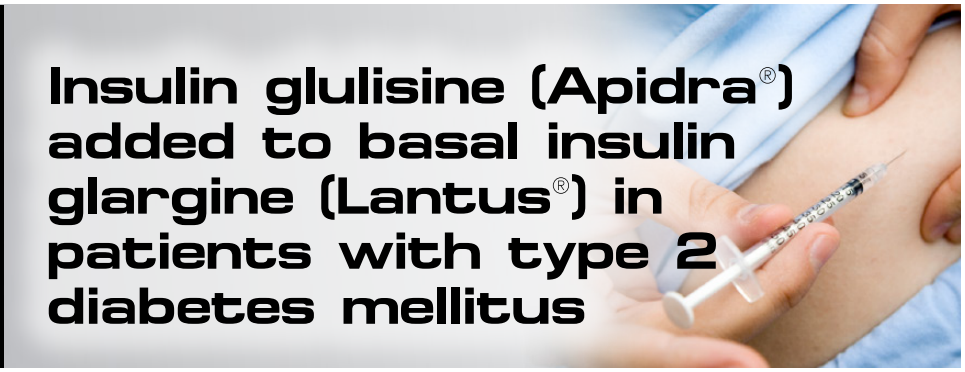
A RESEARCH REVIEW™
PRODUCT REVIEW

Insulin glulisine (Apidra®) added to basal insulin glargine (Lantus®) in patients with type 2 diabetes mellitus



Making Education Easy

About the commentator

Associate Professor Jeremy Krebs
MB ChB, MD, FRACP

Dr Jeremy Krebs is an Endocrinologist and Clinical Leader of Endocrinology and Diabetes at Capital and Coast District Health Board, where he heads the research group. He is also an Associate Professor at the University of Otago, Wellington, and part of the Edgar Diabetes and Obesity Research Centre.

His MD thesis examined the association between obesity and insulin resistance, immersing him in both large intervention studies and small detailed physiological studies, using multiple techniques to measure body composition, insulin sensitivity, and other physiological parameters.

Jeremy continues to develop research projects in both areas, with a particular focus on the association between obesity and type 2 diabetes, both from an aetiology and management perspective.

Abbreviations used in this review
FBG = fasting blood glucose
HbA1c = glycosylated haemoglobin
OADs = oral antidiabetic drugs
PPBG = postprandial blood glucose
T2DM = type 2 diabetes mellitus

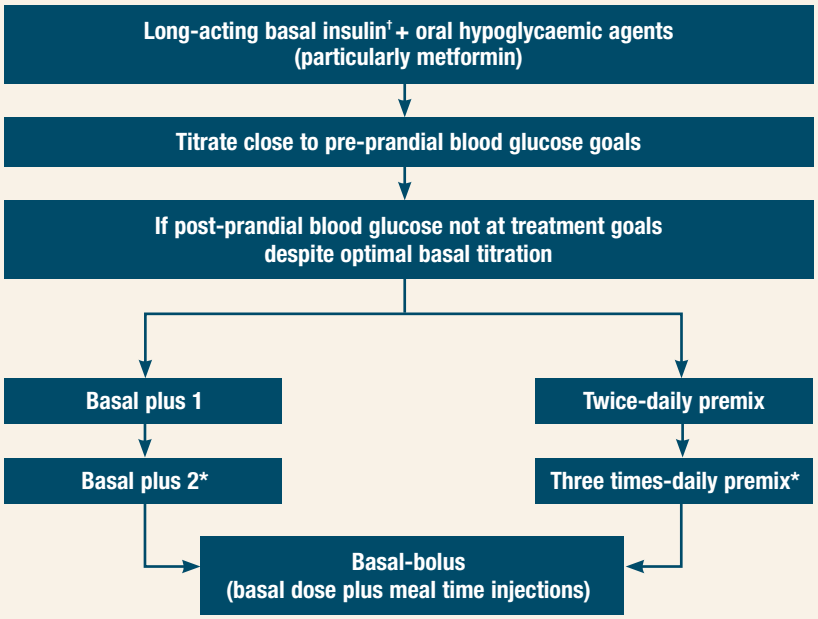
This review summarises evidence for the use of a basal plus regimen of a single prandial injection of insulin glulisine (Apidra®) added to basal insulin glargine (Lantus®) in patients with type 2 diabetes mellitus (T2DM) poorly controlled on oral antidiabetic drugs (OADs). Insulin glulisine and insulin glargine are approved for use in New Zealand for patients with T2DM who require insulin for the control of hyperglycaemia.[1, 2] This review is sponsored by Sanofi NZ Ltd.

