/day (~200 units/day). In a case series review by Crasto *et al*,⁸ U-500R showed substantial improvement in HbA1c (1.1–3.5%) with modest weight gain and was noted to be cost effective. However, U-500R unlike other insulins is expressed as ‘marks’ and delivered via a tuberculin syringe, which may lead to errors in dispensing, prescribing and administration. In recent years, the newer higher concentration insulin analogues, degludec U200, glargine U300 and humalog U200, administered via an insulin pen device as units/mL may provide an advantage over U-500R insulin.⁹

NEW INSULINS

New or analogue insulins are molecular-engineered formulations designed to improve the pharmacokinetics, absorption profile and duration of action of human insulin (figure 1). The first-generation analogues (‘rapid’ and ‘long’ acting analogues), and the second-generation, newer long-acting analogues have been summarised in table 1. Insulin degludec (U100 and U200) is now licensed for use in the EU. Glargine U300 has now been approved by the US Food and Drug Administration (US FDA) for use in adults with T1DM and T2DM. The European Medicines

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Figure 1 (A–D) Pharmacokinetic profile of rapid-acting, premixed, long-acting and newer long-acting insulin analogues.

Agency has so far expressed a positive opinion recommending its approval. Degludec, glargine U300 and PEGylated insulin lispro (under development) will form the new category of second-generation long-acting insulin analogues with more favourable profiles as basal insulins.¹⁰

Rapid-acting and long-acting analogues (glargine, detemir)

The pharmacokinetics and pharmacodynamics of the rapid and long-acting analogues is depicted in [table 1](#). Humalog U200 is by far the only high-strength rapid-acting analogue approved by the US FDA and EU. Pharmacokinetic and pharmacodynamic studies comparing humalog U200 to humalog U100 have met the criteria established for bioequivalence, providing support for comparable efficacy and safety.¹¹

Glycaemic efficacy, safety and patient-reported outcomes with rapid-acting analogues in T1DM

Rapid-acting analogues compared with regular human insulin

In individuals with T1DM, minor improvements in HbA1c are observed with rapid-acting analogues compared with regular human insulin (weighted mean difference (WMD) = -0.12%; 95% CI -0.17% to -0.07%).¹² Furthermore, improved postprandial glucose lowering was observed with significantly lower analogue insulin doses and fewer nocturnal hypoglycaemic episodes.¹³⁻¹⁵ A recent meta-analysis showed that insulin aspart, a rapid-acting analogue compared with regular human insulin, was associated with minor improvements in HbA1c (WMD = -0.11%; 95% CI -0.16 to -0.06) and postprandial glucose, with no change in fasting glucose. However, there were

Table 1 Structural properties, pharmacodynamics and pharmacokinetics of insulin analogues

Insulin analogues	Structural amino acid alterations on the insulin side chains	Onset of action	Peak action	Duration of action
Rapid-acting analogues				
Lispro (Humalog)	Reversal of amino acid proline at position 28 and lysine at position 29 on the insulin B-chain	5–15 min	30–90 min	4–6 h
Aspart (NovoRapid)	Replacing proline at position 28 on the B-chain of insulin with aspartic acid	5–15 min	30–90 min	4–6 h
Glulisine (Apidra)	Replacing asparagine with lysine at position B3 and glutamic acid for lysine at position B29	5–15 min	30–90 min	4–6 h
Pre-mixed analogues				
Humalog Mix 25	25% lispro and 75% neutral protamine lispro	Varies according to preparation		
Humalog Mix 50	50% lispro and 50% neutral protamine lispro			
Novomix 30	30% aspart and 70% protamine-crystallised aspart			
Long-acting analogues				
Glargine (Lantus)	Asparagine replaced with glycine at position A21 and two arginine amino acids added at position B31 and B32	2–4 h	None	20–24 h
Detemir (Levemir)	Fatty acid acylation to the lysine residue on position B-29	1–4 h	None	12–24 h
Newer long-acting analogues				
Degludec	Deletion of threonine at B30 and addition of 16-carbon fatty acid to lysine at B29 via a glutamic acid spacer	30–90 min	None	>24 h
degludecPlus	Degludec combined with insulin aspart suspension	5–15 min	30–60 min	>24 h

significant reductions in nocturnal hypoglycaemic episodes (risk reduction=0.67; 95% CI 0.54 to 0.83) and individuals on insulin aspart were more satisfied with treatment and with treatment flexibility when evaluated using a diabetes treatment satisfaction questionnaire compared with regular human insulin (WMD=0.31; 95% CI 0.15 to 0.47).¹³

Comparative efficacy studies between rapid-acting analogues

A head-to-head trial of insulin aspart and lispro has shown similar glycaemic efficacy.¹⁶ Although glycaemic efficacies in continuous subcutaneous insulin infusion (CSII) are similar, safety data show lower pump occlusion rates with insulin aspart (9.2%) compared with lispro (15.7%) and glulisine (40.9%).¹⁷ Results of a randomised, crossover trial in 20 patients with T1DM on CSII indicate improved patient satisfaction with insulin aspart compared with insulin lispro.¹⁸

Glycaemic efficacy, safety and patient-reported outcomes with rapid-acting analogues in T2DM

Rapid-acting analogues compared with regular human insulin

A meta-analysis of nine studies comparing treatment outcomes with insulin aspart and regular human insulin showed no significant differences in HbA1c, though postprandial glucose was significantly lower with insulin aspart (WMD=-1.18 mmol/L; 95% CI -1.88 to -0.47). There were no significant differences in rates of hypoglycaemic events; no studies of treatment satisfaction or quality of life were identified in this systematic review.¹³

Comparative efficacy studies between rapid-acting analogues

Direct comparisons of metabolic efficacy between insulin analogues in T2DM are lacking. Two separate comparative studies of insulin glulisine, aspart and humalog showed that glulisine, which is a zinc-free formulation, was associated with statistically significant blood glucose lowering in the immediate hour after a meal, with no differences in rates of hypoglycaemia.^{19 20}

Summary of rapid-acting analogues

The rapid-acting analogues (aspart, humalog and glulisine) have similar kinetics and similar glycaemic efficacy. Compared with regular human insulins, favourable attributes with rapid-acting analogues in individuals with T1DM include flexibility of administration, which is linked to adherence and improved treatment satisfaction, more effective lowering of postprandial glucose excursions and reduced risk of nocturnal hypoglycaemia. In T2DM, superior postprandial glucose lowering with similar HbA1c benefits and no differences in the rates of hypoglycaemia have been reported.

Glycaemic efficacy, safety and patient-reported outcomes with long-acting analogues in T1DM

Long-acting analogues (glargine, detemir) compared with basal human insulin in T1DM

Use of analogue basal insulins in a basal-bolus regimen in individuals with T1DM has demonstrated superior HbA1c-lowering effect compared with similar regimens using basal human insulin.²¹ Insulin detemir compared with NPH insulin in individuals with T1DM provides minor lowering of HbA1c (mean difference=-0.073, 95% CI -0.135 to -0.011, $p=0.021$), reduced risk of all-day, nocturnal and severe hypoglycaemia and reduced weight gain.²² A recent meta-analysis comparing long-acting analogues (glargine or detemir, used once daily) and NPH insulin showed no significant differences in HbA1c outcomes. However, twice-daily detemir showed a modest HbA1c

benefit to NPH insulin in comparative studies (mean difference=-0.14%; 95% CI -0.21 to -0.08).²³ Direct comparisons between basal analogues and NPH insulin on patient-reported outcomes including quality of life and treatment satisfaction are lacking.

Comparative efficacy studies between insulin glargine and detemir

Direct comparisons of glargine and detemir in randomised trials have shown no differences in glycaemic efficacy or the risk of overall and nocturnal hypoglycaemia.²³

Glycaemic efficacy, safety and patient-reported outcomes with long-acting analogues in T2DM

Long-acting analogues compared with basal human insulin

Two separate systematic reviews comparing long-acting insulin analogues with NPH insulin have reported no significant glycaemic efficacy benefits, but indicate a reduced risk of nocturnal and symptomatic hypoglycaemia with basal analogues.^{24 25} Compared with NPH insulin, detemir has a distinct weight-sparing effect that may be due to a dual effect on (a) satiety centres by inducing changes in satiety factors, leptin and ghrelin and (b) its hepatoselective action.^{26 27} All types of nocturnal hypoglycaemia are reduced by approximately 50% with insulin glargine compared with NPH insulin when used as basal-only therapy, although a statistical significant result was only observed for symptomatic hypoglycaemia.^{28 29}

Comparative efficacy studies between insulin glargine and detemir

A meta-analysis of four trials involving 2250 individuals with T2DM, randomised to either insulin glargine or detemir, showed no differences in glycaemic efficacy or hypoglycaemia.³⁰ Similar glycaemic control was achieved with both once-daily glargine and twice-daily detemir, with detemir injected at a higher total dose. Other salient observations were the potential for less weight gain with detemir and lower daily basal insulin dose with glargine. There were no differences in outcomes such as health-related quality of life, cost or mortality, though differences in insulin dose could translate in cost differential between these two basal insulins.³⁰

Summary of long-acting basal analogues

Both glargine and detemir have equal efficacy and have comparable glycaemic efficacy to NPH insulin. Beyond HbA1c comparisons, basal analogues are associated with a lower risk of hypoglycaemia, although patient-reported outcomes on quality of life and treatment have not been fully assessed. Insulin detemir has the additional advantage of producing less weight gain compared with glargine, but with higher average-unit dose requirement as shown in comparative studies.

