New treatments for type 2 diabetes: are we any closer to reducing iatrogenic hypoglycaemia?

Dr Jason Seewoodhary1
BSc (Hons), MBCh (Hons), MRCP (UK), MSc (Dist), Specialist Registrar in Diabetes Mellitus & Endocrinology/General Internal Medicine

Dr Stephen Phooi Yew Wong1
BMBS, FRCP (UK), Consultant in Diabetes Mellitus & Endocrinology/General Internal Medicine

Dr Kaharanthilaka Poojanie Ekanayake2
MBBS, MD, MRCP, Consultant Physician

1Glan Clwyd Hospital, Rhyl, Denbighshire, UK
2Watford General Hospital, Hertfordshire, UK

Correspondence to:
Dr Jason Seewoodhary, Specialist Registrar in Internal Medicine, Watford General Hospital, Vicarage Road, Watford WD18 0HB, UK; email: seewoodharyj@hotmail.com

Received: 8 March 2015
Accepted in revised form: 21 May 2015

Abstract
The barrier of iatrogenic hypoglycaemia has limited the utility and safety of conventional diabetes medications. Novel agents for type 2 diabetes aim to surmount the impediment of iatrogenic hypoglycaemia and unmask the full realisation and benefits of achieving sustained euglycaemia over a lifetime of diabetes.

This review aims to critically consider the risk of iatrogenic hypoglycaemia allied with newer agents for type 2 diabetes, used alone and in combination with other diabetes therapies, and how this risk can be minimised. Copyright © 2015 John Wiley & Sons.


Key words
iatrogenic hypoglycaemia; type 2 diabetes; new treatments; combination therapy; risk

Iatrogenic hypoglycaemia
Under physiological conditions venous glucose concentrations fluctuate between 4–7 mmol/L. Criteria referred to as Whipple’s triad are used to determine a diagnosis of hypoglycaemia and consist of: symptoms known to be caused by hypoglycaemia; low glucose at the time the symptoms occur; and reversal of symptoms when the glucose is restored to normal.1

Iatrogenic hypoglycaemia is a serious and common complication of the treatment for diabetes. The main predictors of hypoglycaemia in patients with type 2 diabetes mellitus (T2DM) include a history of previous hypoglycaemia and the duration of sulphonylurea and/or insulin treatment. Self-reported hypoglycaemia is lower in T2DM relative to type 1 diabetes mellitus.2 The United Kingdom Prospective Diabetes Study (UKPDS) reported hypoglycaemia prevalence rates of 70–80% in patients with T2DM requiring insulin.3

Iatrogenic hypoglycaemia is usually the result of interactions between insulin excess and compromised glucose counter-regulation. Accordingly, the clinical approach to minimising the risk of hypoglycaemia while improving glycaemic control includes: addressing underlying predisposing factors; applying the principles of aggressive glycaemic therapy, including flexible and individualised drug regimens; and considering the risk factors for iatrogenic hypoglycaemia. The latter incorporate factors that result in absolute or relative insulin excess, which include: patterns of food ingestion and exercise; interactions with alcohol and other drugs; altered sensitivity to or clearance of insulin; and drug dose, timing and type.

Iatrogenic hypoglycaemia remains a significant barrier precluding the successful maintenance of euglycaemia over a lifetime of T2DM, which both hinders the full realisation of the long-term benefits of euglycaemia and limits the safety of optimising current treatments for diabetes. Newer agents for T2DM aim to overcome these drawbacks. Accordingly, this review will critically consider the risk of iatrogenic hypoglycaemia with novel agents for T2DM, used both alone and in combination with conventional therapies, and how such risks can be minimised.