The global prevalence of diabetes has been dramatically increasing over recent decades.[3] The International Diabetes Federation estimates that by 2040 the number of adults with diabetes will have risen to 642 million. In high-income countries, the vast majority of adults with diabetes (87-91%) will have type 2 diabetes mellitus (T2DM).[3]

T2DM is characterised by a progressive loss of β-cell insulin secretion which is frequently on a background of insulin resistance.[4] The progressive loss of β-cell function is associated with hyperglycaemia, which places patients at risk of developing both micro- and macro-vascular complications.[5]

Treatment of type 2 diabetes mellitus

Lifestyle interventions and oral antidiabetic drugs (OADs) are effective in the early stages of T2DM,[4, 5] with metformin remaining the first-line pharmacological treatment because of its efficacy and safety.[6] However, given the progressive nature of the disease, most patients with T2DM will eventually require an insulin-based regimen (Figure 1).[7, 8] Basal insulin alone is the most convenient initial insulin regimen and it is usually prescribed in conjunction with metformin, with or without other OADs.[4,6,9] Over time this regimen may fail to provide glycaemic control and an intensified insulin regimen may be appropriate.[10] The next stage of treatment generally addresses the postprandial blood glucose (PPBG) excursions with the use of more complex insulin regimens. Typically, this involves the addition of one or more prandial insulin injections ('basal plus' as a single injection before the main meal or 'basal-bolus' before each meal) dependent on the individual and their glycaemic targets, or a switch to premixed insulin (1-3 daily doses) may occur.[7, 9, 11, 12] Rapid-acting analogues are preferred as the prandial insulin due to their prompt onset of action.[4]



† Basal insulin is the preferred option based on simplicity. Once-daily premixed insulin is an option for some people.
* Literature supports but not common in practice.

Figure 1. A practical algorithm for insulin intensification[12]

Insulin glulisine (Apidra®) added to basal insulin glargine (Lantus®) in patients with type 2 diabetes mellitus

In clinical practice, delays in treating patients with T2DM are common and they happen at all stages of this progressive disease.[12, 13] Various barriers exist to the initiation and intensification of insulin therapy, including concerns regarding hypoglycaemia, and weight gain and the fear of injections.[14, 15] A large retrospective cohort study in the United Kingdom in patients with T2DM treated with basal insulin (n = 11 696) indicated that only 31% of those clinically eligible (i.e. HbA1c level ≥58 mmol/mol [≥7.5%]) had their treatment regimen intensified, with a median delay of initiating insulin of 3.7 years.[16] This delay was significantly associated with greater age, diabetes duration, OAD use and the increased presence of comorbidities ($p < 0.05$ for all). Such clinical inertia can impact the patient's quality of life, morbidity and mortality.[17] Consequently, the American Diabetes Association (ADA) recommend that insulin therapy should not be delayed for patients with T2DM who are not achieving glycaemic goals.[18]

The most important aspect of initiating insulin therapy is to individualise the treatment for the needs of the patient, their circumstances and what they are comfortable and willing to do. One approach is to consider basal insulin with the addition of rapid-acting mealtime insulin. A stepwise approach that starts by adding one, then two, then three dose of a rapid-acting insulin analogue to an existing therapy of OADs and once-daily basal insulin may be more convenient and less threatening to patients.[19] The so called basal-plus one regimen involves the administration of a single injection of rapid-acting insulin when PPBG excursion are greatest (at the main meal) to basal insulin.[12] This approach has been associated with significant improvements in HbA1c, low rates of hypoglycaemia, limited increases in weight, and patients reaching recommended HbA1c targets.[19]

Focus on insulin glargine and insulin glulisine

An insulin regimen involving insulin glargine as the basal insulin and a single dose of insulin glulisine with a meal is an example of a basal-plus insulin regimen.[12]

Pharmacological properties

The following is an overview of important pharmacological properties of insulin glargine and insulin glulisine. The respective Data Sheets should be viewed for full details of the pharmacodynamics, pharmacokinetics, precautions, and recommended dosage and administration of these insulin analogues.[1, 2]

Insulin glargine (100 u/mL) pharmacology

The information regarding the insulin glargine pharmacology, as well as being reported in the referenced studies, is presented in the insulin glargine Data Sheet.[2]

Insulin glargine is a recombinant human insulin analogue that is soluble at pH 4.0, but not at physiological pH. Consequently, after subcutaneous injection, it forms amorphous micro-precipitates which delay its absorption and prolongs its duration of action (Figure 2).[20-22]

Insulin glargine exerts a glucose-lowering effect for 24 hours after a single daily injection without a pronounced plasma peak; its onset of action is about 1.5 hours (Figure 2).[2, 23-25] In contrast, NPH insulin has a peak of glucose-lowering activity about 4.5 hour after administration, with a duration of action of about 14.5 hours and an onset of action of 0.8 hours.[25] Insulin glargine allows once-daily dosing and allows patients to meet basal insulin requirements, with flexibility of timing of the injection (morning, pre-dinner, or prebedtime).[26]