Newer long-acting analogue insulins

Chemistry, pharmacokinetics and pharmacodynamics of degludec
Degludec is a long-acting analogue with a molecular structure similar to human insulin, with deletion of threonine at B30 and addition of 16-carbon fatty acid to lysine at B29 via a glutamic acid spacer (table 1).¹⁰ The modified insulin molecule with phenol and zinc forms stable dihexamers in solution and reorganises to multi-hexamers after subcutaneous injection. With the gradual diffusion of zinc ions, degludec slowly dissociates to release monomers in the systemic circulation.⁹ Degludec has a plasma half-life of 25 h in in vivo studies with duration of action beyond 42 h. It reaches a steady state with daily dosing to produce a flat and stable profile (figure 2). Degludec is administered once daily, preferably at the same time of day, although

Figure 2 Analogue insulin formulations with duration of action. s/c, subcutaneous.

varying injection times do not compromise glycaemic control or safety compared with 'same-time', once-daily administered degludec or glargine. This may improve adherence by allowing injection-time adjustment according to individual needs.³¹ Degludec is also available at higher concentrations in a prefilled pen device as U200 (200 units/mL).

Glycaemic efficacy and safety of degludec *Degludec compared with glargine in T1DM*

The BEGIN Basal-Bolus Type 1 study was a 52-week, treat-to-target trial involving 629 individuals that showed that insulin degludec was non-inferior to glargine (estimated

treatment difference in HbA1c between groups = -0.01% ; 95% CI -0.14 to 0.11) for glycaemic efficacy, with similar rates of overall confirmed hypoglycaemia seen with both insulins (table 2). However, nocturnal confirmed hypoglycaemia was significantly lowered by 25% with insulin degludec.³²

Degludec compared with glargine in T2DM

The BEGIN Basal-Bolus Type 2 study was a 52-week, treat-to-target randomised controlled trial involving 1006 individuals, which compared insulin degludec to glargine in combination with prandial insulin, with or without oral hypoglycaemic agents (OHAs). Degludec demonstrated non-

Table 2 Efficacy studies with insulin degludec

Degludec studies	Study participants	Study duration and design	Treatment arms	HbA1c reduction with ETD	Hypoglycaemia	Comments
Heller <i>et al</i> ³²	T1DM individuals (n=629)	52-week, open-label, treat-to-target, non-inferiority trial	IDeg+aspart vs Gla+aspart	0.40% vs 0.39% (ns) ETD (IDeg—IGlar) = -0.01% (95% CI -0.14% to 0.11%), $p < 0.0001$	Nocturnal confirmed hypoglycaemia: 4.41 vs 5.86† episodes per patient-year of exposure	25% lower rates of nocturnal confirmed hypoglycaemia with IDeg compared to Gla
Zinman <i>et al</i> ³³	T2DM individuals (n=1030)	52-week, open-label, treat-to-target, non-inferiority trial	IDeg+Met vs Gla+Met	1.06% vs 1.19% (ns) ETD (IDeg—IGlar) = -0.09% (95% CI -0.04% to 0.22%)	Nocturnal confirmed hypoglycaemia: 0.25 vs 0.39† episodes/patient-year	Comparable glycaemia with lower rates of nocturnal hypoglycaemia with IDeg
Gough <i>et al</i> ³⁴	T2DM individuals (n=457)	26-week open-label treat-to-target	IDeg U200 vs Gla	1.3±1.01%, for both (ns) ETD (IDeg—IGlar) = -0.04% (95% CI -0.11% to 0.19%)	Nocturnal confirmed hypoglycaemia: 0.18 vs 0.28 ^{ns} episodes/patient-year	Lower mean insulin dose (11%) with IDeg U200 compared to Gla
Garber <i>et al</i> ³⁵	T2DM individuals (n=1006)	52-week, open-label, treat-to-target, non-inferiority trial	IDeg+asp±OADs vs Gla+asp±OADs	1.1% vs 1.2% (ns) ETD (IDeg—IGlar) = -0.08% (95% CI -0.05% to 0.21%)	Overall hypoglycaemia risk 11.1 vs 13.6† episodes per patient-year of exposure Nocturnal confirmed hypoglycaemic episodes: -1.4 vs $1.8†$ episodes per patient-year of exposure	IDeg compared to Gla demonstrates non-inferiority with lower rates of hypoglycaemia

†Signifies $p < 0.05$ for between treatment differences.

ETD, estimated treatment difference; Gla, glargine; IDeg, insulin degludec; IGlar, insulin glargine; ns, non-significant; OADs, oral antidiabetes drugs; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

inferiority for glucose lowering, but rates of overall hypoglycaemia (11.1 vs 13.6 episodes/patient-year exposure, estimated rate ratio 0.82; 95% CI 0.69 to 0.99, $p=0.0359$) and nocturnal hypoglycaemia (1.4 vs 1.8 episodes/patient-year exposure, 0.75; 95% CI 0.58 to 0.99, $p=0.0399$) were significantly lower with degludec.³⁵

Effect of degludec on HbA1c and hypoglycaemia in T1DM and T2DM

Comparative trials have shown no differences in glycaemic efficacy between insulin degludec and the first-generation basal analogues (glargine or detemir).³⁶ In a meta-analysis using pooled patient-level data ($n=4330$) for self-reported hypoglycaemia, degludec compared with glargine significantly lowered rates of confirmed nocturnal hypoglycaemia (estimated rate ratio (RR) 0.75, 95% CI 0.60 to 0.94) in individuals with T1DM and showed significantly lower rates of overall (RR 0.83, 95% CI 0.70 to 0.98) and severe hypoglycaemia (RR 0.14, 95% CI 0.03 to 0.70) in individuals with T2DM.³⁷

degludecPlus compared with Biphasic Aspart 30

degludecPlus is a soluble co-formulation of insulin degludec (70%) and insulin aspart (30%). A meta-analysis of two trials comparing degludecPlus to Biphasic Aspart 30 (BIAsp 30) among study participants who achieved an HbA1c target of $<7\%$ showed lower rates of overall confirmed hypoglycaemia (RR 0.70 (0.55 to 0.90), $p=0.0047$) and nocturnal hypoglycaemia (RR 0.34 (0.22 to 0.51), $p<0.0001$) with no differences in rates of severe hypoglycaemia between groups.³⁸

Degludec U200 compared with glargine in T2DM

Degludec U200 formulation is a twice-concentrated formulation with bioequivalence and similar pharmacodynamic profile to 100 units/mL degludec.³⁹ Degludec U200 compared to insulin glargine as a basal insulin in insulin-naïve individuals with T2DM has similar glycaemic efficacy, with a lower risk of overall hypoglycaemia (1.22 and 1.42 episodes/patient-year, respectively), nocturnal confirmed hypoglycaemia (0.18 and 0.28 episodes/patient-year, respectively) and an 11% lower mean daily basal insulin dose requirement.³⁴

Insulin glargine U300 (U300)

U300 is a new concentrated insulin glargine formulation that requires a smaller injection volume and forms a smaller, compact subcutaneous depot after injection; this results in a gradual and prolonged release of insulin. It has a flatter profile compared with insulin glargine and prolonged duration of action beyond 24 h (figures 1C).⁴⁰

Clinical efficacy studies with glargine U300 compared with glargine in T2DM

The efficacy and safety of glargine U300 in T1DM and T2DM has been compared with glargine U100 in the phase-3 EDITION trials. A patient-level meta-analysis of EDITION studies has consistently demonstrated comparable glycaemic control (mean (SE) change in HA1c of -1.02% (0.03)) with both the basal insulins.⁴¹ A meta-analysis of 12 months data showed sustained glycaemic control in both groups, with more sustained HbA1c reduction for glargine U300 at 12 months (mean difference between groups in HbA1c change from baseline -0.10 (-0.18 to -0.02); $p=0.0174$).⁴² A meta-analysis of these trials confirmed that risk of nocturnal hypoglycaemia with glargine U300 was significantly reduced by 31%.⁴³

Summary of insulin degludec and glargine U300

Degludec has a more physiological basal profile, a longer duration of action and provides greater flexibility with injection timing without compromising glycaemic control, with lower risk of hypoglycaemia compared with glargine. Degludec U200 and degludecPlus are non-inferior to glargine and BIAsp for glycaemic control, with lower rates of hypoglycaemia. Degludec is approved by the European Medicines Agency, though the US FDA has requested cardiovascular safety data prior to approval.⁴⁴ Glargine U300 has comparable glycaemic control as insulin glargine and looks promising particularly in terms of reduced rates of nocturnal hypoglycaemia.