Dipeptidyl peptidase-4 (DPP-4) inhibitors
Since their first availability nearly 10 years ago, DPP-4 inhibitors have demonstrated a desirable tolerability and safety profile. Although in clinical practice the glucose-lowering effects of DPP-4 inhibitors are inferior to those of sulphonylureas based on comparisons of hypoglycaemic risk, weight gain, and durability, DPP-4 inhibitors may be considered an alternative to sulphonylureas. Furthermore, safety concerns regarding DPP-4 inhibitors have been negated by the recently reported data from the SAVOR4 and EXAMINE5 trials, which found
DPP-4 inhibitors do not increase overall adverse cardiovascular outcomes or the risk of pancreatic cancer and pancreatitis. Accordingly, DPP-4 inhibitors now occupy a position comparable to sulphonylureas within treatment algorithms and clinical practice guidelines. Leading on from this, the proposed new NICE guidelines for T2DM, which are currently in the consultation stage, assert that sulphonylureas should no longer be automatic second-line treatment. This recognises the adverse effects of sulphonylureas, namely that they dramatically increase the risk of hypoglycaemia compared with other oral agents.6,7

Notwithstanding their glucose-dependent glucose-lowering effects, the utility of DPP-4 inhibitors is limited by the risk of hypoglycaemia when combined with sulphonylureas. The group of patients at highest risk of hypoglycaemia appears to be the elderly with renal impairment and high levels of HbA1c on maximal doses of sulphonylureas. Current expert opinion recommends that, before co-administration of DPP-4 inhibitors with pre-prescribed sulphonylureas, the risk of hypoglycaemia posed—especially in the elderly and/or patients with renal insufficiency—can be minimised by dose-titration as follows: gliclazide ≤40mg, glimepiride ≤2.0mg, and glibenclamide ≤1.25mg.8 Incidences of severe hypoglycaemia have been drastically reduced by this recommendation. However, this recommendation is limited in its application by using data from non-obese Japanese patients with T2DM requiring sulphonylureas as first-line treatment as opposed to metformin, which is first-line therapy in the USA and Europe where T2DM is more closely associated with obesity. Furthermore, the data obtained were confined to the co-prescription of sitagliptin, which is excreted via the kidneys; of the newer agents, linaglaptin, for example, is excreted through the biliary system, and has been associated with a very low risk of severe hypoglycaemia in patients with chronic kidney disease stage 4 or 5.9

The combination of DPP-4 inhibitors and metformin has been shown to be tolerable with a very low risk of hypoglycaemia.10 Additionally, in patients who cannot tolerate metformin or a sulphonylurea, the addition of DPP-4 inhibitors to pioglitazone does not increase the incidence of hypoglycaemia.11

Evidence from the Sit2Mix trial involving 582 insulin-naïve patients showed significantly lower rates of hypoglycaemia when sitagliptin was combined with either once-daily or twice-daily biphasic insulin aspart 30 (1.17 and 1.50 episodes/patient-year, respectively) compared to twice-daily biphasic insulin aspart 30 (2.24 episodes/patient-year), with no significant increase in the risk of severe hypoglycaemia or nocturnal hypoglycaemia.12

Several clinical trials have reported a consistent reduction in HbA1c when DPP-4 inhibitors were added to basal insulin therapy with no increased risk of hypoglycaemia.13

**Glucagon-like peptide-1 (GLP-1) analogues/agonists**

The 2012 European Association for the Study of Diabetes and the American Diabetes Association joint position statement on a patient-centred approach to treating T2DM recommended GLP-1 analogues as third-line agents for two- and three-drug combinations.14 Accordingly, patients who may benefit from GLP-1 therapy include those who are taking metformin, a sulphonylurea, or a thiazolidinedione, either alone or in combination, who fail to achieve target HbA1c.

GLP-1 analogues stimulate insulin secretion only during hyperglycaemia and therefore have a low hypoglycaemic risk. However, the risk of hypoglycaemia increases when a GLP-1 analogue is combined with a sulphonylurea because, while the actions of GLP-1 to stimulate insulin secretion are glucose-dependent, administration of GLP-1 in the presence of a sulphonylurea leads to enhanced insulin secretion even at normal or low glucose concentrations. Leading on from this, evidence from the 26-week LEAD-6 clinical trial reported severe hypoglycaemia in two out of 231 patients treated with exenatide and a sulphonylurea; in contrast, no cases of severe hypoglycaemia were reported in patients treated with liraglutide. Minor hypoglycaemia was reported by 42% of patients co-prescribed exenatide and a sulphonylurea compared to 33% in patients administered liraglutide and concomitant sulphonylurea therapy.15