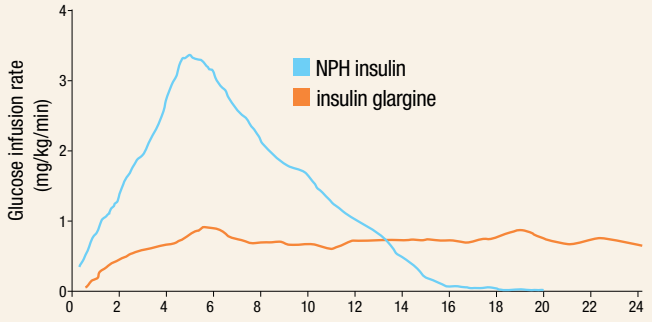


Figure 2. Insulin activity measured according the rate of glucose infusion needed to maintain a target plasma glucose of 7.2 mmol/L during an isoglycaemic clamp study in 20 patients with type 1 diabetes administered a single subcutaneous injection of 0.3 U/kg insulin glargine (100 u/mL) or NPH insulin[2, 25]

Insulin glulisine (100 u/mL) pharmacology

The information regarding the insulin glulisine pharmacology, as well as being reported in the referenced studies, is presented in the insulin glulisine Data Sheet.[1]

Insulin glulisine is also a recombinant human insulin analogue.[1] The molecular structure of insulin glulisine differs only slightly from regular human insulin,[27] but the difference allows the insulin to be rapidly absorbed compared with human insulin.[27, 28] Insulin glulisine, unlike other insulin analogues, such as insulin aspart and insulin lispro, does not contain zinc.[29] However, the affinity of insulin glulisine for the insulin receptor is similar to that of regular human insulin.[30, 31]

Studies in healthy volunteers and patients with diabetes show that insulin glulisine has a more rapid onset of action and a shorter duration of activity than regular human insulin when given subcutaneously (Figure 3).[27, 29, 32] The onset of action of insulin glulisine is within 5-15 minutes, its peak glucose lowering activity occurs after approximately 90 minutes and its duration of action is about 3-5 hours.[29] Importantly, insulin glulisine maintains its rapid-acting profile across a range of body mass index (BMI) and skin thickness.[32-34]

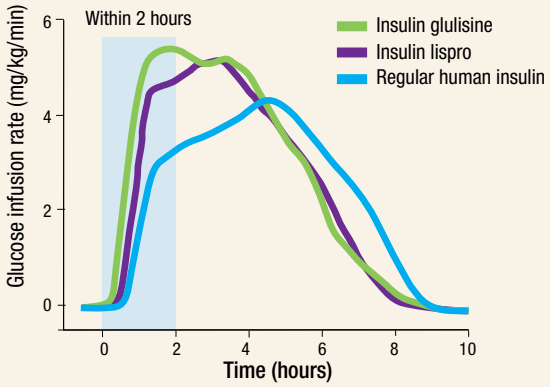


Figure 3. Glucose-lowering activity of a subcutaneous injection of 0.3 U/kg insulin glulisine, insulin lispro and regular human insulin in a euglycaemic clamp study of 18 obese (mean BMI 34.7 kg/m^2) non-diabetic patients[27]

Dosage and Administration

Insulin glargine is administered subcutaneously once daily at the same time every day.[2] Insulin glulisine should be given by subcutaneous injection within 15 minutes before, or immediately after, a meal.[1] The glycaemic control achieved when insulin glulisine is added 0–15 minutes before a meal is similar to that when insulin glulisine is added 20 minutes after a meal,[35] indicating that this 35 minute-dosing interval is also acceptable.

The doses and timing of insulin glargine must be determined and adjusted individually.[2] Similarly, the dosage of insulin glulisine should be individualised and determined based on the physician's advice in accordance with the needs of the patient.[1] As with all insulins, the injection sites of these analogues must be rotated from one injection to the next.

Insulin glargine cannot be diluted or mixed with any other insulin or solution as this may alter the time-action profile and may result in precipitation.[2] Insulin glulisine should normally be used in regimens that include a longer-acting insulin or basal insulin analogue.[1]

Various algorithms for starting and intensifying insulin therapy in patients with T2DM are available, such as those provided by the ADA[4] and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE),[11] the European Association for the Study of Diabetes (EASD)[9] and the New Zealand Ministry of Health.[6]

Based on recommendations from these guidelines, insulin glargine can be initiated at a dose of 10 units and added to the OADs that the patient is currently taking (Figure 4).[6] The insulin glargine dose should then be adjusted to achieve an agreed individual fasting blood glucose target. One of many approaches is to add Insulin glulisine with the largest meal of the day. A common starting dose might be 4 units. The insulin glulisine dose should then be increased by 1-2 units once or twice weekly until the 2-hour PPBG is ≤10 mmol/L.[4] HbA1c should be measured regularly

(3–6 monthly),[6] and the insulin intensified if appropriate (Figure 4).[12] Importantly, glycaemic targets should consider the preferences of each individual patient with respect to how they wish to manage their diabetes and prevent complications.[6]

Contraindications

Insulin glargine and insulin glulisine must not be used in patients hypersensitive to insulin glargine or insulin glulisine and any of their excipients. The Data Sheets should be consulted for the full list of excipients.[1, 2]

Interactions

A number of substances affect glucose metabolism and may require dose adjustment of the insulin analogues. The Data Sheets should be consulted for the full list of these substrances.[1, 2]