PEGylated lispro or Basal Insulin pegLispro (under development)

Basal Insulin pegLispro (BIL) is a novel basal insulin analogue in which insulin lispro (5.8 kDa) is attached to a polyethylene glycol chain (~ 20 kDa).⁴⁵ The large molecular size alters the absorption properties leading to slow insulin absorption and may induce a preferential entry through hepatic sinusoids, which in turn leads to higher insulin concentrations in the liver with effective suppression of hepatic glycogenolysis. Lower weight gain observed in clinical trials with BIL may be a result of increased lipid oxidation, increased lipolysis and reduced lipogenesis due to potentially reduced peripheral action resulting from its hepatoselective effect.⁴⁶

Efficacy studies of BIL compared with glargine in T1DM and T2DM

The core phase III clinical development programme of BIL, consisting of seven IMAGINE trials in individuals with T1DM and T2DM, is complete, and the results suggest consistent superior improvements in HbA1c, lower rates of nocturnal hypoglycaemia and significantly less weight gain with BIL.^{47–50} Hepatic safety findings from integrated analyses of clinical trials show an increase in the liver enzyme alanine aminotransferase (ALT) in patients taking BIL compared with glargine. Mean ALT increased from baseline and plateaued after 4 weeks in T1DM (median increase up to 5 IU/L) and 26 weeks in T2DM (median increase 3 IU/L). Aspartate aminotransferase results were similar. More patients on BIL had ALT $\geq 3 \times$ upper limit of normal compared to glargine but returned to or trended towards baseline on continuing BIL. There was also an increase in liver fat in patients treated with BIL compared with glargine. Nonetheless, no severe, hepatocellular drug-induced liver injury was observed with BIL treatment for up to 78 weeks.⁵¹ Non-hepatic safety findings showed higher triglycerides and higher injection-site reactions with BIL compared with insulin glargine.⁴⁷

Summary of newer long-acting insulin analogues (PEGylated lispro and glargine U300)

The initial results of BIL look promising, with reduced rates of hypoglycaemia. Weight loss may be a particular advantage with BIL, though comparative studies with insulin detemir have not yet been evaluated. Its effects on liver function, liver fat and triglyceride levels will need further evaluation.

HEALTH ECONOMICS OF ANALOGUE PRESCRIBING IN INDIVIDUALS WITH T1DM AND T2DM

In individuals with T1DM, rapid-acting analogues are more cost-effective compared with regular human insulin, whereas treatment with basal analogues compared with NPH insulin is associated with higher incremental costs. Routine use of insulin analogues in T2DM has not been found to be cost-effective.^{52 53}

In this regard, a comprehensive review conducted by the National Institute for Health and Care Excellence (NICE), UK, concluded that glargine is cost-effective at current willingness to pay thresholds in people with T1DM, but not cost-effective in individuals with T2DM.⁵⁴ Furthermore, NICE recommends human insulin as first-line therapy in most individuals with T2DM and suggests the use of long-acting analogues in special circumstances, such as benefits accrued from reduced frequency of insulin administration and recurrent symptomatic hypoglycaemic episodes with human insulins.⁵¹

Analogue prescribing in individuals with diabetes has had a significant global financial impact on healthcare resources,⁵⁵ though a few studies indicate that the cost differential between analogues and human insulins is not significantly different.^{56–57} Furthermore, a study that evaluated use of insulin and value for money in T2DM in the UK concluded that, although there were drug acquisition benefits when human insulin was substituted for analogues, total expenditure costs increased fourfold with increased use of human insulins.⁵⁸ Importantly, models by NICE in the UK assessing the cost-effective evaluation of insulin analogues compared with human insulin therapy only included costs for treating severe hypoglycaemia, and these may fail to take into account the 'true costs' of hypoglycaemia. Total expenditure costs incurred with the use of human insulins, such as higher rates of monitoring due to mild and moderate hypoglycaemia episodes, possible hospitalisation and loss of work hours, are not accounted for in most health economic models.⁵⁹

NEWER INSULIN REGIMENS IN DIABETES

Insulin regimens differ in their complexity, glycaemic efficacy, weight gain and risk of hypoglycaemia, and may require subsequent intensification (table 3). Furthermore, education and empowerment of individuals to self-manage their own insulin regimen is of vital importance.⁶¹

Types of insulin regimen in T2DM

Basal only regimens

A 'basal-only regimen' involves adding a long-acting or intermediate-acting insulin to OHAs or non-insulin injectables, that is, glucose-like peptide-1 receptor agonists (GLP-1 RA), and is commonly recommended when glycaemic targets are difficult to achieve despite intensification of oral therapy.^{62–63} A basal regimen is straightforward, easy to initiate and associated with fewer hypoglycaemic episodes and less weight gain compared with more complex insulin regimens requiring two or more insulin injections a day.⁶³ Broad principles include a once-daily or twice-daily injection regimen, starting at a relatively modest dose with patient-directed insulin titration towards targeted control of fasting blood glucose (table 3).⁶⁴

Basal insulin combination therapy with newer classes of glucose-lowering agents

Combining newer glucose-lowering agents such as GLP-1 RA (incretin mimetics), dipeptidyl peptidase (DPP)-4 inhibitors (incretin enhancers) and SGLT-2 inhibitors (agents that block reabsorption of filtered glucose in the kidney) with insulin therapy offer novel and useful treatment options in T2DM (table 4).

Insulin and GLP-1 receptor agonist combination therapy

Intervention trials with GLP-1 RAs added to basal insulin have shown improvements in HbA1c, postprandial glucose, beneficial effects on weight and reduced basal insulin requirements without increased risk of major hypoglycaemia (table 4).^{66–78–79} Furthermore, glycaemic benefits from structured titration of

insulin to glycaemic targets and weight reduction resulting from a protocol-specified insulin-sparing regimen are important considerations.⁷⁹

Fixed ratio combinations of insulin with GLP-1 analogues

In phase III trials—DUAL-I and DUAL-II—the glycaemic efficacy and safety of once-daily IDegLira (combination of Insulin Degludec (IDeg)/Liraglutide (Lira)) were evaluated in individuals with inadequately controlled T2DM. DUAL-I evaluated individuals who were insulin-naïve on OHAs, whereas the DUAL-II study evaluated individuals on basal insulin with OHAs.^{80–81} In both trials, IDegLira was titrated in dose steps (IDeg 1 unit/Lira 0.0036 mg=1 dose step) with an initial 16-dose step (16 units IDeg+0.6 mg Lira for IDegLira and 16 units for IDeg), which was titrated upwards in both arms to a maximum of 50-dose steps to achieve fasting plasma glucose levels of 4–5 mmol/L. IDegLira demonstrated consistent and significant HbA1c reductions of 1.9% (estimated treatment difference=−1.05%, 95% CI −1.25 to −0.84) with mean weight reduction of 2.7 kg and lower rates of hypoglycaemia compared with insulin degludec.^{73–80}

LixiLan, a fixed-ratio premixed formulation of lixisenatide 1 µg/glargine 2 units, has also demonstrated glycaemic superiority compared with glargine alone (estimated treatment difference=−0.17%; −0.312 to −0.037%, $p=0.0130$) with significant weight loss and no increase in hypoglycaemic events.⁸²

Insulin and DPP-4 inhibitor combination therapy

Studies with DPP-4 inhibitors such as sitagliptin, saxagliptin, vildagliptin and alogliptin in combination therapy with basal insulin have demonstrated improved glycaemic efficacy, and a weight-neutral effect with no increased rates of hypoglycaemia.^{70–71–73–83} In contrast to the aforementioned drugs, linagliptin is a DPP-4 inhibitor with a non-renal route of elimination and hence does not need dose adjustment with impaired renal function. The glycaemic efficacy and safety of linagliptin added to basal insulin in people with T2DM with poor glycaemic control on a basal insulin regimen (with or without OHAs) showed a placebo-adjusted mean change in HbA1c of −0.65% and −0.53% at 24 and 52 weeks respectively, with no increase in hypoglycaemia or body weight.⁶⁹

Insulin and SGLT-2 inhibitor combination therapy

The SGLT-2 inhibitor drugs, including dapagliflozin, canagliflozin and empagliflozin, are a novel treatment approach in T2DM (table 4). They reduce hyperglycaemia by preventing the reabsorption of excess glucose, which is largely regulated by SGLT-2 proteins in the proximal renal tubule. This results in glycosuria and promotes weight loss without an increased risk of hypoglycaemia. Dapagliflozin as add-on therapy to insulin was evaluated in a 2-year follow-up study among individuals with T2DM with inadequate glycaemic control despite high doses of insulin, with or without OHAs. At 104 weeks, dapagliflozin (10 mg/day) added to insulin reduced HbA1c levels (treatment difference=−0.35%, 95% CI −0.55 to −0.15) without increasing overall insulin dose, no reported major hypoglycaemia and weight reduction of ~3 kg over 2 years. Dapagliflozin was well tolerated, though genital infection and urinary tract infection (UTI) were more common in women and occurred as single events during the first 24 weeks of therapy.⁷⁴ Canagliflozin at doses of 100 and 300 mg added to existing stable insulin therapy, with or without OHAs, reduced HbA1c by −0.65% to −0.73% and body weight by −1.9% and −2.4%,