Further corroboratory evidence on the predisposition towards hypoglycaemia in patients co-prescribed GLP-1 therapy and a sulphonylurea was provided by the 26-week LEAD-1 clinical trial. One severe hypoglycaemic episode occurred nine days after treatment started in a patient receiving liraglutide 1.8mg in combination with glimepiride 4mg. The investigator judged the episode to be related to glimepiride and reduced the dose from 4mg to 3mg after the incident. Minor hypoglycaemic events occurred more frequently in patients treated with glimepiride plus liraglutide 1.2mg or 1.8mg relative to glimepiride monotherapy. However, patients treated with liraglutide 1.2mg or 1.8mg achieved a lower HbA1c than those receiving glimepiride alone; sulphonylureas are known to elicit hypoglycaemia more readily at lower HbA1c levels.16 These findings were corroborated by a separate study where, out of 13 patients on exenatide who reported hypoglycaemia, 10 were co-prescribed a sulphonylurea. Similar to the previous study, higher hypoglycaemia rates were observed in patients with good glycaemic control.17

The risk of hypoglycaemia in patients co-prescribed GLP-1 analogues with a sulphonylurea can be minimised by reducing the dose of sulphonylurea. Evidence in support of this was provided by a study comparing exenatide + metformin + sulphonylurea (n=253) to biphasic insulin aspart + metformin + sulphonylurea (n=248); the rate of hypoglycaemia in the exenatide group fell from 27 to six events per patient-year once the dose of sulphonylurea was reduced.18 Leading on from this, the risk of hypoglycaemia in patients co-prescribed GLP-1 analogues and a sulphonylurea is highest in the elderly and/or those with renal and/or hepatic impairment. While no formal quantitative guidelines exist to guide down-titrating the dose of sulphonylurea if hypoglycaemia remains a
problem, the risk can be reduced by using a short-acting drug such as tolbutamide, or one of the newer sulphonylureas, e.g. glimepiride. If hypoglycaemia persists, the meglitinides, e.g. repaglinide and nateglinide, are an alternative option to sulphonylureas. The role of meglitinides in the management of T2DM has resurfaced – the proposed new NICE guidelines for T2DM, which are currently in the consultation stage, recommend using repaglinide as a first-line agent where metformin is not tolerated or contraindicated, or second-line in combination with metformin. The advantages of meglitinides are that they are shorter acting with a half-life of 60 minutes, which lowers the risk of hypoglycaemia. The disadvantages of meglitinides are their limited efficacy and a cumbersome thrice-daily dosing regimen.

Evidence from the AWARD-1 randomised controlled trial revealed that dulaglutide and exenatide used in combination with pioglitazone and metformin is not associated with an increased risk of hypoglycaemia. At 26 and 52 weeks, total hypoglycaemia incidence was lower in patients receiving dulaglutide 1.5mg than in those receiving exenatide; no dulaglutide-treated patients reported severe hypoglycaemia.

It has been illustrated in healthy subjects that subcutaneous and intravenous administration of GLP-1 concomitant with intravenous glucose resulted in reactive hypoglycaemia; however, this is not the case in patients with T2DM. Accordingly, exenatide twice-daily and li-raglutide are licensed for use in combination with basal insulin with no significant increased risk of hypoglycaemia. A study by Knop et al. concluded that GLP-1 analogues are not associated with an increased risk of hypoglycaemia in insulin-sensitive patients.