Adverse events

The most common adverse reactions associated with insulin therapy are allergic reactions, injection site reactions, hypoglycaemia and visual disturbances. The Data Sheet for insulin glargine and insulin glulisine should be consulted for further information regarding the adverse event profile associated with each of these specific insulin analogues.[1, 2]

Initiate insulin glargine (basal insulin) + oral anti-hyperglycaemic agents (usually includes metformin)

Start: 10 U/day or 0.1-0.2 U/kg/day morning or night

Adjust: 10-15% or 2-4 units once or twice weekly to reach FBG target*

For hypoglycaemia: Determine and address cause, if not clear reason for hypo decrease dose by 4 units or 10-20%

↓

If HbA1c not controlled then consider basal plus therapy**

↓

Add a single injection of insulin glulisine before the largest meal

Start: 4 U, 0.1 U/kg or 10% basal dose. If HbA1C <64 mmol/mol, consider decreasing basal insulin by same amount

Adjust: Increase the dose by 1-2 units or 10-15% once or twice weekly until self-monitored blood glucose target*** is reached

For hypoglycaemia: Determine and address the cause; if no clear reason for hypo, then decrease corresponding dose by 2-4 units or 10-20%

↓

If HbA1c not controlled then consider basal-bolus therapy**

FBG = fasting blood glucose; PPBG = post-prandial blood glucose.

*FBG target 4-6 mmol/L (or as individually agreed).[6]

**HbA1c target is 50–55 mmol/mol (or as individually agreed).[6] Measure every 3-6 months according to individual needs.

***2-hour PPBG target of ≤10 mmol/L (or as individually agreed).[4, 8]

Figure 4. Algorithm for adjustment of insulin glargine and insulin glulisine.[4, 8, 9] Glycaemic targets should be individualised and take into account diabetes duration, the presence of co-morbidities, life expectancy, social circumstances and the personal beliefs and priorities of the patient.

KEY TRIALS OF BASAL PLUS REGIMEN OF INSULIN GLARGINE PLUS INSULIN GLULISINE

The use of 'basal-plus' insulin treatment regimen involving a single preprandial injection of insulin glulisine given before the meal on a background of basal insulin glargine has been investigated in randomised, controlled trials in patients with T2DM.[36-43] In all these trials, patients continued to receive OADs (usually metformin). This approach was associated with significant improvements in HbA1c, low rates of hypoglycaemia, limited increases in weight, and patients reaching recommended HbA1c targets. The improved quality of life, reduced glucose variability, and better glycaemic control that is associated with the basal-bolus regimen have resulted in improved measures of patient satisfaction, despite the increase in injections that is associated with this intensified insulin regimen.[43]

Individual summaries of the main features and findings of the pivotal clinical trials of a basal plus regimen of basal insulin glargine and prandial insulin glulisine in patients poorly controlled on OADs are presented below:

A stepwise approach to insulin therapy in patients with type 2 diabetes mellitus and basal insulin treatment failure (1, 2, 3 study)[36]

Authors: Davidson et al.

Summary: In this randomised, open-label study,[36] patients with T2DM poorly controlled on two or three OADs for at least 3 months entered a run-in period during which they received insulin glargine for 14 weeks. At the end of the run-in period, patients whose HbA1c remained >53 mmol/mol (>7.0%) were randomised to insulin glulisine once, twice or three times daily for 24 weeks. Insulin doses were adjusted weekly dependent on PPBG values. The reductions in HbA1c from randomisation to the study endpoint with once- and twice-daily insulin glulisine were non-inferior to the reduction achieved with three-times-daily administration (–0.44%, –0.36% vs –0.43%; Figure 5).The proportion of patients achieving an HbA1c target of <53 mmol/mol (<7%) with one, two or three prandial insulin glulisine injections was 30%, 33% and 46%, respectively. Severe hypoglycaemia occurred in 16% of patients receiving three preprandial injections compared with 8% of patients receiving two injections and 7% of those receiving one injection, but these differences were not statistically significant. Weight gain ranged from 3.8 to 4.1 kg, and was also not significantly different between the three groups.

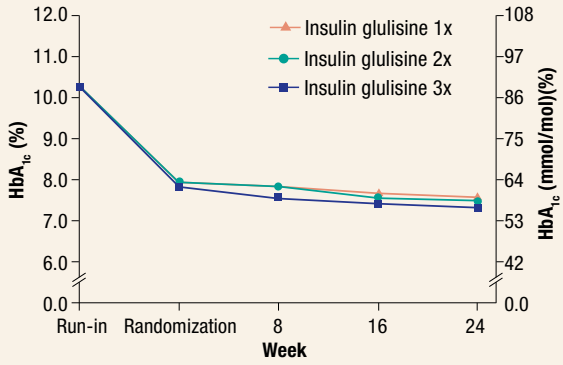


Figure 5. Change in HbA1c in patients with T2DM randomised to 1, 2 or 3 preprandial insulin glulisine injections who continued to receive basal insulin glargine and OADs[36]

Comment: This study was designed to test whether a single preprandial injection of short-acting insulin was as effective as an injection with each of three meals. The results demonstrate no significant difference between treatments, though there is a trend to better glycaemic control with three injections at the expense of more frequent hypoglycaemic events. Sulphonylureas were withdrawn at the commencement of prandial insulin, presumably to reduce the risk of hypoglycaemia. This is often, but not always, done in New Zealand, and often initially associated with worsening of glucose control and a need for additional insulin titration. The main conclusion from this study is that introduction of meal-time, short-acting insulin for any or all meals effectively reduces HbA1c in a highly controlled and well supported clinical trial setting over a relatively short follow-up period.