Table 3 Insulin regimen in type 2 diabetes

Insulin regimen	Choice of insulin	Duration of action			Initiation	Titration	Indication for change	Other comments
		Onset	Peak	Duration				
Basal-only insulin regimen	Basal or intermediate acting human insulin, eg, Insulatard, Insuman basal, Humulin I	2–4 h	4–8 h	14–16 h	Usual start is 10 units or 0.1–0.2 units/kg	<ul style="list-style-type: none">▶ Patient-led titration by 2 units at approximately three day intervals aiming for target FPG of 5.5–6 mmol/L without nocturnal hypoglycaemia▶ Reduce the dose by at least 2–4 units or 20%, whichever is greater if FPG falls <4 or unexplained hypoglycaemia	<ul style="list-style-type: none">▶ Suboptimal HbA1c targets or fasting blood glucose or both▶ Fasting glucose levels at target but postprandial glucose levels remain high despite maximum tolerated OHAs▶ Recurrent and/or unresolving hypoglycaemia and/or nocturnal hypoglycaemia	<ul style="list-style-type: none">▶ Simple and easy to initiate with a lower risk of hypoglycaemia and weight gain▶ Compared to human basal insulin, analogues offer advantage of lower rates of nocturnal hypoglycaemia▶ Continue OHAs at current doses unless contraindicated or not tolerated
	Long-acting analogues, eg, glargine (Lantus), Levemir (Detemir)	1–4 h	None	Up to 24 h				
	Newer long-acting analogues*, eg, Tresiba (Degludec), glargine U300† (Tougeo)	30–90 h	None	Up to 42 h				
The three newer classes of glucose-lowering agents that is, DPP-4 inhibitors, GLP-1 agonists and sodium glucose co-transporter-2 inhibitors all have licence to use in combination with insulin and can be useful in select individuals if not already considered in the treatment paradigm prior to intensification to basal-bolus regimen or pre-mix insulin regimen ⁶⁰								
Premixed twice-daily insulin regimen	Pre-mixed or biphasic human insulins, eg, Humulin M3 (30% short-acting insulin with 70% intermediate-acting insulin), Insuman comb 15, 25 or 50	30 min	2–8 h	Up to 24 h	Usual start is 10 units twice daily (consider lower dose in frail, elderly or ‘slim’ individuals)	<ul style="list-style-type: none">▶ Titrate morning dose by 2 units or 10% increments against target blood glucose of <6 mmol/L before lunch and before evening meal▶ Titrate evening dose by 2 units or 10% increments against target blood glucose of 6–8 mmol/L before bed and 5.5–6 mmol/L before breakfast	<ul style="list-style-type: none">▶ Suboptimal HbA1c targets or FPG or both▶ If pre-evening meal blood glucose are high and further increase in morning dose results in mid-morning hypoglycaemia▶ Patient preference or lack of flexibility with regimen	<ul style="list-style-type: none">▶ Simple and easy to initiate▶ Effective in addressing both fasting and prandial glycaemia▶ Preferred for initiation when HbA1c >9.5%▶ Higher risk of hypoglycaemia (may preclude regular use in certain groups, eg, elderly) and weight gain
	Pre-mixed or biphasic analogue insulin, eg, Humalog Mix 25 (25% lispro and 75% neutral protamine lispro), Novomix 30 (30% aspart and 70% protamine-crystallised aspart)	5–15 min	1–4 h	24 h				
Basal-bolus regimen	Short-acting human insulin TDS with basal/intermediate-acting human insulin, eg, Humulin S TDS with Insulatard BD	Short-acting human insulin 30 min	2–4 h	6–8 h	<ul style="list-style-type: none">▶ Calculate total daily insulin dose of 0.3–0.5 units/kg body weight; give 50% as basal and 50% as prandial insulin▶ If already on basal insulin, add 4–6 units prandial insulin	<ul style="list-style-type: none">▶ Adjust the basal insulin doses by 2 unit increments to target FPG of 5.5–6 mmol/L, waiting 3–4 days between adjustments▶ Adjust the short/rapid-acting insulin with dose titration by 10%	Difficulty in complying with multiple injections a day	<ul style="list-style-type: none">▶ Commonly involves multiple injections (at least four to six insulin injections a day)▶ Useful regimen in individuals with a flexible and/or erratic lifestyle, irregular eating habits or shift workers▶ Improved glycaemic benefits are best achieved in motivated individuals with regular and optimal insulin dose titration
	Rapid acting analogue TDS, eg, lispro (Humalog), aspart (NovoRapid), glulisine (Apidra) with long-acting analogue, eg, glargine OD	Duration of basal/intermediate acting human insulin: 12–16 h	Rapid-acting analogue insulin 5–15 min	30–4 h				
		Duration of long-acting analogue insulin: varies according to choice of basal insulin (18–42 h)						

*Individual patient factors, their experience with hypoglycaemia and higher costs incurred needs to be taken into account prior to the use of newer long-acting analogues.

†Need for diligence when prescribing higher strength insulins.

DPP, dipeptidyl peptidase; FPG, fasting plasma glucose; GLP, glucose-like peptide; OD, once daily; OHA, oral hypoglycaemic agent.

Table 4 Efficacy studies of combination therapies with insulin and GLP-1 agonist, DPP-4 and sodium glucose co-transporter-2 (SGLT-2) inhibitors

Study reference	Study details	Treatment groups	HbA1c (%)		Body weight (kg)		Insulin (TDD)		Overall rates of hypoglycaemia	Other comments
			BL	Δ	BL	Δ	BL	Δ		
(A) Insulin and GLP-1 agonist combination therapy										
Buse <i>et al</i> ⁶⁵	Parallel group, 30-week RCT	Exen+Gla±Met±Pio (n=137) vs PBO+Gla±Met ±Pio (n=122)	8.35 8.53	↓1.74† ↓1.04	95.4 93.8	↓1.8† ↑1.0	49.5 u 47.4 u	↑13u† ↑20u	1.4 ^{ns} vs 1.2 (event/patient-year)	Significant reductions in SBP/DBP (3 and 2 mm Hg, respectively) with Exen. Discontinuation due to nausea, vomiting and diarrhoea with Exen vs PBO (9 vs 1%†)
Riddle <i>et al</i> ⁶⁶	Double-blind, parallel group, 24-week RCT	Lixi+Basal ins±Met (n=327) vs PBO+Basal ins ±Met (n=166)	8.4 8.4	↓0.7† ↓0.3	87 89	↓1.8† ↓0.5	54 u 58 u	↓6u† ↓2u	26%† vs 21%	Basal insulin used were Gla (50%) and NPH (40%) Discontinuation due to nausea, vomiting and diarrhoea with Lixi vs PBO (7.6% vs 4.8%)
Seino <i>et al</i> ⁶⁷	Double-blind, parallel group, 24-week RCT	Lixi+Basal ins±SU (n=154) vs PBO+Basal ins ±SU (n=157)	8.5 8.5	↓0.8† ↑0.1	66 66	↓0.4 ^{ns} ↑0.1	25 u 24 u	↓1.4u† ↓0.1u	43%† vs 24%	Basal insulin used were Gla (60%), Det (27%), NPH (13%). Discontinuation due GI side effects with Lixi vs PBO (9.1% vs 3.2%)
Rosenstock <i>et al</i> ⁶⁸	Open-label, 52-week extension phase RCT	Lira (1.8 mg)+Det+Met (n=162) vs Lira (1.8 mg)+Met (n=161)	8.2 8.3	↓0.5† ↑0.1	96 95.3	↓3.7 ↓4.6†	10 u NR	↑32u	0.23 ^{ns} vs 0.03 (event/patient-year)	Det as add-on therapy and intensified to achieve A1c <7%
(B) Insulin and DPP-4 inhibitor combination therapy										
YkiJarvinen <i>et al</i> ⁶⁹	Double-blind, parallel group, ≥52 week RCT	Lina+Basal Ins±Met±Pio (n=631) vs PBO +Basal Ins±Met±Pio (n=630)	8.3 8.3	↓0.6† ↑0.1	NR NR	↓0.3 ^{ns} ↓0.04	NR NR	↑3u ^{ns} ↑4u	31.4% ^{ns} vs 32.9%	Dose adjustment not required in the elderly or with impaired renal function
Barnett <i>et al</i> ⁷⁰	Double-blind, parallel group, 52-week RCT	Saxa+Basal Ins±Met(n=304) vs PBO+Basal Ins ±Met(n=151)	8.7 8.6	↓0.8† ↓0.4	87.7 86.2	↑0.8 ^{ns} ↑0.5	54u 54u	↑6u ^{ns} ↑7u	22.7% ^{ns} vs 26.5%	Common AEs (≥5% with Saxa vs PBO ^{ns}) were UTI, respiratory infection and nasopharyngitis
Vilsbøll <i>et al</i> ⁷¹	Double-blind, parallel group, 24-week RCT	Sita+Ins±Met (n=322) vs PBO+Ins±Met (n=319)	8.7 8.6	↓0.6† 0.0	86.5 87.3	↑0.1 ^{ns} ↑0.1	51u 52u	NR NR	16% ^{ns} vs 8%	74% subjects on long-acting or intermediate-acting insulin, 26% on premixed insulin. Common AEs (≥2% with Sita vs PBO ^{ns}) were UTI, respiratory infection and nasopharyngitis
Rosenstock <i>et al</i> ⁷²	Double-blind, parallel group, 26-week RCT	Alo (12.5 mg)+Ins±Met (n=131) and Alo (25 mg)+Ins±Met (n=129) vs PBO+Ins±Met (n=130)	9.3 9.3 9.3	↓0.6† ↓0.7† ↓0.1	91.0 87.9 86.7	↑0.6 ^{ns} ↑0.7 ↑0.6	58u 55u 57u	↑0.4u ^{ns} ↑0.2u ^{ns} ↑0.6u	26.7% ^{ns} 27.1% ^{ns} 24%	Common AEs such as UTI, nasopharyngitis, diarrhoea and skin/gastrointestinal/infection related events were similar across groups
Fonseca <i>et al</i> ⁷³	Double-blind, parallel group, 52-week extension phase RCT	Vilda (100 mg)+Ins (n=96) (core+extension) vs PBO+Ins/Vilda (50 mg) +Ins (n=104) (subjects on PBO at end of core phase (24 week) were switched to Vilda (50 mg) for the 28 week extension phase)	8.4 8.4	↓0.5† ↓0.4*	92.9 95.1	↑1.8 ^{ns} ↑0.5	76u 82u	↑2u ^{ns} ↑2u	1.8 ^{ns} 1.78 (event/patient-year)	Efficacy more pronounced in patients ≥65 years age, in whom Vilda 100 mg/day+Ins regimen resulted in an HbA1c reduction of 0.94% after 52 weeks of treatment
(C) Insulin and SGLT-2 inhibitor combination therapy										
Wilding <i>et al</i> ⁷⁴	Double-blind, multicentre, 56-week extension phase RCT. (efficacy data at 2 years)	PBO+Ins (n=193) vs Dapa 2.5 mg+Ins (n=202) and Dapa 5/10 mg+Ins (n=211) and Dapa 10 mg+Ins (n=194) (after 48 weeks, Dapa 5 mg switched to 10 mg for the remainder of the study (referred to as 5/10 mg group))	8.5 8.5 8.6 8.6	↓1.0 ↓1.14 ↓1.89†† ↓1.30	94.5 93.0 93.4 94.6	↑1.83 ↓0.99† ↓1.03† ↓1.50†	74.0u 79.9u 77.1u 78.0u	↑18.3u ↑4.1u ↑1.6u ↓0.8u	61.9% 69.3% 61.3% 60.7%	Dapa well tolerated, but genital infection and UTI more common in women compared to PBO
Matthews <i>et al</i> ⁷⁵	Double-blind, placebo-controlled study	Cana 100 mg+Ins (n=565) vs Cana 300 mg +Ins (n=566) vs PBO+Ins (n=587)	8.3 8.3 8.3	↓0.65†† ↓0.73†† ↓0.73††	97.0 97.0 93.4	↓1.9%†† ↓2.4%†† ↓2.4%††	Mean TDD (83u) in all groups was unchanged throughout the study.	49% 48% 37%		Cana was generally well tolerated; †frequency of genital fungal infections and slightly †risk of hypos