Table 1. Clinical trial data on hypoglycaemia risk for GLP-1 analogues when used in combination therapies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Aim</th>
<th>Duration</th>
<th>Sample size</th>
<th>Main outcome(s) on hypoglycaemia risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEAD-6</td>
<td>Compare the efficacy and safety of liraglutide with exenatide</td>
<td>26 weeks</td>
<td>231 patients</td>
<td>• Severe hypoglycaemia in 2/231 patients treated with exenatide and sulphonylurea (SU) • No cases of severe hypoglycaemia in patients treated with li-raglutide • 42% of patients treated with exenatide and SU developed minor hypoglycaemia • 33% of patients treated with li-raglutide and SU developed minor hypoglycaemia</td>
</tr>
<tr>
<td>LEAD-1</td>
<td>Compare the effects of li-raglutide with glimepiride on efficacy and safety</td>
<td>26 weeks</td>
<td>1041 patients</td>
<td>• One episode of severe hypoglycaemia in a patient receiving li-raglutide and glimepiride • More frequent minor hypoglycaemic episodes in patients receiving li-raglutide and glimepiride versus glimepiride monotherapy</td>
</tr>
<tr>
<td>Davis et al., 2007</td>
<td>Explore the safety of substituting exenatide for insulin in patients using insulin in combination with oral antidiabetes agents</td>
<td>16 weeks</td>
<td>49 patients</td>
<td>• Out of 13 patients on exenatide who reported hypoglycaemia, 10 were co-prescribed an SU • Higher hypoglycaemia rates were observed in patients with good glycaemic control</td>
</tr>
<tr>
<td>Nauck, et al., 2007</td>
<td>Compare the safety and efficacy of exenatide with that of biphasic insulin aspart</td>
<td>52 weeks</td>
<td>501 patients</td>
<td>• The risk of hypoglycaemia in patients co-prescribed exenatide with an SU can be minimised by reducing the SU dose</td>
</tr>
<tr>
<td>AWARD-1</td>
<td>Compare the efficacy and safety of dulaglutide with placebo and exenatide</td>
<td>52 weeks</td>
<td>978 patients</td>
<td>• Dulaglutide and exenatide used in combination with pioglitazone and metformin is not associated with an increased risk of hypoglycaemia • At 26 and 52 weeks, total hypoglycaemia incidence was lower in patients receiving dulaglutide 1.5mg than in those receiving exenatide; no dulaglutide-treated patients reported severe hypoglycaemia</td>
</tr>
<tr>
<td>Diamant, et al., 2014</td>
<td>Compare the efficacy and safety of exenatide twice daily or mealtime insulin lispro in patients inadequately controlled by insulin glargine and metformin despite up-titration</td>
<td>30 weeks</td>
<td>627 patients</td>
<td>• Adding exenatide to titrated glargine with metformin resulted in glycaemic control similar to that of adding lispro, and was well tolerated • The addition of exenatide to glargine resulted in a lower fasting plasma glucose, less nocturnal hypoglycaemic episodes, and improved patient satisfaction and quality of life relative to patients in the lispro arm of the study</td>
</tr>
</tbody>
</table>
patients with T2DM nor in patients with diabetes secondary to chronic pancreatitis; however, GLP-1 use is not recommended in patients with chronic pancreatitis.25

Further corroboratory evidence was recently provided by a 30-week, open-label, multicentre, randomised, non-inferiority trial which reported that adding exenatide to titrated glargine with metformin resulted in glycaemic control similar to that when adding lispro, and was well tolerated. In this study the addition of exenatide to glargine resulted in a significantly lower fasting plasma glucose (6.5 vs 7.2 mmol/L), less nocturnal hypoglycaemic episodes and improved patient satisfaction and quality of life relative to patients in the lispro arm of the study.26

Additional evidence from a meta-analysis of 11 pooled studies reported no significant difference in the relative risk of developing hypoglycaemia between GLP-1 analogue/basal insulin combination therapy and other treatments.27

The low risk of hypoglycaemia in patients on GLP-1 analogue/basal insulin combination therapy corroborates the safety argument of encouraging clinicians to use GLP-1 analogues as next-line after basal insulin. However, progress on this front may be hindered by the recent NICE guidelines on T2DM – the consultation document25 recommends that GLP-1 analogue/basal insulin combination therapy should only be commenced within specialist care, despite it being much easier to use relative to insulin intensification regimens.

Table 1 summarises the main clinical trial evidence on the risk of hypoglycaemia associated with GLP-1 analogue therapy when used in combination with other diabetes therapies.