Effects of initiation and titration of a single pre-prandial dose of insulin glulisine while continuing titrated insulin glargine in type 2 diabetes: a 6-month 'proof-of-concept' study[38]

Authors: Owens et al.

Summary: This open-label, phase IV study was conducted in the US, UK and Russia in patients with T2DM who underwent a 3-month run-in period on insulin glargine, titrated to optimise FBG.[38] At the end of this run in period, patients whose HbA1c was >53 mmol/mol (>7.0%) were then randomised to continue with basal insulin glargine (n = 57) or add a single injection of insulin glulisine immediately before their main meal (n = 49).

After 3 months, significantly more patients treated with insulin glargine plus insulin glulisine achieved a HbA1c target of <53 mmol/mol (<7.0%) than treatment with basal insulin glargine alone (22.4% vs 8.8%; $p < 0.05$). A subgroup analysis of those treated with the basal plus regimen showed a similar proportion of patients achieved the HbA1c target irrespective of timing of the prandial injection time (i.e. before breakfast, lunch or dinner). The reduction in HbA1c was significantly greater with the basal-plus than the basal only insulin regimen (–0.37% vs –0.11% [-4.04 vs -1.2 mmol/mol]; $p = 0.029$). Rates of hypoglycaemia and weight change were not significantly different between the two groups.

Comment: Once again this study examines whether the addition of prandial insulin after optimising basal insulin facilitates improved glycaemic control. Here, there is clear benefit of a single daily dose of prandial insulin compared with none, irrespective of which meal it is added to. This should come as no surprise, since after optimising basal insulin any residual excess of glucose exposure is in the immediate post-prandial period. All of the participants were taking metformin, but it is not reported whether any were also on a sulphonylurea, which would be the standard of care in New Zealand as the most common second-line oral agent used before the initiation of basal or bolus insulin. Furthermore the intervention period is only three months and the contact with study staff intensive. So whilst these data show that the addition of a single dose of mealtime insulin improves glycaemic control, we must be cautious not to extrapolate these findings to long-term, real-world settings in people who are also using sulphonylureas.

Randomized, 1-year comparison of three ways to initiate and advance insulin for type 2 diabetes: twice-daily premixed insulin versus basal insulin with either basal-plus one prandial insulin or basal-bolus up to three prandial injections[41]

Authors: Riddle et al.

Summary: In this 60-week, open-label All to Target study, 588 patients with poorly controlled T2DM (HbA1c >53 mmol/mol [>7.0%]) on OADs were randomised to initiate insulin treatment with insulin glargine plus one injection of insulin glulisine [basal plus one], insulin glargine plus up to three injections of insulin glulisine [basal plus three], or two injections of premixed insulin (biphasic insulin aspart 70/30).[41] Insulin glargine and insulin glulisine were titrated weekly throughout the 60-week trial to meet pre-specified glycaemic targets.

Both insulin glargine/insulin glulisine regimens lowered FBG levels (-4.4 and -4.8 mmol/L) to a significantly greater extent ($p < 0.001$) than premixed biphasic insulin (-3.4 mmol/L). The basal plus one regimen was non-inferior to the biphasic premixed insulin regimen in reducing HbA1c (Figure 6), but more patients achieved HbA1c targets with the basal plus one regimen and basal plus three regimens (49% and 46% vs 39%; $p < 0.05$).

Hypoglycaemia (plasma glucose <2.8 mmol/L) was more common with the biphasic premixed insulin regimen than the basal plus one or basal plus two regimens (1.9 vs 0.8 and 0.9 events per patient-year, $p \leq 0.0001$; Figure 6). The overall percentage of adverse events did not differ between the treatment groups (79%, 80% and 73%, respectively).

The insulin dosage and weight gain were similar between the treatment groups.

Comment: This study may have more direct relevance to the New Zealand setting, although participants were all taken off their sulphonylurea at the start of the study. Practice around the country will vary with this, but it is certainly not universal, particularly when only basal insulin is used. However, in this study, we have a comparison of using a premixed insulin twice daily compared with a glargine and mealtime insulin either as one dose or with multiple meals. It must be noted that the study was sponsored and run by the insulin company and data were analysed and interpreted by them also. To me, the main finding is that all regimens achieved a similar lowering of HbA1c. However glargine with once-daily mealtime insulin stimulated less weight gain and had fewer hypoglycaemic events, particularly in comparison with twice-daily premixed insulin. Therefore, in the right patient who is willing to adopt a basal and bolus regimen, this may be an advantage.