Continued

Table 4 Continued

Study reference	Study details	Treatment groups	HbA1c (%)			Body weight (kg)			Insulin (TDD)			Overall rates of hypoglycaemia	Other comments
			BL	Δ	BL	BL	Δ	BL	BL	Δ			
Rosenstock et al ⁷⁶	Double-blind, placebo-controlled, week RCT	PBO+Ins (n=170) vs Empa 10 mg+Ins (n=169) vs Empa 25 mg+Ins (n=155)	8.2	↓0.02	90.5	↑0.70	47.8u	↓1.2u	45.1u	↓0.4u	36.1%	Empa was generally well tolerated; frequency of genitourinary infections	
			8.2	↓0.48†‡	91.6	↓2.2†	48.3u	53+40u	49+40u	↓1.3u	58%	Empa was generally well tolerated; events consistent with genital infections were reported in more patients on empagliflozin and were common in women	
			8.2	↓0.64†‡	93.4	↓2.0†	51+41u	(mean basal+prandial)			51.1%		
Rosenstock et al ⁷⁷	Double-blind, placebo-controlled, 52-week RCT	PBO+Ins (n=188) vs Empa 10 mg+Ins (n=186) vs Empa 25 mg+Ins (n=189)	8.25	↓0.81	96.6	↓0.44	↓10.2u	51+41u	51+41u	↓1.1u	57.7%		
			8.4	↓1.18†‡	94.5	↓1.95†	↓1.3u						
			8.37	↓1.27†‡	93.4	↓2.04†							

*Significant change from 24 weeks (core phase) to 28 weeks (extension phase).

†p<0.05.

‡Compared with placebo.

AE, adverse events; Alo, alogliptin; Basal ins, basal insulin; BD, twice per day; BL, baseline; Cana, canagliflozin; Dapa, dapagliflozin; DPP, dipeptidyl peptidase; Empa, empagliflozin; Exen, exenatide; FPG, fasting plasma glucose; Gla, glargine; GLP, glucose-like peptide; Lira, liraglutide; Lixi, lixisenatide; MET, metformin; NR, not reported; OD, once daily; PBO, placebo; PIO, pioglitazone; SU, sulfonylurea; TDD, total daily dose; TDS, three times per day; UTI, urinary tract infection; Vilda, vildagliptin; Δ, mean change.

respectively, compared with placebo.⁷⁵ The side-effect profile was similar to dapagliflozin. Empagliflozin at 10 and 25 mg/day showed reduced HbA1c levels when added to basal insulin (treatment difference=−0.56%, 95% CI −0.75 to −0.36 and −0.76%, CI −0.90 to −0.50, respectively) and to multiple daily injections of insulin (treatment difference=−0.38%, 95% CI −0.59 to −0.16 and −0.46%, CI −0.67 to −0.25, respectively) without increasing the overall insulin dose. Empagliflozin was well tolerated except for increased genitourinary infections.^{76 77}

Twice-daily premixed insulin regimen

A premixed insulin regimen is commonly employed as a treatment intensification measure in individuals with T2DM failing to achieve HbA1c targets despite a 'basal insulin add-on to oral antidiabetes drugs (OADs)' regimen.^{84 85} The rationale for choosing a twice-daily premixed insulin over a basal insulin regimen to intensify therapy in OAD failure may be influenced by a higher baseline HbA1c (>9.5%) and/or the dominance of postprandial hyperglycaemia with most fasting glucose readings closer to target.⁸⁶ A drawback with biphasic regimens is the lack of flexibility in insulin dose titration between long-acting and short-acting components, higher rates of hypoglycaemia and weight gain, and increased rates of adverse events that may preclude its regular use for elderly individuals.^{87–89} A premixed insulin analogue regimen has a superior advantage over biphasic human insulin in terms of improved glycaemic control, fewer hypoglycaemic events, lower treatment discontinuation rates and cost-effectiveness.⁹⁰

Prandial-only insulin regimen

A review of studies comparing prandial-only insulin with OHA to a basal insulin regimen with OHA regimens showed greater improvements in HbA1c (mean reduction=−0.40; 95% CI −0.29 to −0.51) with prandial insulin regimens, although most studies used three prandial injections and provoked more hypoglycaemia and weight gain.⁸⁷

Basal-bolus regimens

A basal-bolus intensive regimen is best suited for individuals with an active lifestyle and variable eating habits, and requires frequent blood glucose monitoring. The 4 T study was a 3-year randomised trial conducted to estimate the optimal starting insulin regimen in 708 individuals with poorly controlled T2DM. Study subjects were randomised to biphasic insulin aspart twice daily, prandial insulin aspart three times daily or basal insulin detemir once daily (twice if required). A basal insulin regimen was associated with fewer hypoglycaemic episodes and less weight gain compared to premix and prandial insulin regimens.⁶³ Importantly, two thirds of subjects in the basal or prandial groups wherein treatment intensification led to a basal–prandial regimen reached an HbA1c target of <7.0%. A meta-analysis of 16 randomised trials involving 7759 individuals with T2DM, which compared glycaemic efficacies of insulin regimens using analogue insulins, reported that basal-bolus compared to biphasic insulin regimens provided a greater chance of reaching HbA1c targets of <7% (OR 1.75; 95% CI 1.11 to 2.77) without increased hypoglycaemia or weight gain.⁹¹

Summary of insulin regimens in T2DM

Insulin initiation with a basal insulin and dose titration to maximise the possibility of achieving fasting blood glucose targets is an optimal first-line option. Combination therapy of basal insulin with an incretin-based therapy or SGLT-2 inhibitor

therapy because of their complementary profiles are a potential treatment option in obese individuals or in a select group of individuals who, despite escalating doses of insulin, fail to achieve glycaemic targets and may further offer weight reduction with an insulin-sparing effect. In the event of inadequate control of postprandial hyperglycaemia, a deterrent to achieving target HbA1c, the addition of prandial insulin, a short-acting GLP-1 agonist or a twice-daily biphasic regimen are useful strategies.

Types of insulin regimen in T1DM

- ▶ Multiple dose injection (MDI) or basal-bolus therapy
- ▶ CSII
- ▶ Twice-daily premixed insulin regimen

Since our earlier publication in this journal on insulin regimens in T1DM,⁶ more studies have been published supporting our earlier observations. The use of insulin analogues in basal-bolus regimens remains an ideal option for many patients and has shown improved patient treatment satisfaction.¹³ The results of a recent systematic review suggest that CSII (insulin pump) therapy has superior glycaemic efficacy compared with a basal-bolus regimen, with significant reduction in severe hypoglycaemia but it may not result in complete avoidance of mild-to-moderate hypoglycaemic events.⁹² Studies estimating the cost-effectiveness of CSII indicate that it represents good value for money.^{93–95}

A twice-daily premixed insulin regimen is a potential option in individuals with T1DM since the regimen is simple, easy to adopt by carers and may be a useful option in those individuals who struggle to comply with MDI or CSII therapy, although early intensification of insulin therapy should be encouraged.⁹⁶ However, in a 10-year follow-up of insulin regimens among 7206 children and adolescents with T1DM who were attending summer camps, premixed regimens were least favoured for use and showed no glycaemic superiority over other intensive insulin therapies.⁹⁷

Summary of insulin regimens in T1DM

CSII is more effective at improving glycaemia compared with multidose injections; nonetheless, it is not the panacea for superior glycaemic efficacy in all individuals with T1DM. Careful individual consideration, education and support are vital ingredients for its effective use.⁹⁸

CONCLUSION

In this review article, we provide a broad overview and up-to-date evidence on new insulin analogues, including those in clinical development and newer insulin regimens in individuals with T1DM and T2DM. There is some evidence that analogue insulins positively affect quality of life and reduce rates of hypoglycaemia; the advent of newer long-acting analogues with more physiological basal profile and significantly lower risk of nocturnal hypoglycaemia holds promise. However, given the thrust of quality initiatives and health-economics assessments, healthcare providers in recent times have been keen to re-establish human insulin prescribing. Additionally, human insulins may have a modestly higher projected cost than analogues as the impact of hypoglycaemia is not accounted for in many of the economic models. With the advent of newer regimens combining incretin-based therapies and SGLT-2 inhibitors with insulin, the management of select individuals with T2DM failing to meet glycaemic targets on basal insulin regimen has expanded. Although initial results of such combination therapies are reassuring, trial data on their long-term safety and

economic impact are awaited. Finally, strategies such as patient-centred collaborative care, education and training are vital and recommended in the management of individuals with diabetes alongside more efforts to demystify the inertia of insulin initiation among healthcare teams caring for individuals with T2DM.