**Sodium glucose co-transporter-2 (SGLT-2) inhibitors**

The relatively low rates of hypoglycaemia associated with SGLT-2 inhibitors are attributed to their inherent complex pharmacokinetic and pharmacodynamic relationship in respect of secretion and active reabsorption in the proximal tubule and slow-off rate from the SGLT-2 target. Therefore, despite the fact that the high-capacity and low-affinity SGLT2 co-transporters mediate 90% of renal glucose reabsorption, SGLT2 inhibitors only impede 30–50% of the filtered glucose load.28

SGLT2 inhibitors have the potential to be used as either monotherapy or in combination with metformin, sulphonylureas, thiazolidinediones, or insulin. The risk of hypoglycaemia is much lower with SGLT2 inhibitor monotherapy relative to sulphonylureas and compares favourably with that reported for metformin, pioglitazone or sitagliptin.29 Leading on from this, evidence from a meta-analysis of dapagliflozin and canagliflozin trials concluded that the hypoglycaemia risk was similar to that of other agents.30

While dapagliflozin monotherapy is not associated with an increased risk of major hypoglycaemia, data from a 24-week, randomised, double-blind, placebo-controlled trial of 597 patients reported an increased risk of minor hypoglycaemic events when dapagliflozin was used in combination with glimepiride relative to placebo (7.1–7.9% vs 4.8%).31 Furthermore, evidence from open-label, randomised, three-period, three-treatment, crossover studies submitted the lack of pharmacokinetic interaction between dapagliflozin and other oral hypoglycaemic agents, and suggests that dapagliflozin can be co-administered with pioglitazone, metformin, glimepiride or sitagliptin without dose adjustment of either drug.32

Evidence from a randomised controlled trial of 808 subjects with T2DM evaluating the safety of co-administering dapagliflozin to patients inadequately controlled on at least 30 units of insulin daily with or without oral antidiabetic drugs reported no significant increased risk of severe hypoglycaemia.33 However, patients in the pooled dapagliflozin groups had a higher rate of minor hypoglycaemic episodes relative to placebo (56.6% vs 51.8%). While no recommendations were provided to guide down-titrating the dose of insulin, it was observed that the daily insulin dose decreased by: 0.63–1.95 units with 2.5 mg dapagliflozin; 6.28 units with 5 mg dapagliflozin; and 6.82 units with 10 mg dapagliflozin. However, the findings of this study are limited by the fact that insulin doses were not titrated to target and the study was not designed to evaluate long-term safety.

Canagliflozin monotherapy is not associated with an increased risk of hypoglycaemia. However, evidence from a randomised, double-blind, placebo-controlled trial of 469 patients evaluating the efficacy and safety of canagliflozin as an add-on to metformin plus sulphonylurea in patients with T2DM observed no significant increase in the risk of severe hypoglycaemia, but reported an augmented incidence of minor hypoglycaemia episodes compared to placebo.34 Furthermore, in a separate study, an increased incidence of minor hypoglycaemia was observed when canagliflozin was used in combination with insulin.35

Empagliflozin monotherapy is not associated with an enhanced frequency of hypoglycaemia.36 However, evidence from a 24-week, randomised, double-blind, placebo-controlled trial reported an increased risk of minor hypoglycaemia in patients randomised to empagliflozin, metformin plus sulphonylurea compared to placebo, but no episodes of severe hypoglycaemia were observed.37 In contrast to dapagliflozin and canagliflozin, the addition of empagliflozin to insulin is not associated with an increased risk of hypoglycaemia.38

While no formal quantitative guidelines exist to guide adjusting the dose of sulphonylurea or insulin if hypoglycaemia remains a problem in patients on concomitant SGLT-2 inhibitor therapy, the prescribing information for dapagliflozin and canagliflozin advocates using a subordinate dose of sulphonylurea or insulin to negate this risk.

**Degludec**

Degludec is an ultra-long-acting basal insulin analogue with a half-life of >25 hours and a duration of action of >42 hours, which produces a constant steady-state profile characterised by negligible variation and irregularities in respect of administrative timing.39 This contrasts favourably with other basal insulins that do not afford a peakless
sustained effect over 24 hours from once-daily dosing. Degludec’s unique pharmacological profile has been associated with a reduced risk of hypoglycaemia compared to glargine in both basal-only and basal-bolus insulin regimens.

