Title: Are newer insulin analogues better for people with type 1 diabetes?
Short title: New insulin analogues

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Novelty Statement – What's New?

- Successfully balancing the risk of hypoglycaemia whilst maintaining tight glycaemic control is the aim of optimum insulin delivery in type 1 diabetes
- Many new insulin analogues are available for people with type 1 diabetes, including more rapidly acting mealtime insulins and longer-acting and more concentrated basal insulins.
- In this paper we discuss the challenges of insulin delivery using first-generation insulin analogues, the potential benefits and disadvantages of newer agents and assess the risk of hypoglycaemia and safety of all insulin analogues

Abstract

Achieving optimal blood glucose control in type 1 diabetes is a delicate balance between ensuring tight glycaemic control, without the expense of hypoglycaemia and weight gain, two major factors impacting quality of life.
This is a real challenge for people with type 1 diabetes and underpins many of the struggles they face in self-managing on a day-to-day basis.
The main goals of insulin delivery are to try to simulate the physiology of beta-cell insulin secretion as closely as possible and to overcome the challenges of peripheral insulin administration by achieving rapidity of onset with mealtime insulins and stability of the glucose lowering effects of long-acting insulins. Since the early days of human insulin use, there have been many developments in insulin formulations that aim to achieve these goals as much as possible, thus contributing to better glycaemic control whilst minimising hypoglycaemia.

In this review we discuss the currently available insulin analogues, the challenges of achieving glucose control using current analogues in those on multiple daily injections and appraise the evidence-base for newer generation insulin analogues such as insulin degludec, glargine U300, faster acting insulin aspart and bio-chaperone lispro. We also highlight new insulins in development and unmet needs in people with type 1 diabetes.

Key Words
Insulin therapy
Hypoglycaemia
Clinical trials
Novel agents

Introduction

The primary aim in the treatment of people with type 1 diabetes is to replace insulin that the pancreatic beta cells, destroyed by an autoimmune process, are unable to produce in sufficient amounts to maintain euglycaemia. How insulin gets replaced, is increasingly sophisticated in comparison to the early years after the discovery of insulin [1, 2]. However substantial improvements in insulin delivery are constrained by several factors that limit considerably the pharmacokinetic improvements of insulin analogues, these include; continued subcutaneous administration; the absence of reliable real-time and permanent glucose sensing; challenges in calculating doses of prandial insulin; absence of feedback of glycaemia to insulin action; and unpredictable variations in individual insulin sensitivity impacting basal insulin dose.

The efforts directed towards new and different insulins seek to achieve two main goals; the first is to try to simulate the beta-cells in their insulin secretion profile, essentially maintaining basal insulin levels between meals and rapid release in relation to mealtimes [1]. The second is to overcome pharmacokinetic and physiological challenges of peripheral insulin administration, which is in contrast to beta-cells that deliver insulin directly into the portal circulation. Trying to achieve both aims, however, is further challenged by the risk of hypoglycaemia, as administration of exogenous insulin breaks the closed homeostatic mechanism of counter-regulation and insulin delivery into the peripheral circulation is not linked to glucose sensing [2, 3]. Successfully balancing the risk of hypoglycaemia whilst simulating a physiological profile to maintain euglycaemia is the 'sweet spot' of insulin delivery in type 1 diabetes and critical for the many individuals who take multiple daily insulin injections and indeed, those on continuous subcutaneous insulin pump therapy.

In this review, we examine whether newer insulin analogues are better for people with type 1 diabetes. We specifically discuss developments in insulin analogues, their benefits, safety and disadvantages, and review major trial data. We focus on pivotal studies that compare first generation analogues to human insulin and newer analogues to existing analogues in people with type 1 diabetes.

The evolution of insulin therapy

Human insulin was one of the first drugs to be produced using recombinant technologies in the early 1980's [2]. Two major forms were manufactured; regular insulin (short acting) and longer-acting forms in which short-acting insulin was combined with protamine, for example neutral protamine Hagedorn (NPH) and zinc protamine insulin [2]. Once injected subcutaneously, insulin arranged in hexamers around a central zinc ion, must dissociate to

monomers to be absorbed from subcutaneous tissues [1]. The necessity to pre-mix longer-acting forms in vials prior to injection and the variable absorption from peripheral tissues, were also recognised early on and accounted for the variable duration of action observed [1, 4].