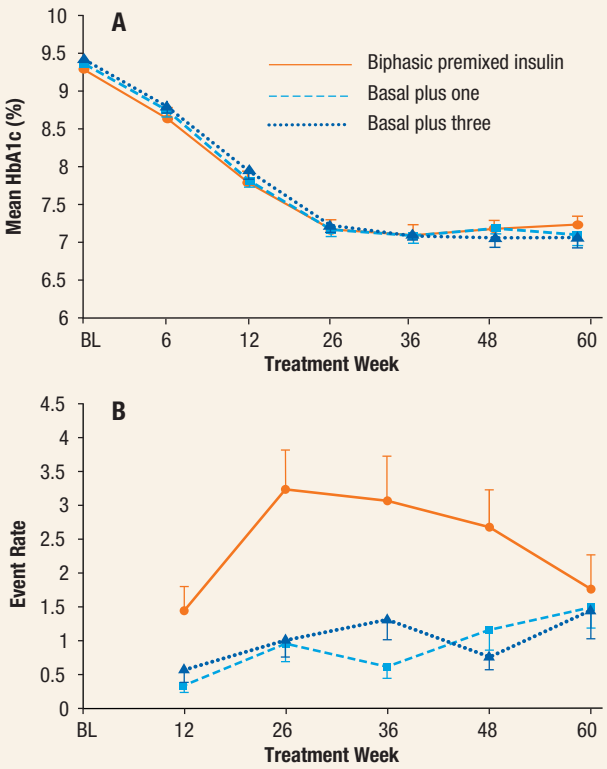


Figure 6. (A) Mean HbA1c (B) Events per person-year for symptomatic hypoglycaemia (plasma glucose <2.8 mmol/L), in patients treated with a basal plus one insulin regimen, basal plus three insulin regimen or a biphasic premixed insulin regimen[41]

Use of a basal-plus insulin regimen in persons with type 2 diabetes stratified by age and body mass index: a pooled analysis of four clinical trials[42]

Authors: Lankisch et al.

Summary: A meta-analysis[42] involving 711 T2DM patients with poorly controlled T2DM on OADs pooled data from four studies involving treatment with a basal plus regimen of insulin glargine plus insulin glulisine.[36-39] This meta-analysis confirmed significant decreases in mean HbA1c occurred with up to 6 months of treatment with this regimen compared with baseline (–0.4% [-4.37 mmol/mol]; $p < 0.0001$). Changes in FBG (+2.8 mg/dL [0.16 mmol/L]; $p = 0.05$) and PPBG (–58.9 mg/dL [3.27 mol/L]; $p < 0.0001$) were also significant over a 6-month follow-up.

More than twice as many patients achieved target HbA1c levels (<7% [<53.0 mmol/mol]) at end of study compared with baseline (45.3% vs 20.3%, $p < 0.001$) with this basal one plus regimen. Across the four studies, the rates for symptomatic, nocturnal and severe hypoglycaemia were 4.7, 0.6 and 0.03 events per patient-years, respectively, with no significant differences between patients stratified by age or BMI. The small increase in weight (+0.9 kg) and BMI (+0.3 kg/m^2) with the basal plus regimen was statistically significant over the 6 months of follow-up.

Comment: This meta-analysis included four clinical trials, two of which are reported above by Owens et al. and Davidson et al. The meta-analysis was sponsored by the insulin producing company. I think the best we can conclude from this is further confirmation that, in individuals with type 2 diabetes whose HbA1c is not optimal on oral agents, the addition of basal insulin with at least one prandial insulin dose with the main meal is one effective strategy to improve glycaemic control. In this analysis, the degree of weight gain was not as great as in the Riddle et al. study above and rates of hypoglycaemia were low.

EXPERT'S CONCLUDING COMMENTS

There is a strong evidence base that achieving tight glycaemic control in people with type 2 diabetes minimises the risk of microvascular complications, and growing evidence that it may also reduce macrovascular events. However, there remains a great deal of uncertainty of how best to achieve this for an individual patient. The ACCORD study highlighted the risk of assuming that tight control, no matter how achieved, was beneficial, and moreover that attempting tight glycaemic control, but not achieving it, may be harmful. Therefore the common theme to international guidelines has become a strong message for the need to individualise therapy. This means not only glycaemic targets, but also the therapies used to achieve these goals.

This product review of insulin glargine and insulin glulisine provides a summary of the data relevant to one option for improving glycaemic control in those on maximal available oral agents at the time of the studies. It highlights that using basal insulin, with or without one or more doses of prandial short-acting insulin, is effective in reducing fasting glucose and HbA1c. There is some associated weight gain, and some increased risk of hypoglycaemia, but overall it is a very good therapeutic option. However, despite the promotional material supporting these insulins, insulin glargine does not always have a 24-hour basal cover and is not always a once-daily insulin. NPH insulin remains a very useful basal insulin in some people, particularly where fasting hyperglycaemia is the predominant pattern. Furthermore, in practical terms, insulin glulisine has an identical profile to other short-acting analogue insulins available.