Evidence from a post-hoc meta-analysis of five randomised controlled trials from the Phase 3a degludec clinical trial programme, which evaluated the risk of hypoglycaemia in a subset of patients with T2DM, reported a 21% lower rate of overall hypoglycaemia and a 52% reduced rate of nocturnal hypoglycaemic episodes in patients randomised to degludec relative to glargine.40 Furthermore, an additional meta-analysis examining the duration of hypoglycaemia experienced by insulin-naive T2DM patients, treated with either degludec or glargine, concluded that there were no statistically significant differences in terms of the duration, time to recognisance, recovery time, or impact on daily activities between treatment groups.41 When used as basal therapy in combination with metformin, an 86% lower rate of severe hypoglycaemia and a 36% lower rate of nocturnal hypoglycaemia were reported with degludec relative to glargine.42

In the BEGIN Basal-Bolus Type 2 study comparing degludec with glargine in basal-bolus treatment with aspart, the rates of overall confirmed hypoglycaemia and nocturnal hypoglycaemia were lower with degludec than with glargine (11.1 vs 13.6 episodes/patient-year of exposure and 1.4 vs 1.8 episodes/patient-year of exposure, respectively). However, the frequency of severe hypoglycaemia was similar (0.06 vs 0.05 episodes/patient-year, respectively), but too low for assessment of differences.43

There is scant and inconclusive evidence on hypoglycaemic risk when degludec is combined with sulphonylureas, gliptides or thiazolidinediones. Data comparing degludec with sitagliptin, in insulin-naive patients with T2DM uncontrolled on sulphphonylurea/glinide and pioglitazone treatment, reported a significantly higher rate of hypoglycaemia with degludec compared with sitagliptin (3.1 vs 1.3 episodes/patient-year, respectively). There was no difference between treatment groups in the rate of nocturnal hypoglycaemia. Subgroup analysis revealed that the rate of hypoglycaemia was clearly influenced by concomitant oral antidiabetic drugs; lower rates for confirmed hypoglycaemia were seen in the degludec group and there were no hypoglycaemic episodes in the sitagliptin group in patients who were not treated with a sulphonylurea or a glinide.44

There are no data on the cumulative risk of hypoglycaemia when degludec is combined with a DPP-4 inhibitor or isophane insulin.

**IDegLira**

IDegLira is a novel fixed-ratio combination of liraglutide and degludec which has been developed as a once-daily injection for the treatment of T2DM. IDegLira was approved in the European Union in combination with oral glucose-lowering drugs when these alone or combined with basal insulin do not provide adequate glycaemic control. Accordingly, IDegLira was launched in the UK in November 2014. Data from the DUAL-I trial of 1663 insulin-naive patients with T2DM comparing IDegLira (n=834) with degludec (n=414) and liraglutide (n=415) reported the number of hypoglycaemic episodes/patient-year was 1.8 for IDegLira, 0.2 for liraglutide, and 2.6 for degludec. Severe hypoglycaemia occurred in 2% of patients treated with IDegLira, in 2% treated with degludec and in 3% treated with liraglutide.45 Furthermore, data from the DUAL-II trial, which aimed to assess the distinct liraglutide component of IDegLira on safety indices, revealed the hypoglycaemic incidence was comparable between groups.46

There are no conclusive data on the cumulative risk of hypoglycaemia when IDegLira is combined with a sulphonylurea, glinide, thiazolidinedione or isophane insulin.

**IDegAsp**

Another unique pharmacological property of degludec is that it can be co-formulated with aspart, resulting in a soluble preparation comprising two different insulin analogues, namely 30% aspart and 70% degludec or, alternatively, 45% aspart and 55% degludec. In solution, the two insulin components exist in soluble and stable forms, which provides a pharmacological profile with a clear distinction between the effects of its constituents.