Main messages

- ▶ New insulin analogues and new insulin regimens may be appropriate in a defined group of patients with diabetes.
- ▶ Insulin degludec, alongside glargine U300 and PEGylated insulin lispro (under development) form a new category of long-acting insulin analogues with more physiological basal profile and all demonstrate a lower risk of nocturnal hypoglycaemia.
- ▶ Basal insulin combination therapy with newer classes of glucose-lowering agents such as GLP-1 receptor agonists, DPP-4 inhibitors and SGLT-2 inhibitors are novel and useful treatment options in individuals with T2DM.
- ▶ Insulin regimens differ in complexity, glycaemic efficacy, weight gain and risk of hypoglycaemia, and may require subsequent intensification.
- ▶ Education and empowering individuals to self-manage their own insulin regimen is of vital importance.

Current research questions

- ▶ What are the long-term glycaemic and safety effects of synergistic treatment with insulin and incretin mimetics?
- ▶ What are the long-term glycaemic and safety effects of synergistic treatment with insulin and newer class of glucose-lowering agents, SGLT-2 inhibitors?
- ▶ What are the effective strategies and system-level interventions that can be applied in primary care to address clinical inertia in the initiation and self-management of insulin therapy?

Key references

- ▶ Davies MJ, Gagliardino JJ, Gray LJ, *et al.* Real-world factors affecting adherence to insulin therapy in patients with Type 1 or Type 2 diabetes mellitus: a systematic review. *Diabetic Med* 2013;30:512–24.
- ▶ Crasto W, Jarvis J, Khunti K, *et al.* New insulins and new insulin regimens: a review of their role in improving glycaemic control in patients with diabetes. *Postgrad Med J* 2009;85:257–67.
- ▶ Wang F, Surh J, Kaur M. Insulin degludec as an ultra-long acting basal insulin once a day: a systematic review. *Diabetes Metab Syndr Obes* 2012;5:191–204.
- ▶ Lasserson DS, Glasziou P, Perera R, *et al.* Optimal insulin regimens in type 2 diabetes mellitus: systematic review and meta-analyses. *Diabetologia* 2009;52:1990–2000.

Self assessment questions

Please answer true (T) or false (F) to the below,

1. NICE guidelines in the UK recommend analogue insulins as first-line therapy in all individuals with T2DM.
2. Insulin detemir is equivalent to glargine but with higher average unit requirement as shown in comparative studies and induces less weight gain.
3. Comparative trials with insulin degludec and glargine or detemir have shown no differences in glycaemic efficacy.
4. PEGylated lispro insulin has shown superior improvements in HbA1c compared with glargine.
5. Biphasic insulin regimens are most suited in elderly individuals since they allow flexibility with insulin dose titration and induce lower rates of hypoglycaemia and weight gain.

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Addendum On Dec 4 2015 Eli Lilly and Company stated that they were encouraged by the efficacy data of basal insulin peglispro (BIL). BIL consistently demonstrate superior glycaemic benefits with lower HbA1c at the primary endpoints compared with those on insulin glargine (IMAGINE-1 trial at 26 weeks (7.1% vs. 7.4%) and in the IMAGINE-3 trial at 52 weeks (7.4% vs. 7.6%)). BIL also demonstrated a reduction in nocturnal hypoglycaemia and an advantage in weight compared to insulin glargine. However, due to the requirement of additional clarity on liver fat data, the company announced that the development of BIL would be ceased.

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Disclaimer The views expressed are those of the author and not necessarily those of the NHS, the named universities, the NIHR or the Department of Health.

Contributors JJ had the idea for the article and had contacted PMJ editorial office in the past. JJ has also contributed towards reviewing the article. WC had authored the original publication on new insulins that was published in *PMJ* 2008 titled 'New insulins and regimens in diabetes'. SS, UHL librarian, performed the literature search. This is a follow-up review written by SGS in view of recent developmental changes in this field since the earlier publication. KK and MJD have provided guidance and have also reviewed the article. MJD is the guarantor, who has kindly agreed to publish this review article.

Competing interests WC has received educational grants and speaker fees from Eli Lilly, Novo Nordisk, Boehringer-Ingelheim and Sanofi-Aventis. KK has acted as consultant, advisory board member and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Servier, BMS and Roche. He has received grants in support of investigator and investigator-initiated trials from Boehringer-Ingelheim, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Merck Sharp & Dohme, GlaxoSmithKline and Servier. MJD has acted as consultant, advisory board member and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen and as a speaker for Mitsubishi Tanabe Pharma Corporation. She has received grants in support of investigator and investigator-initiated trials from Novo Nordisk, Sanofi-Aventis and Lilly.

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REFERENCES

- 1 Whiting DR, Guariguata L, Weil C, *et al.* IDF Diabetes Atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract* 2011;94:311–21.
- 2 U.K. Prospective Diabetes Study Group. U.K. Prospective Diabetes Study 16: overview of 6 years therapy of type II diabetes; a progressive disease. *Diabetes* 1996;45:1655.
- 3 Khunti K, Damci T, Meneghini L, *et al.* Study of Once Daily Levemir (SOLVE™): insights into the timing of insulin initiation in people with poorly controlled type 2 diabetes in routine clinical practice. *Diabetes Obes Metab* 2012;14:654–61.
- 4 Peyrot M, Rubin RR, Lauritzen T, *et al.* Resistance to Insulin Therapy Among Patients and Providers: Results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. *Diabetes care* 2005;28:2673–9.
- 5 Davies MJ, Gagliardino JJ, Gray LJ, *et al.* Real-world factors affecting adherence to insulin therapy in patients with Type 1 or Type 2 diabetes mellitus: a systematic review. *Diabet Med* 2013;30:512–24.
- 6 Crasto W, Jarvis J, Khunti K, *et al.* New insulins and new insulin regimens: a review of their role in improving glycaemic control in patients with diabetes. *Postgrad Med J* 2009;85:257–67.
- 7 Ahmad B. Review: Pharmacology of insulin. *Br J Diabetes Vasc Dis* 2004;4:10–14.
- 8 Crasto W, Jarvis J, Hackett E, *et al.* Insulin U-500 in severe insulin resistance in type 2 diabetes mellitus. *Postgrad Med J* 2009;85:219–22.
- 9 Jonassen I, Havelund S, Hoeg-Jensen T, *et al.* Design of the novel protraction mechanism of insulin degludec, an ultra-long-acting basal insulin. *Pharm Res* 2012;29:2104–14.
- 10 Drab SR, Philis-Tsimikas A. A new option for glycemic control: insulin degludec, a new-generation basal insulin with an ultralong duration of action. *Pharmacotherapy* 2014;34:291–302.
- 11 <https://investor.lilly.com/releaseDetail.cfm?ReleaseID=914999>
- 12 Plank J, Siebenhofer A, Berghold A. Systematic review and meta-analysis of short-acting insulin analogues in patients with diabetes mellitus. *Arch Intern Med* 2005;165:1337–44.
- 13 Rys P, Pankiewicz O, Łach K, *et al.* Efficacy and safety comparison of rapid-acting insulin aspart and regular human insulin in the treatment of type 1 and type 2 diabetes mellitus: a systematic review. *Diabetes Metab* 2011;37:190–200.
- 14 Home PD, Lindholm A, Riis A, for the European Insulin Aspart Study Group. Insulin aspart vs. human insulin in the management of long-term blood glucose control in Type 1 diabetes mellitus: a randomized controlled trial. *Diabet Med* 2000;17:762–70.
- 15 Davey P, Grainger D, MacMillan J, *et al.* Clinical outcomes with insulin lispro compared with human regular insulin: a meta-analysis. *Clin Ther* 1997;19:656–74.
- 16 Plank J, Wutte A, Brunner G, *et al.* A direct comparison of insulin aspart and insulin lispro in patients with type 1 diabetes. *Diabetes Care* 2002;25:2053–7.
- 17 Bode BW. Comparison of pharmacokinetic properties, physicochemical stability, and pump compatibility of 3 rapid-acting insulin analogues—aspart, lispro, and glulisine. *Endocr Pract* 2011;17:271–80.
- 18 Siegmund T, von Amelunxen S, Kaiser M, *et al.* Pump compatibility of insulin aspart compared to insulin lispro with respect to catheter complications and dermal/subcutaneous irritations in type 1 diabetes patients undergoing insulin pump therapy (CSII). *Diabetes* 2005;54(Suppl 1):A105.
- 19 Bolli GB, Luzio S, Marzotti S, *et al.* Comparative pharmacodynamic and pharmacokinetic characteristics of subcutaneous insulin glulisine and insulin aspart prior to a standard meal in obese subjects with type 2 diabetes. *Diabetes Obes Metab* 2011;13:251–7.
- 20 Luzio S, Peter R, Dunseath GJ, *et al.* A comparison of preprandial insulin glulisine versus insulin lispro in people with Type 2 diabetes over a 12-h period. *Diabetes Res Clin Pract* 2008;79:269–75.
- 21 Hermansen K, Fontaine P, Kukolja KK, *et al.* Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with Type 1 diabetes. *Diabetologia* 2004;47:622–9.
- 22 Szybowska A, Golicki D, Groele L, *et al.* Long-acting insulin analogue detemir compared with NPH insulin in type 1 diabetes: a systematic review and meta-analysis. *Pol Arch Med Wewn* 2011;121:237–46.
- 23 Sanches AC, Correr CJ, Venson R, *et al.* Insulin analogues versus human insulin in type 1 diabetes: direct and indirect meta-analyses of efficacy and safety. *Braz J Pharma Sci* 2013;49:501–9.
- 24 Horvath K, Jeitler K, Berghold A, *et al.* Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2007;(2):CD005613.
- 25 Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: a meta-analysis. *Diabetes Res Clin Pract* 2008;81:184–9.
- 26 Davies MJ, Derezinski T, Pedersen CB, *et al.* Reduced weight gain with insulin detemir compared to NPH insulin is not explained by a reduction in hypoglycemia. *Diabetes Technol Ther* 2008;10:273–7.
- 27 Zachariah S, Sheldon B, Shojaei-Moradie F, *et al.* Insulin Detemir Reduces Weight Gain as a Result of Reduced Food Intake in Patients With Type 1 Diabetes. *Diabetes care* 2011;34:1487–91.
- 28 Rosenstock J, Dailey G, Massi-Benedetti M, *et al.* Reduced Hypoglycemia Risk With Insulin Glargine: A meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. *Diabetes Care* 2005;28:950–5.
- 29 Home PD, Fritsche A, Schinzel S, *et al.* Meta-analysis of individual patient data to assess the risk of hypoglycaemia in people with type 2 diabetes using NPH insulin or insulin glargine. *Diabetes Obes Metab* 2010;12:772–9.
- 30 Swinnen SG, Simon AC, Holleman F, *et al.* Insulin detemir versus insulin glargine for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2011;(7):CD006383.
- 31 Mathieu C, Hollander P, Miranda-Palma B, *et al.* Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1

- diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. *J Clin Endocrinol Metab* 2013;98:1154–62.
- 32 Heller S, Buse J, Fisher M, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet* 2012;379:1489–97.
 - 33 Zinman B, Philis-Tsimikas A, Cariou B, et al. Insulin degludec versus insulin glargine in insulin-naïve patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). *Diabetes Care* 2012;35:2464–71.
 - 34 Gough SCL, Bhargava A, Jain R, et al. Low-volume insulin degludec 200 units/mL once daily improves glycemic control similarly to insulin glargine with a low risk of hypoglycemia in insulin-Na+ve patients with type 2 diabetes: a 26-week, randomized, controlled, multinational, treat-to-target trial: The BEGIN LOW VOLUME trial. *Diabetes Care* 2013;36:2536–42.
 - 35 Garber AJ, King AB, Prato SD, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet* 2012;379:1498–507.
 - 36 Wang F, Surh J, Kaur M. Insulin degludec as an ultralong-acting basal insulin once a day: a systematic review. *Diabetes Metab Syndr Obes* 2012;5:191–204.
 - 37 Ratner RE, Gough SCL, Mathieu C, et al. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. *Diabetes Obes Metab* 2013;15:175–84.
 - 38 Vaag A, Christiansen JS, Niskanen L, et al. IDegAsp Lowers the Rate of Hypoglycemia vs. Biphasic Insulin Aspart 30 in Adults with T2D Achieving Glycemic Target (HbA1c <7.0%): A Meta-analysis. *American Diabetes Association: 74th Scientific sessions 888-P*; 2014.
 - 39 Korsatko S, Deller S, Koehler G, et al. A Comparison of the Steady-State Pharmacokinetic and Pharmacodynamic Profiles of 100 and 200 U/mL formulations of ultra-long-acting insulin degludec. *Clin Drug Investig* 2013;33:515–21.
 - 40 Tillner J, Bergman K, Teichert L, et al. Euglycemic Clamp Profile of New Insulin Glargine U300 Formulation in Patients With Type 1 Diabetes (T1DM) is Different from Glargine U100. *American Diabetes Association: 73rd Scientific sessions, Poster 920-P*; 2014.
 - 41 Goldman J, White JR Jr. New insulin glargine 300 u/mL for the treatment of type 1 and type 2 diabetes mellitus. *Ann Pharmacother* 2015;49:1153–61.
 - 42 Robert Ritzel, Ronan Roussel, Andrea Giaccari, Jiten P. Vora, Marie-Lise Grisoni, Claire Brulle-Wohlhueter, Stanislav Glezer, Hannele Yki-Jarvinen, Munich, Germany, Paris, France, Rome, Italy, Liverpool, United Kingdom, Levallois-Perret, France, Helsinki, Finland. Glycemic Control and Hypoglycemia with Insulin Glargine 300 U/mL (Gla-300) vs. Glargine 100 U/mL (Gla-100) in Type 2 Diabetes (T2DM) in a Patient-Level Meta-analysis of 1-Yr Phase 3a. y <https://ada.scientificposters.com/epsAbstractADA.cfm?id=8>
 - 43 Ritzel R, Roussel R, Bolli GB, et al. New Insulin Glargine 300 U/mL: Glycemic Control and Hypoglycemia in a Meta-analysis of Phase 3a EDITION Clinical Trials in People with T2DM. *American Diabetes Association: 74th Scientific sessions. 90-LB*; 2014. EDITION Studies ADA 2015 1030-P.
 - 44 Endocrinologic and Metabolic Drug Advisory Committee. Insulin Degludec/Insulin Aspart NDA 203313. 8-11-2012. <http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugs/advisorycommittee/ucm327015.pdf>
 - 45 Sinha VP, Howey DC, Soon D, et al. Single-dose pharmacokinetics (PK) and glucodynamics (GD) of the novel long-acting basal insulin LY2605541 in healthy subjects. *72nd Scientific Sessions of the American Diabetes Association*; June 8-12, Philadelphia. Poster 106-P. 2012.
 - 46 Rosenstock J, Bergenstal RM, Blevins TC et al. Better glycemic control and weight loss with the novel long-acting basal insulin LY2605541 compared with insulin glargine in type 1 diabetes: a randomized, crossover study. *Diabetes care* 2013;36:522–8.
 - 47 Lilly's Basal Insulin Peglispro Shows Superiority in HbA1c Reduction Compared to Insulin Glargine in Three Phase III Trials in Patients with Type 2 Diabetes. 12-5-2014. <https://investor.lilly.com>
 - 48 Buse J, Rodbard H, Serrano C, et al. Superior HbA1c Reduction with Basal Insulin Peglispro (BIL) vs Insulin Glargine (GL) Alone or with Oral Antihyperglycemic Medications (OAMs) in T2D Patients (Pts) Previously Treated with Basal Insulin: IMAGINE 5. Abstract 984-P. Presented at *75th American Diabetes Association (ADA) Scientific Sessions*; June 5–9, 2015. Boston, MA. IMAGINE 5. <https://ada.scientificposters.com/epsAbstractADA.cfm?id=3>
 - 49 Davies MJ, Russell-Jones D, Selam JL, et al. Basal Insulin Peglispro (BIL) Is Superior to Insulin Glargine in Reducing HbA1c at 52 Wks in Insulin-Naïve T2D Patients treated with Oral Antihyperglycemic Medications (OAMs): IMAGINE 2. *Diabetes* 2015;64(Suppl 1):A1–100.
 - 50 Richard M. Bergenstal, Helen Lunt, Edward Franek, et al. Hartman, Myriam Rosilio, Edward J. Bastyr III, for the IMAGINE 3 study group, Minneapolis, MN, Christchurch, New Zealand, Warsaw, Poland, Paris, France, Indianapolis, IN, Neuilly sur Seine, France. Superior Reduction of HbA1c in a Double-Blind, Randomized Study of Basal Insulin Peglispro (BIL) vs. Insulin Glargine (GL) in Patients (pts) with T1D: IMAGINE 3 <https://ada.scientificposters.com/epsAbstractADA.cfm?id=5>
 - 51 Hartman ML, Zhang S, Bastyr III EJ, et al. Indianapolis. <https://ada.scientificposters.com/epsAbstractADA.cfm?id=6>
 - 52 Cameron CG, Bennett HA. Cost-effectiveness of insulin analogues for diabetes mellitus. *CMAJ* 2009;180:400–7.
 - 53 Kostev K, Dippel FW, Bierwirth R. Resource consumption and costs of treatment in patients with type 1 diabetes under intensified conventional therapy under german real-life conditions. *J Diabetes Sci Technol* 2013;7:736–42.
 - 54 SCHARR Rapid Reviews Group School of Health and Related Research University of Sheffield. *The clinical and cost-effectiveness of long-acting insulin analogue, insulin glargine*. National Institute of Clinical Excellence 2008.
 - 55 Holden SE, Poole CD, Morgan CL, et al. Evaluation of the incremental cost to the National Health Service of prescribing analogue insulin. *BMJ Open* 2011;1:e000258.
 - 56 Tunis SL, Minshall ME, Conner C, et al. Cost-effectiveness of insulin detemir compared to NPH insulin for type 1 and type 2 diabetes mellitus in the Canadian payer setting: modeling analysis. *Curr Med Res Opin* 2009;25:1273–84.
 - 57 Schöffski O, Breitschdel L, Benter U et al. Resource utilisation and costs in patients with type 2 diabetes mellitus treated with insulin glargine or conventional basal insulin under real-world conditions in Germany: LIVE-SPP study. *J Med Econ* 2008;11:695–712.
 - 58 Gordon J, Evans M, McEwan P, et al. Evaluation of Insulin Use and Value for Money in Type 2 Diabetes in the United Kingdom. *Diabetes Ther* 2013;4:51.
 - 59 Brod M, Christensen T, Thomsen TL, et al. The impact of non-severe hypoglycemic events on work productivity and diabetes management. *Value Health* 2011;14:665–71.
 - 60 Inzucchi SE, Bergenstal RM, Buse JB, et al. Matthews Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 2015;58:429–42.
 - 61 Skinner TC, Craddock S, Arundel F, et al. Four theories and a philosophy: self-management education for individuals newly diagnosed with type 2 diabetes. *Diabetes Spectrum* 2003;16:75–80.
 - 62 Lasserion DS, Glasziou P, Perera R, et al. Optimal insulin regimens in type 2 diabetes mellitus: systematic review and meta-analyses. *Diabetologia* 2009;52:1990–2000.
 - 63 Holman RR, Farmer AJ, Davies MJ, et al. Three-Year Efficacy of Complex Insulin Regimens in Type 2 Diabetes. *N Engl J Med* 2009;361:1736–47.
 - 64 Blonde L, Merilainen M, Karwe V, et al. TITRATE Study Group. Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets—the TITRATE study. *Diabetes Obes Metab* 2009;11:623–31.
 - 65 Buse JB, Bergenstal RM, Glass LC, et al. Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes: a randomised controlled trial. *Ann Intern Med* 2011;154:103–12.
 - 66 Riddle MC, Aronson R, Home P, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). *Diabetes Care* 2013;36:2489–96.
 - 67 Seino Y, Min KW, Niemoeller E, et al. Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). *Diabetes Obes Metab* 2012;14:910–17.
 - 68 Rosenstock J, Rodbard HW, Bain SC, et al. One-year sustained glycemic control and weight reduction in type 2 diabetes after addition of liraglutide to metformin followed by insulin detemir according to HbA1c target. *J Diabetes Complicat* 2013;27:492–500.
 - 69 Yki-Järvinen H, Rosenstock J, Durán-García S, et al. Effects of adding linagliptin to basal insulin regimen for inadequately controlled type 2 diabetes: a >52-week randomized, double-blind study. *Diabetes care* 2013;36:3875–81.
 - 70 Barnett AH, Charbonnel B, Donovan M, et al. Effect of saxagliptin as add-on therapy in patients with poorly controlled type 2 diabetes on insulin alone or insulin combined with metformin. *Curr Med Res Opin* 2012;28:513–23.
 - 71 Vilsbøll T, Rosenstock J, Yki-Järvinen H, et al. Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes. *Diabetes Obes Metab* 2010;12:167–77.
 - 72 Rosenstock J, Rendell MS, Gross JL, et al. Alogliptin added to insulin therapy in patients with type 2 diabetes reduces HbA1c without causing weight gain or increased hypoglycaemia. *Diabetes Obes Metab* 2009;11:1145–52.
 - 73 Fonseca V, Baron M, Shao Q, et al. Sustained efficacy and reduced hypoglycemia during one year of treatment with vildagliptin added to insulin in patients with type 2 diabetes mellitus. *Horm Metab Res* 2008;40:427–30.
 - 74 Wilding JPH, Woo V, Rohwedder K et al. Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: efficacy and safety over 2 years. *Diabetes Obes Metab* 2014;16:124–36.
 - 75 Matthews DR, Fulcher G, Perkovic V, et al. Efficacy and safety of canagliflozin (CANA), an inhibitor of sodium glucose co-transporter 2 (SGLT2), added-on to