In 1993, the Diabetes Control & Complication Trial demonstrated that intensive insulin therapy, using multiple daily injections of rapid acting human insulin combined with NPH insulin or human regular insulin delivered using continuous subcutaneous insulin infusion (CSII), was superior to 'conventional' insulin therapy consisting of regimens of once or twice daily insulin administrations (typically NPH or mixes of regular and NPH insulin) [5].
Though this 'basal bolus' approach was superior in achieving better glycaemic control and fewer long-term complications, like retinopathy and nephropathy, these benefits were associated with a risk of severe hypoglycaemia and weight gain [1, 3, 6]. Although, the greater risk of nocturnal hypoglycaemia observed in the DCCT study may, in part, reflect the administration of regular and NPH insulin contemporaneously with evening meals and subsequent studies have demonstrated fewer events when doses are split in time [7].

Recognising the need for better insulin preparations permitting more precise simulation of the physiological insulin excursions at mealtimes and more stable profiles at night signalled the start of the development of insulin analogues.

How do analogue insulin injections work?

Analogue insulins are similar to human insulin but modified in their amino acid sequence or by the addition of free fatty acid chains to the parent molecule (see table 1), resulting in changes to the pharmacokinetic profile, primarily through altered absorption from the subcutaneous tissue. This led, either to faster-acting insulins, with more rapid onset of action and shorter duration or slower-acting insulin preparations with longer durations and more stable daily profiles.

First generation insulin analogues, known as rapid acting aspart, lispro and glulisine insulin or long-acting insulin glargine U100 and insulin detemir, have now become the standard of care for people with type 1 diabetes in many countries. However, cost of insulin analogues have precluded global uptake, with human insulin still the preferred choice in people with type 1 diabetes in resource-limited countries [8]

Compared to regular human insulin, the preformed hexamers in rapid acting insulin analogues, lispro [9], aspart [10] and glulisine [11], dissociate faster in the subcutaneous space, allowing dimeric and monomeric insulin to be rapidly absorbed through the capillaries and thus more rapid onset of insulin action and less protracted insulin action [3, 12]. These analogues permitted insulin injection closer to meal onset, allowing greater flexibility in daily

life, but also lowered the risk of hypoglycaemia for several hours after the meal, particularly in the early hours of night [9]. This was very relevant to those individuals who had to snack to avoid hypoglycaemia from the protracted action of human insulin. Rapid acting insulin analogues have also rapidly become the insulins of choice for use in CSII, where algorithms for bolus calculation and basal rate adaptations rely on the more rapid onset of action of these insulins.

Insulin glargine has several amino acid changes compared to human insulin and is acidic in pH in its formulation (the only such analogue preparation) [2]. Upon injection into the subcutaneous space, the acidic pH is neutralised and results in the formation of micro-precipitates of insulin that are gradually absorbed over time [2, 13]. Insulin glargine is rapidly and almost completely processed to metabolites M1 and M2 that lack the di-arginine, with M1 responsible for metabolic actions [14, 15]. Insulin detemir also has amino acid changes but in addition a fatty acid residue attached, myristic acid [1, 2]. The slow onset of action reflects dihexamer formation under the skin after injection, with additional albumin binding in the subcutaneous space and then, also, in circulation [16]. Once the insulin detemir dissociates from albumin, it becomes active at target tissues.
These alterations lead to a more protracted insulin profile and in particular in insulin glargine U100, obviate the need for twice or even three daily injections to cover basal insulin needs as observed with NPH. Some people with type 1 diabetes can also cover their basal needs with one injection of insulin detemir, but others need two injections of insulin detemir [17].

The inherently soluble nature of insulin glargine U100 and detemir reduces variability in insulin profiles compared to NPH, as inconsistency in resuspension is an important contributor to absorption variation [1, 6, 18]. This decreased variability results in less hypoglycaemia risk, particularly at night. Additionally, some studies of insulin detemir, have shown a small but consistent reduction in weight compared to NPH insulin [18, 19] but this is modest at best.