Data from a Phase 2 randomised controlled trial comparing once-daily IDegAsp (30/70) with glargine in patients with T2DM on concomitant metformin therapy reported hypoglycaemia rates were comparable between the groups (1.2 and 0.7 events/patient-year, respectively). Nocturnal hypoglycaemic events were rare, with one episode reported in patients randomised to IDegAsp and three episodes observed in patients randomised to glargine.47 In a separate randomised controlled trial comparing IDegAsp (30/70) with biphasic insulin aspart 30% in patients with T2DM, IDegAsp was associated with a significant 58% lower rate of confirmed hypoglycaemia relative to biphasic insulin aspart 30.48

**Emerging therapies**

**Oxidative phosphorylation inhibitors.**

Imeglimin, an oxidative phosphorylation inhibitor, is the first in a new class of oral antidiabetic drugs known as ‘the glimens’, which target the three key defects of T2DM: insufficient insulin production; excessive hepatic gluconeogenesis; and impaired glucose uptake by skeletal muscles. Data from two studies suggest that imeglimin monotherapy offers a superior benefit–risk profile compared with metformin in T2DM with no reported hypoglycaemia.49 Combination imeglimin-metformin therapy is well tolerated with no increased risk of hypoglycaemia.50 Furthermore, in combination therapy with sitagliptin, no increased risk of hypoglycaemia was reported.51

**Fructose 1,6-bisphosphatase inhibitors.**

Recently, the use of selective inhibitors of fructose 1,6-bisphosphatase, a rate-controlling enzyme of hepatic gluconeogenesis, has been explored. Data from rodent models of diabetes reported that the inhibition of hepatic gluconeogenesis was not associated with hypoglycaemia. Furthermore, in early-phase clinical trials this novel class of...
New treatments for type 2 diabetes: are we any closer to reducing iatrogenic hypoglycaemia?

<table>
<thead>
<tr>
<th>Class of drug</th>
<th>Metformin</th>
<th>Sulphonylurea/meglitinide</th>
<th>Thiazolidinedione</th>
<th>Prandial insulin</th>
<th>Biphasic insulin</th>
<th>Basal insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 inhibitor</td>
<td>No</td>
<td>Yes, in the elderly and in patients with renal impairment</td>
<td>No</td>
<td>Limited data</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>GLP-1 analogue</td>
<td>No</td>
<td>Yes, lowest risk with tolbutamide, glimepiride or meglitinides</td>
<td>No</td>
<td>Limited data</td>
<td>Limited data</td>
<td>No</td>
</tr>
<tr>
<td>SGLT-2 inhibitor</td>
<td>No</td>
<td>Highest risk with dapagliflozin</td>
<td>No</td>
<td>Limited data</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Degludec</td>
<td>No</td>
<td>Yes, scant data</td>
<td>Limited data</td>
<td>Yes</td>
<td>Limited data</td>
<td>No data</td>
</tr>
<tr>
<td>IDegLira</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>IDegAsp</td>
<td>No</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
</tbody>
</table>

Table 2. Summary data for hypoglycaemia risk

Key points
- The barrier of iatrogenic hypoglycaemia has limited the utility and safety of conventional diabetes medications.
- Novel agents for type 2 diabetes aim to surmount the impediment of iatrogenic hypoglycaemia.
- Unravelling the full value of novel therapies for type 2 diabetes is hindered by the lack of large-scale data on their utility and safety in combination therapies with other treatments, and this warrants further research.

Summary
Table 2 summarises the data regarding hypoglycaemia risk in relation to combination therapies.

Conclusion
As patients approach the insulino-paenic spectrum of type 2 diabetes, the potential for optimising conventional treatments is deterred by the limiting factor of iatrogenic hypoglycaemia, which impedes the full realisation and benefits of attaining sustained euglycaemia. Newer treatments for type 2 diabetes with innovative mechanisms of action are beginning to negate this risk.

Unravelling the full value of these novel agents is hindered by the lack of large-scale data on their utility and safety in combination therapies with other treatments for type 2 diabetes, and this warrants further research.

Finally, comparing the safety and efficacy of new therapies for type 2 diabetes is tantamount to a ‘double-edged sword’ and should therefore be contextualised on an individual patient basis; it is to be expected that agents with superior HbA1c-lowering properties – for example, sulphonylureas – would have an inferior hypoglycaemia safety profile.

Declaration of interests
There are no conflicts of interest declared.

References
References are available in Practical Diabetes online at www.practicaldiabetes.com.
New treatments for type 2 diabetes: are we any closer to reducing iatrogenic hypoglycaemia?

References