Although not currently funded in New Zealand, there are other treatment options to add to a regimen of maximal metformin and sulphonylurea, which have similar glucose lowering benefits, less weight gain and risk of hypoglycaemia and now there is clinical trial evidence of reduced cardiovascular events. I draw your attention to a useful review by Raccah D.[44]

Therefore, my concluding remark is that basal insulin, such as insulin glargine, with or without one or more mealtime doses of short-acting insulin, is a very good option for intensification of glucose-lowering therapy in people with type 2 diabetes who are not achieving their goals on oral therapy. However, this is one of several options, and each should be considered in the setting of the individual in front of you; individualise therapy to optimise the risks and benefits of any treatment approach for that person.

TAKE HOME MESSAGES

- The basal plus one regimen of a single injection of rapid–acting insulin glulisine added to basal insulin glargine provides glycaemic control for patients with T2DM treated with OADs but who require an intensified insulin regimen
- This approach is associated with significant improvements in HbA1c, low rates of hypoglycaemia, limited increases in weight, and patients reaching recommended HbA1c targets
- This regimen allows flexibility of timing of injections and the ability to titrate the basal and bolus insulin analogues separately
- The improved quality of life, reduced glucose variability, and better glycaemic control associated with this basal-bolus regimen positively impacts patient satisfaction

REFERENCES

1 Sanofi-aventis New Zealand Limited. 2017. New Zealand Data Sheet: Apidra - insulin glulisine. Available at: http://www.medsafe.govt.nz/profs/Datasheet/a/ApidraApidraSoloStarinj.pdf.

2 Sanofi-aventis New Zealand Limited. 2017. New Zealand Data Sheet: Lantus - insulin glargine. Available at: http://www.medsafe.govt.nz/profs/Datasheet/l/lantusinj.pdf.

3 Ogurtsova K, da Rocha Fernandes JD, Huang Y, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract. 2017;128:40-50.

4 American Diabetes Association. American Diabetes Association Position Statement: Standards of Medical Care in Diabetes - 2017. Diabetes Care. 2017;40 (Suppl. 1:S1–S138).

5 Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. Lancet. 2017;389(10085):2239-2251.

6 New Zealand Guidelines Group. New Zealand Primary Care Handbook. 3rd ed. Wellington, New Zealand: New Zealand Guidelines Group, 2012.

7 Ampudia-Blasco FJ, Rossetti P, Ascaso JF. Basal plus basal-bolus approach in type 2 diabetes. Diabetes Technol Ther. 2011;13 Suppl 1:S75-83.

8 Owens DR. Stepwise intensification of insulin therapy in type 2 diabetes management - exploring the concept of the basal-plus approach in clinical practice. Diabet Med. 2013;30(3):276-288.

9 Inzucchi SE, Bergenstal RM, Buse JB, et al. 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(3):429-442.

10 Raccah D, Bretzel RG, Owens D, et al. When basal insulin therapy in type 2 diabetes mellitus is not enough - what next? Diabetes Metab Res Rev. 2007;23(4):257-264.

11 Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus Statement by the American Association Of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm-2016 Executive Summary. Endocr Pract. 2016;22(1):84-113.

12 Fulcher G, Colagiuri S, Phillips P, et al. Insulin intensification for people with type 2 diabetes: a practical approach. Australas Med J. 2010;3(12).

13 Khunti K, Wolden ML, Thorsted BL, et al. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. Diabetes Care. 2013;36(11):3411-3417.

14 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(11):2673-2679.

15 Meece J. Dispelling myths and removing barriers about insulin in type 2 diabetes. Diabetes Educ. 2006;32(1 Suppl):9s-18s.

16 Khunti K, Nikolajsen A, Thorsted BL, et al. Clinical inertia with regard to intensifying therapy in people with type 2 diabetes treated with basal insulin. Diabetes Obes Metab. 2016;18(4):401-409.

17 Reach G, Pechtner V, Gentilella R, et al. Clinical inertia and its impact on treatment intensification in people with type 2 diabetes mellitus. Diabetes Metab. 2017. [Epub ahead of print].

18 American Diabetes Association. Standards of Medical Care in Diabetes - 2017 Abridged for Primary Care Providers. Clin Diabetes. 2017;35(1):5-26.

19 Owens DR. Stepwise intensification of insulin therapy in type 2 diabetes management-exploring the concept of the basal-plus approach in clinical practice. Diabet Med. 2013;30(3):276-288.

20 Hilgenfeld R, Seipke G, Berchtold H, et al. The evolution of insulin glargine and its continuing contribution to diabetes care. Drugs. 2014;74(8):911-927.

21 Luzio SD, Beck P, Owens DR. Comparison of the subcutaneous absorption of insulin glargine (Lantus) and NPH insulin in patients with type 2 diabetes. Horm Metab Res. 2003;35(7):434-438.

22 Owens DR, Coates PA, Luzio SD, et al. Pharmacokinetics of 125I-labeled insulin glargine (HOE 901) in healthy men: comparison with NPH insulin and the influence of different subcutaneous injection sites. Diabetes Care. 2000;23(6):813-819.

23 Heinemann L, Linkeschova R, Rave K, et al. Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. Diabetes Care. 2000;23(5):644-649.