What are the limitations of established insulin analogues?

Despite the advances on regular insulin, rapid acting insulin analogues such as aspart, lispro and glulisine still have a relative delay in timing of effect, meaning they need to be taken well in advance of the meal, to enable the peak insulin to coincide with the glucose excursion associated with food ingestion [3, 9–11]. We know from studies that the timing of the bolus is best when given at least 15-20 minutes before eating. This achieves better prandial glucose control, lower HbA1c levels and less hypoglycaemia than administration immediately before or after the meal [3, 20]. This requirement is at best inconvenient and also difficult to achieve much of the time in practical terms. Thus, the delayed effect of established analogue insulins is a real problem for people with type 1 diabetes.

Meanwhile, existing basal insulins do not last 24 hours in all people with type 1 diabetes; insulin detemir requires twice daily dosing in many individuals as it has a significantly shorter duration of action compared to insulin glargine U100. In addition, insulin glargine U100 may not last 24 hours in some individuals. Existing basal insulins also need to be administered at the same time of the day and there is still significant variability in the glucose lowering effects both within and between individuals [21]. This variability may not be relevant between people, but within the same individual, can cause fluctuation in glycaemic levels, resulting in episodes of hypoglycaemia and hyperglycaemia [22].

Insulin glargine U100 and insulin detemir have also shown significant peaks and troughs following once daily injection [23, 24]. Measurement of 'free insulin' in serum is not possible, and so profiles of these insulins are determined by monitoring glucose infusion rates to achieve euglycaemia during clamp studies [25].

Long-acting insulin analogues – what's new?

Insulin Degludec

Insulin degludec is an ultra-long acting insulin lasting well-beyond 24 hours, available in U100 and U200 formulations [26]. The extended action is primarily achieved by the addition of a fatty acid moiety and other conformational changes in the molecule, enabling albumin to bind to the insulin [2, 26, 27]. Once injected, insulin degludec forms multihexamer chains of insulin in the subcutaneous space, essentially forming a reservoir from which active monomers are progressively released [27].
These changes to the insulin molecule have two effects. The first is that the profile of degludec is relatively stable, as reflected by the flat glucose infusion profile during clamp studies [23, 26]. This contrasts insulin glargine U100 and determir insulin, where there are discernible peaks and troughs to the glucose infusion rates required over the 24 hours post-injection [21]. The second effect is the low variability in the glucose lowering effects of insulin degludec; the coefficient of variation of the glucose lowering effect of degludec is much lower than has been observed with insulin glargine U100 when studied in steady state conditions (chronic administration) [23, 26]. Taken together, these unique modifications in degludec could address several limitations of insulin glargine U100 and insulin detemir – lasting more than 24 hours, low intra-individual variability, and minimal peaks or troughs in pharmacodynamic studies.

So, how does it fair in head to head comparisons with other basal insulins in people with type 1 diabetes? The BEGIN Basal-Bolus study compared insulin degludec to insulin glargine U100 with insulin aspart as the short acting insulin analogue in an open-label non-inferiority study design in people with type 1 diabetes [28]. HbA1c, post-prandial glucose and overall rates of hypoglycaemia were similar across both groups. However, a sub-analysis of the

hypoglycaemia episodes, revealed that there was a 25% reduction in rates of nocturnal hypoglycaemia with insulin degludec compared to insulin glargine U100 (4.41 vs 5.86 per patient year of exposure, p=0.021) [28]. Interestingly, only 11% of all hypoglycaemia was nocturnal, however as daytime hypoglycaemia may be confounded by bolus insulin use, the reduced overnight rate is likely a unique effect of insulin degludec. This may be explained by the very even distribution of insulin degludec from the injected reservoir across 24 hours. In contrast, 60% of insulin glargine U100 exposure occurs in the first 12 hours of a once daily dose [28].
A second open-label study non-inferiority study (BEGIN: Flex T1) also demonstrated reduced rates of nocturnal hypoglycaemia and also non-inferiority when changing the timing of the degludec dose [29]. In one arm of this study flexibility was enforced, requiring participants to vary the timing of their daily injection of insulin degludec between 8 and 40 hours. This forced flexibility arm did not impact HbA1c, nor was there an increase in hypoglycaemia, confirming the greater flexibility of injection time with this basal insulin.