- insulin therapy with or without oral agents in type 2 diabetes. *Diabetologie und Stoffwechsel* 2013;8:P251.
- 76 Rosenstock J, *et al.* Empagliflozin as add on to basal insulin for 78 weeks improves glycemic control with weight loss in insulin-treated type 2 diabetes (T2DM). *Can J Diab* 2013;37:S32.
 - 77 Rosenstock J, Jelaska A, Frappin G, *et al.*, on behalf of the EMPA-REG MDI Trial Investigators. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2. *Diabetes Care* 2014;37:1815–23.
 - 78 Riddle MC, Forst T, Aronson R, *et al.* Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: a 24-week, randomized, placebo-controlled study (GetGoal-Duo 1). *Diabetes care* 2013;36:2497–503.
 - 79 Balena R, Hensley IE, Miller S, *et al.* Combination therapy with GLP-1 receptor agonists and basal insulin: a systematic review of the literature. *Diabetes Obes Metab* 2013;15:485–502.
 - 80 Buse JB, Vilsboll T, Thurman J, *et al.* Liraglutide contributes significantly to glycaemic control achieved in IDegLira: a double-blind Phase 3 trial in type 2 diabetes. *Oral presentation (OP—0082) at the World Diabetes Congress for the International Diabetes Federation (IDF); 3 December 2013.*
 - 81 Gough SCL, Buse JB, Woo VC, *et al.* IDegLira, a Novel Fixed Ratio Combination of Insulin Degludec and Liraglutide, is Efficacious and Safe in Subjects with Type 2 Diabetes: A Large, Randomized Phase 3 Trial. *Oral presentation (OP 37) at the 49th Annual European Association for the Study of Diabetes (EASD) Congress; 27 September 2013.*
 - 82 Rosenstock J, Diamant M, Silvestre L, *et al.* Benefits of a Fixed-Ratio Formulation of Once-Daily Insulin Glargine/Lixisenatide (LixiLan) vs. Glargine in Type 2 Diabetes (T2DM) Inadequately Controlled on Metformin. *American Diabetes Association: 74th Scientific sessions. 332-OR. 2014.*
 - 83 Hollander P, Raslova K, Skjøth TV, *et al.* Efficacy and safety of insulin detemir once daily in combination with sitagliptin and metformin: The TRANSITION randomized controlled trial. *Diabetes Obes Metab* 2011;13:268–75.
 - 84 Jang HC, Guler S, Shestakova M, on behalf of the PRESENT study group. When glycaemic targets can no longer be achieved with basal insulin in type 2 diabetes, can simple intensification with a modern premixed insulin help? Results from a subanalysis of the PRESENT study. *Int J Clin Pract* 2008;62:1013–18.
 - 85 American Diabetes Association. Standards of Medical Care in Diabetes. *Diabetes care* 2014;37(Suppl 1):S14–80.
 - 86 Wei N, Zheng H, Nathan DM. Empirically establishing blood glucose targets to achieve HbA1c goals. *Diabetes Care* 2014;37:1048–51.
 - 87 Yki-Järvinen H, Kottrönen A. Is there evidence to support use of premixed or prandial insulin regimens in insulin-naïve or previously insulin-treated type 2 diabetic patients? *Diabetes care* 2013;36(Suppl 2):S205–11.
 - 88 Haddad J, Khoshnati Nikoo M, Benabbas Y, *et al.* Safety and Effectiveness of Switching from a Basal-only to Biphasic Insulin Aspart 30 Insulin Regimen. *Diabetes Ther* 2013;4:309–19.
 - 89 Oyer DS, Shepherd MD, Coulter FC, *et al.* Efficacy and tolerability of self-titrated biphasic insulin aspart 70/30 in patients aged >65 years with type 2 diabetes: an exploratory post hoc subanalysis of the INITIATEplus Trial. *Clin Ther* 2011;33:874–83.
 - 90 Morgan CL, Evans M, Toft AD, *et al.* Clinical effectiveness of biphasic insulin aspart 30:70 versus biphasic human insulin 30 in UK general clinical practice: a retrospective database study. *Clin Ther* 2011;33:27–35.
 - 91 Giugliano D, Maiorino MI, Bellastella G, *et al.* Efficacy of insulin analogs in achieving the hemoglobin a1c target of <7% in type 2 diabetes: meta-analysis of randomized controlled trials. *Diabetes care* 2011;34:510–17.
 - 92 Misso ML, Egberts KJ, Page M, *et al.* Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. *Cochrane Database Syst Rev* 2010;(1):CD005103.
 - 93 Cummins E, Royle P, Snaith A, *et al.* Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation. *Health Technol Assess* 2010;14:iii–xvi, 1–181.
 - 94 Petkova E, Petkova V, Konstantinova M, *et al.* Economic evaluation of continuous subcutaneous insulin infusion for children with diabetes—a pilot study: CSII application for children—economic evaluation. *BMC Pediatr* 2013;13:155.
 - 95 St Charles M, Lynch P, Graham C, *et al.* A cost-effectiveness analysis of continuous subcutaneous insulin injection versus multiple daily injections in type 1 diabetes patients: a third-party US payer perspective. *Value Health* 2009;12:674–86.
 - 96 Pihoker C, Badaru A, Anderson A, *et al.* Insulin regimens and clinical outcomes in a type 1 diabetes cohort: the SEARCH for diabetes in youth study. *Diabetes Care* 2013;36:27–33.
 - 97 Redon I, Beltrand J, Martin D, *et al.* Changes in insulin therapy regimens over 10 yr in children and adolescents with type 1 diabetes attending diabetes camps. *Pediatr Diabetes* 2014;15:329–35.
 - 98 National Institute of Clinical Excellence. Type 2 diabetes: the management of type 2 diabetes (partially updated by CG87) (CG66). 2008. <http://www.nice.org.uk/guidance>

Answers

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5. F