24 Mane K, Chaluvaraju K, Niranjan M, et al. Review of insulin and its analogues in diabetes mellitus. J Basic Clin Pharm. 2012;3(2):283-293.

25 Lepore M, Pampanelli S, Fanelli C, et al. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. Diabetes. 2000;49(12):2142-2148.

26 Ashwell SG, Gebbie J, Home PD. Optimal timing of injection of once-daily insulin glargine in people with Type 1 diabetes using insulin lispro at meal-times. Diabet Med. 2006;23(1):46-52.

27 Becker RH, Frick AD, Burger F, et al. Insulin glulisine, a new rapid-acting insulin analogue, displays a rapid time-action profile in obese non-diabetic subjects. Exp Clin Endocrinol Diabetes. 2005;113(8):435-443.

28 Home PD. The pharmacokinetics and pharmacodynamics of rapid-acting insulin analogues and their clinical consequences. Diabetes Obes Metab. 2012;14(9):780-788.

29 Becker RH, Frick AD. Clinical pharmacokinetics and pharmacodynamics of insulin glulisine. Clin Pharmacokinet. 2008;47(1):7-20.

30 Kurtzhals P, Schaffer L, Sorensen A, et al. Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. Diabetes. 2000;49(6):999-1005.

31 Vajo Z, Duckworth WC. Genetically engineered insulin analogs: diabetes in the new millenium. Pharmacol Rev. 2000;52(1):1-10.

32 Rave K, Klein O, Frick AD, et al. Advantage of premeal-injected insulin glulisine compared with regular human insulin in subjects with type 1 diabetes. Diabetes Care. 2006;29(8):1812-1817.

33 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(2):269-275.

34 Heise T, Nosek L, Spitzer H, et al. Insulin glulisine: a faster onset of action compared with insulin lispro. Diabetes Obes Metab. 2007;9(5):746-753.

35 Ratner R, Wynne A, Nakhle S, et al. Influence of preprandial vs. postprandial insulin glulisine on weight and glycaemic control in patients initiating basal-bolus regimen for type 2 diabetes: a multicenter, randomized, parallel, open-label study (NCT00135096). Diabetes Obes Metab. 2011;13(12):1142-1148

36 Davidson M, Raskin P, Tanenberg R, et al. A stepwise approach to insulin therapy in patients with type 2 diabetes mellitus and basal insulin treatment failure. Endocrine Practice. 2011;17(3):395-403.

37 Del Prato S, Nicolucci A, Lovagnini-Scher AC, et al. Telecare provides comparable efficacy to conventional self-monitored blood glucose in patients with type 2 diabetes titrating one injection of insulin glulisine-the ELEONOR study. Diabetes Technol Ther. 2012;14(2):175-182.

38 Owens DR, Luzio SD, Sert-Langeron C, et al. Effects of initiation and titration of a single pre-prandial dose of insulin glulisine while continuing titrated insulin glargine in type 2 diabetes: a 6-month 'proof-of-concept' study. Diabetes Obes Metab. 2011;13(11):1020-1027.

39 Lankisch MR, Ferlinz KC, Leahy JL, et al. Introducing a simplified approach to insulin therapy in type 2 diabetes: a comparison of two single-dose regimens of insulin glulisine plus insulin glargine and oral antidiabetic drugs. Diabetes Obes Metab. 2008;10(12):1178-1185.

40 Vora J, Cohen N, Evans M, et al. Intensifying insulin regimen after basal insulin optimization in adults with type 2 diabetes: a 24-week, randomized, open-label trial comparing insulin glargine plus insulin glulisine with biphasic insulin aspart (LanScape). Diabetes Obes Metab. 2015;17(12):1133-1141.

41 Riddle MC, Rosenstock J, Vlajnic A, et al. Randomized, 1-year comparison of three ways to initiate and advance insulin for type 2 diabetes: twice-daily premixed insulin versus basal insulin with either basal-plus one prandial insulin or basal-bolus up to three prandial injections. Diabetes Obes Metab. 2014;16(5):396-402.

42 Lankisch MR, Del Prato S, Dain MP, et al. Use of a basal-plus insulin regimen in persons with type 2 diabetes stratified by age and body mass index: A pooled analysis of four clinical trials. Prim Care Diabetes. 2016;10(1):51-59.

43 Testa MA, Gill J, Su M, et al. Comparative effectiveness of basal-bolus versus premix analog insulin on glycemic variability and patient-centered outcomes during insulin intensification in type 1 and type 2 diabetes: a randomized, controlled, crossover trial. J Clin Endocrinol Metab. 2012;97(10):3504-3514.

44 Raccah D. Basal insulin treatment intensification in patients with type 2 diabetes mellitus: A comprehensive systematic review of current options. Diabetes Metab. 2017;43(2):110-124.

SANOFI

This publication has been created with an educational grant from Sanofi NZ Ltd. The content is entirely independent and based on published studies and the author's opinions. It may not reflect the views of Sanofi. Treatment decisions based on these data are the full responsibility of the prescribing physician.