The SWITCH 1 study a few years later, corroborated the findings of BEGIN Basal-Bolus using a double-blinded randomized crossover design study with no wash-out [30]. Over a 16-week maintenance period, there was an 11% risk reduction in symptomatic hypoglycaemia, a 36% reduction in nocturnal symptomatic hypoglycaemia and a 35% reduction in severe hypoglycaemia with insulin degludec compared to insulin glargine U100 despite standardised insulin titration protocols between the groups [30].

A later meta-analysis of several studies comparing insulin degludec to insulin glargine U100 in type 1 diabetes, demonstrated only marginal benefits of insulin degludec in reducing hypoglycaemia. However, of note, when examining people with type 2 diabetes there were significant reductions in nocturnal and severe hypoglycaemia when using insulin degludec, compared to insulin glargine U100 [31].

There appear to be some potential clinical benefits of insulin degludec over insulin glargine U100, which it achieves without compromising glycaemic control, these include; longer duration with flexibility around timing of the dose, stable glucose lowering effects and potentially less hypoglycaemia, in particular a reduction of nocturnal events. However, cost is currently prohibitive in some healthcare settings, although cost effectiveness analyses for the UK do show benefit in certain groups [32]. It is likely that healthcare practitioners will make localised decisions around what is deemed cost-effective, whether benefits are clinically significant [33] and how use of insulin degludec fits into the multiple other strategies to prevent hypoglycaemia. These decisions should also be offset against the cost and impact on quality of life of hypoglycaemia itself [34, 35].

Insulin glargine U300

In concentrated formulation insulin glargine U300 has a different pharmacokinetic and pharmacodynamic profile to insulin glargine U100 [36]. The micro-precipitates that form with the concentrated and smaller volume of insulin glargine U300 take longer to be absorbed from the 'depot' [1, 37]. Thus, the release of insulin glargine U300 occurs more slowly than the U100 formulation. Studies confirm that U300 glargine lasts longer than U100. In one study after 7 days at steady state dosing, the half-life of U300 was 19 hrs compared to 13.5 hrs for insulin glargine U100 [36, 38]. It has a flatter 24-hour profile and lower variability than insulin glargine U100. Due to subcutaneous enzymatic degradation, the bioavailability of insulin glargine U300 is reduced compared to U100 and so higher doses are needed [1, 36, 38].

The EDITION trials were non-inferiority studies in people with type 1 and type 2 diabetes comparing insulin glargine U300 to insulin glargine U100 [39]. HbA1c reduction was similar and although there was a suggestion of lower rates of nocturnal hypoglycaemia, the study in type 1 diabetes had not been powered to adequately detect these changes [39, 40].
In one study, outcomes related to continuous glucose monitoring were examined in people with type 1 diabetes receiving insulin glargine U100 or U300. Although time in range and HbA1c was equal between the two groups at the end of the 16 week study, glucose levels in the last 4 hours of the 24-hour profile were significantly lower in those receiving insulin glargine U300 [41].

The benefit of glargine U300 may lie in achieving 24-hour coverage with more stable profiles and less variability. However, whether achieving less variability is clinically meaningful remains to be seen. It is therefore currently unclear, who benefits most from insulin glargine U300, but as clinical experience increases, this knowledge gap is likely to be addressed.

Insulin degludec versus insulin glargine U300

Two pharmacokinetic/pharmacodynamic studies have now compared insulin degludec to insulin glargine U300 in people with type 1 diabetes. In the first, exploring differences in action assessed using the euglycaemic clamp, insulin degludec U200 was shown to have lower day-to-day and within-day variability and the glucose-lowering effect was also shown to be more consistent than insulin glargine U300 [42]. However, a second study comparing insulin degludec U100 with insulin glargine U300 demonstrated less variability with insulin glargine U300 [43]. These contradictory findings may be explained by different definitions of variability and different assessment techniques (steady-state versus acute measurements) [44].
To date, there are no head-to-head clinical studies comparing diabetes outcomes between glargine U300 and degludec in people with type 1 diabetes. The BRIGHT study (randomising insulin-naive people with type 2 diabetes) compared insulin degludec U100 to insulin glargine U300, showed non-inferiority in HbA1c reduction and similar hypoglycaemia across the entire study period, with however fewer hypoglycaemic events during the dose titration phase,

favouring insulin glargine U300 [45]. The BRIGHT study also confirmed the higher insulin dose needed with insulin glargine U300, possibly explaining the difference in hypoglycaemia risk in the titration phase. The CONFIRM study (a retrospective analysis of healthcare records) compared efficacy of insulin degludec and insulin glargine U300 in insulin-naïve people with type 2 diabetes, showing greater reduction in HbA1c and hypoglycaemia with insulin degludec [46]. Similar head-to-head studies in type 1 diabetes, are now needed.

Biosimilar glargine

An important event was the end of the patent of insulin glargine, allowing the manufacturing of biosimilar glargine. To date, several companies have successfully manufactured biosimilar insulin glargine U100, with several preparations already in clinical use [47]. These have similar pharmacokinetic and pharmacodynamics profiles compared to the original insulin glargine U100, and to date all clinical studies and real world evidence confirms equivalence between preparations [48]. Of even greater importance, to date, no immune reactions have been described [49].

Short-acting insulin analogues – what's new

Faster-acting insulin aspart (FIASP)

There are many new short acting insulins on the horizon. The most recent addition to the routinely available analogues is fast acting insulin aspart (FIASP) [50]. The structure of the insulin molecule in FIASP is identical to aspart insulin, but the formulation contains nicotinamide and L-arginine as excipients [1, 50]. Both of these excipients are naturally occurring entities and are considered safe by regulators. Addition of these substances results in a formulation that is absorbed faster. In pooled analyses, the onset of action of FIASP was 23% faster than insulin aspart and the glucose lowering effect was 74% greater in the first 30 minutes post injection [50].
In double-blinded studies randomising people with type 1 diabetes on basal bolus regimens to FIASP or the original aspart formulation injected immediately before the start of the meal (with insulin detemir as basal insulin), there was a significant reduction in HbA1c favouring FIASP (-0.08% versus +0.01%) and lower post-prandial glucose levels, with no effect on hypoglycaemia [51]. In an open label study arm, no loss of glucose control was observed when people with type 1 diabetes were asked to inject their FIASP up to 20 minutes after the initiation of their meals, compared to injecting the original aspart before the meal.

FIASP has also been explored in those on continuous subcutaneous insulin infusion. In two randomised studies, FIASP was shown to have a faster onset of action (by 11 minutes), with

lower glucose peaks and less time spent in hypoglycaemia [52, 53]. However, the ONSET 5 study has not shown improvements in HbA1c or postprandial glucose control [54].

Still, as outlined earlier, the delay in onset of rapid acting insulin analogues is a significant challenge for people with type 1 diabetes and it is likely that any improvement in rapidity of onset of action will be of benefit. However, this will need to be offset against the potential disadvantages of earlier cessation of action of such rapidly acting analogues. Provided there is no cost increase in the use of FIASP, this benefit of flexibility in daily life may also be cost neutral.

Ultra Rapid Lispro

An ultra-rapid acting version of insulin lispro (URLi) is also in development, where exactly the same principle as for FIASP was used, namely, the original lispro molecule with a novel formulation. The addition of citrate and treprostinil lead to a more rapid resorption of lispro from under the skin [55]. Suggested mechanisms are that citrate would increase vascular permeability at the injection site, whereas treprostinil accelerates lispro absorption by local vasodilation with no measurable systemic exposure [55]. First pharmacokinetic and dynamic data are quite comparable to data on FIASP, with minutes gained in rapidity of onset of action [56].

BioChaperone insulin Lispo

BioChaperone insulin Lispro is currently entering its clinical development program, with promising initial clinical results [57]. In this formulation, the traditional lispro insulin is combined with a novel excipient, BioChaperone BC222, an oligosaccharide, and citrate [58]. Pharmacokinetic and pharmacodynamics studies demonstrate a 40% reduction in 2-hour post-prandial excursion compared to traditional insulin lispro and was found to be safe with persistent effects up to 14 days [57]. However, this study used a solid test meal, in contrast to the studies investigating FIASP, which use liquid test meals. Further studies are awaited to see if this novel approach can improve patient outcomes.

Safety apart from hypoglycaemia risk?

Carcinogenic potential

The fact that insulin also binds to the insulin-like growth factor-1 receptor, underlies the potential carcinogenic risk that has, in the past, been suggested in relation to the use of long-acting insulin analogues [2]. Several studies have compared the binding affinities of insulin analogues to the IGF-1 receptor to human insulin [59]. Although *in vitro* insulin glargine was

found to have a 6-8 fold higher affinity for the IGF-1 receptor compared to human insulin, it is rapidly degraded to its predominant metabolite M1, which has a 0.4 fold binding affinity compared to insulin [2, 59, 60]. To date, no differences in cancer prevalence have been convincingly shown between any insulin preparations in any studies. The largest such study is the ORIGIN study, conducted in people with pre-diabetes or type 2 diabetes who were randomised to glargine U100 or standard care and after 6 years follow-up, did not show any differences in the risk of cancers between the two groups [61]. Care should be taken when translating *in vitro* and experimental data to clinic In particular, care should be taken not to unnecessarily alarm people living with type 1 diabetes, for whom insulin and tight glycaemic control are of the utmost importance and greatly exceed theoretical risks of cancer [60].

Immunogenicity

Since the development of recombinant human insulin and insulin analogues, the formation of IgG insulin antibodies is now relatively rare, compared to when animal insulins were used [62]. Sporadic case reports exist of antibodies forming to recombinant human insulins, but these are unheard of in analogue insulins, where the amino acid substitutions are selected to be least immunogenic [62]. Hypersensitivity reactions have been reported to analogue insulins, but these are likely to be related to excipients in the formulation e.g. metacresol [63, 64]. Fortunately for the rare individuals who do have allergic reactions to metacresol, one insulin formulation without this excipient is available, Insuman Infusat (Sanofi) [65].

Pregnancy

Insulin aspart, lispro, detemir and the human insulins (NPH and regular insulin) have a good evidence base for safety in pregnancy [1, 66] and as no insulin analogues have evidence of placental transfer, risks are likely to be low. Newer insulins such as FIASP and degludec, but also glulisine are lacking data. Interestingly, the widely used insulin glargine U100 (and glargine U300) still lacks a formal regulatory approval for use in pregnancy. A metanalysis of glargine during pregnancy found it to be safe and effective and a small study comparing insulin detemir to NPH found positive glucose lowering effects, but effects on foetal outcomes were not formally tested [67].
However, healthcare professionals should appreciate that in reality the benefits of tight glycaemic control probably outweigh the potential risks of insulin analogues during pregnancy and case by case decision-making is recommended.

So, are newer insulins better than existing analogues?
Summarised below are the key findings from published studies, questions that remain unanswered and areas that warrant further study.

- Studies confirm that longer acting and higher strength basal insulins are as good as existing analogues in reducing HbA1c.
- Newer analogues have more stable profiles and less variability in glucose lowering, which could be clinically useful traits, particularly as the concept of 'time in range' becomes more favourable
- There is some potential additional benefit in the reduction of nocturnal hypoglycaemia and severe hypoglycaemia events.
- There are no studies, yet, that examine whether existing pathways to address problematic hypoglycaemia are better options compared to changes in basal insulin, in the long term. Studies that carefully compare outcomes and cost effectiveness of different treatment modalities for problematic hypoglycaemia are needed.
- Insulin degludec and glargine U300 could be considered in those individuals with disabling hypoglycaemia who decline insulin pump therapy (the current gold standard in this context) or in whom pump therapy is not appropriate. However, no studies examining this specific comparison have been undertaken.
- Newer short acting insulin analogues are an exciting development addressing the delay in onset of action of the existing bolus insulin repertoire.
- The flexibility that fasting acting analogues could bring to individuals with type 1 diabetes should not be underestimated and delay in onset of action is associated with higher HbA1c.
- More studies that examine efficacy of newer basal and bolus insulins, in different subsets of people with type 1 diabetes will provide the granularity needed in identifying who will benefit the most from the newer analogues.
- Of course, it should not be forgotten that the type of insulin itself, is merely a component of a multimodal approach to management of type 1 diabetes, which is underpinned by structured education supporting self-management and access to the multi-disciplinary team.

Summary

The expanding repertoire of available insulins for the treatment of people living with type 1 diabetes is both exciting and important. Technology has come a long way from the early days and newer insulin analogues with novel concepts help address the challenges of insulin delivery and bring with them the hope of improving both glycaemic control and quality of life for individuals with type 1 diabetes.

The 'sweet spot' of achieving tight glycaemic control without excess hypoglycaemia may yet be elusive. The evolution of long-acting insulins is particularly significant in ensuring better 24-hour coverage, less variability in glucose lowering effects and fewer hypoglycaemic episodes. Newer rapid acting insulin analogues show promise of faster onset and give people with type 1 diabetes more flexibility around timing of meal-time insulin. In time the place of these newer analogues in the existing range will become apparent. It is clear that further

innovation is still needed to overcome challenges of peripheral insulin delivery and in particular, for special groups of patients who struggle with traditional insulin regimens.
Aside from the potential for hypoglycaemia, all insulin types including recombinant human and analogue insulins available are safe with no additional risks.
The real current challenge, is to form clear guidelines on whom these analogues should be trialed in, where they are most cost-effective and who stands to benefit the most. This evidence is likely to follow as experience with the agents increase and they are studied in higher-risk patient groups.

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Table 1: Summary of modifications to insulin molecule in analogue and human insulins

Name of insulin	Protein sequence	Additional modifications	Following injection
Rapid acting insulins			
Human regular insulin	Single insulin molecule consists of an A and B chain, connected by two disulphide bridges. Six molecules of insulin are positioned around a zinc ion to form a hexamer.	Nil	Hexamers slowly dissociate to dimers and monomers
Insulin lispro	Similar to human insulin, except that the amino acids at position 28 and 29 on the B chain are swapped over to lysine at position 28 and proline at 29.	Nil	Hexamers rapidly dissociate to dimers and monomers
Insulin aspart	Similar to human insulin, except that the amino acid at position 28 is aspartate not proline.	Nil	Hexamers rapidly dissociate to dimers and monomers
Insulin glulisine	Similar to human insulin, except lysine substituted for valine at position 3 or the B chain and glutamate for lysine at position 29.	Nil	Hexamers rapidly dissociate to dimers and monomers
Fast acting insulin aspart	Identical to insulin aspart	Formulation contains nicotinamide and L-arginine as excipients	Hexamers rapidly dissociate to dimers and monomers

Ultra rapid lispro	Identical to insulin lispro	Formulation contains citrate and treprostinil, a vasodilator.	Hexamers rapidly dissociate to dimers and monomers
BioChaperone lispro	Identical to lispro	Formulation contains a novel biochaperone molecule BC222, an oligosaccharide and citrate.	Hexamers rapidly dissociate to dimers and monomers
Intermediate acting insulins			
NPH or zinc protamine	Single insulin molecule consists of an A and B chain, connected by two disulphide bridges. 6 molecules of insulin are positioned around a zinc ion to form a hexamer	Resuspended in zinc or protamine, respectively which results in the formation of 'conglomerates' that prolongs duration of action.	Forms hexamer-protamine conglomerates
Insulin detemir	Like human insulin except for deletion of threonine at position 30 on the B chain	Fatty acid moiety attached to end of B chain	Forms dihexamers and bound to albumin
Long-acting insulins			
Insulin glargine	Like regular insulin, but glycine at position 21 of A chain & prolongation of B chain with 2 additional arginine residues	Changes in amino acid alter the isoelectric point of the insulin.	Forms hexamer aggregates.
Insulin degludec	Like human insulin except for deletion of threonine at position 30 on the B chain	Fatty acid moiety attached to end of B chain	Forms multihexamers that slowly dissociate and bind to albumin