# Exenatide: role in management of Type 2 diabetes and associated cardiovascular risk factors

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## Practice Points

- Obesity in Type 2 diabetes poses a challenge in choosing the right combination of glucose-lowering agents, particularly due to the potential side effect of weight gain with many of the existing glucose-lowering medications.
- One of the incretin-based therapies, the glucagon-like peptide-1 analog, exenatide, is found to be a promising new agent that not only provides glucoregulatory effect in improving glycemic control without increase risk of hypoglycemia but also often results in weight loss.
- Treatment with exenatide results in reduction in HbA1c comparable to many of the existing glucose-lowering agents including basal insulin analog, galrgine or biphasic insulin aspart.
- Exenatide is of particular benefit in obese patients with Type 2 diabetes whose control in inadequate on a combination of oral glucose-lowering agents.
- To date, exenatide is not licensed for use in combination with insulin.

**SUMMARY** Management of Type 2 diabetes, particularly in obese patients, is rather challenging as treatment with the majority of the available glucose-lowering therapies is often associated with side effects of weight gain and hypoglycemia, in addition to failure to maintain durable glycemic control. The first available glucagon-like peptide-1 analog, exenatide, adds a new therapeutic option to the currently available glucose-lowering agents for obese patients with Type 2 diabetes. Both randomized controlled trials and retrospective observational studies have shown that treatment with exenatide not only improves glycemic control with a low risk of hypoglycemia, but also results in concurrent weight loss with the additional benefit of improvement in cardiovascular risk factors of hypertension and hyperlipidemia.

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## Background

### The need for newer glucose-lowering therapies

Type 2 diabetes (T2DM) is characterized by multiple pathophysiological defects. Insulin resistance in multiorgans (liver, muscle, adipose tissue and brain), progressive decline in β-cell function of the pancreas, inappropriate hyperglucagonemia, increased glucose reabsorption from the kidney and reduced resistance to gastrointestinal (GI) hormones termed incretins, all interplay in the pathogenesis [1].

In practice, when lifestyle measures and metformin therapy fails, many clinicians traditionally adopt a step-wise approach in adding other oral glucose-lowering agents before initiation of insulin. However, with an improved understanding of the pathophysiology, there has been a shift in treatment paradigm with early insulin initiation recommended as the first-tier approach in the consensus statement by the American Diabetes Association and European Association for the Study of Diabetes after lifestyle modification and metformin therapy [2]. The UK Prospective Diabetes Study confirmed that despite implementation of lifestyle and medical management with metformin or sulfonylurea (SU), or combination therapy, β-cell function continues to decline with the resultant worsening of glycemic control as the condition progresses [3,4]. The use of metformin, SU or thiazolidinediones (TZDs), either as monotherapy or in combination, is limited by the inability to maintain durable glycemic control [5]. Moreover, undesirable side effects, including weight gain, hypoglycemia, GI intolerance, peripheral edema, fracture risk and suspected risk of bladder cancer [6–8] lead to reduced patient adherence or physician reluctance to prescribe these medications. Intensifying therapy even with modern insulin analog regimes invariably results in weight gain [2,9].

In selected clinical settings, specifically when hypoglycemic or weight gain is particularly undesirable, addition of TZD (pioglitazone) or newer agents, such as glucagon-like peptide-1 (GLP-1), may be considered as the second tier [2]. Similarly, in the American Association Clinical Endocrinologists guidelines, early combination of oral antidiabetic drugs (OADs) and treatment with newer agents, such as incretin-based therapies are advocated at an earlier stage [10].

It is well established that poor glycemic control in T2DM and obesity, either in combination or independent of each other, increase the risk of cardiovascular disease and mortality [9,11]. The availability of new glucose-lowering therapies that can achieve or maintain acceptable glycemic control without weight gain is therefore highly desirable to clinicians [12]. The development of GLP-1 analogs, which not only improve glycemic control but also results in weight loss, is a welcome addition to the treatment options in T2DM.

### Background to incretin-based therapy

Physiologically, ingestion of glucose elicits a greater insulin response than intravenous glucose infusions. This phenomenon is known as the incretin effect [13]. Glucose-dependent insulinotropic peptide (GIP) and GLP-1 are gut hormones produced in response to oral glucose ingestion and are collectively known as incretins. Their action is short-lived as a result of rapid inactivation by the enzyme dipeptidyl peptidase-4 (DPP-4) [14,15]. The incretin effect is deemed to be impaired in T2DM [16]. Although GLP-1 secretion and activity are maintained, a supraphysiological concentration is needed to compensate for the disease-associated impairment of GIP activity [17]. Unlike GIP, GLP-1 is capable of stimulating both early- and late-phase insulin secretion in T2DM. However, the exact mechanism remains debatable. Thus, the incretin effect could be potentially enhanced by either supplementing with incretin analogs, which mimic GLP-1 action such as exenatide and liraglutide, or by preventing GLP-1 breakdown by DDP-4 inhibitors, such as sitagliptin, saxagliptin, linagliptin or vildagliptin, also termed incretin enhancers.

## Role of the incretin mimetics

Exenatide is the first synthetic GLP-1 analog, originally isolated from the saliva of the desert lizard, Gila monster (*Heloderma suspectum*). This synthetic peptide has 53% homology with the human GLP-1 amino acid sequence, thus allowing it to bind avidly to the GLP-1 receptor but resist enzymatic degradation by DPP-4 [13,15].

By mimicking GLP-1 action, exenatide improves the glucoregulatory effect by enhancing glucose-dependent insulin secretion, restoring first-phase insulin response, suppressing inappropriate glucagon secretion [15,18,19] and thus has an effect on both fasting and postprandial glucose levels [20,21]. It also delays gastric emptying

and decreases food intake by promoting satiety leading to weight loss [15,18,19]. Since exenatide is resistant to inactivation by DPP-4, it has a longer half-life of 2.4 h and a duration of action of 4–6 h compared with human GLP-1, which has a half-life of 2–3 min [13,15]. It is mainly eliminated via the kidney by glomerular filtration.

The exenatide twice daily (Ex b.i.d.) preparation is manufactured by Eli Lilly (Byetta®, Exendin-4) and was first approved by the US FDA in 2005 to be used as an adjunctive therapy in T2DM [22]. It was originally recommended by NICE in the UK in 2008 to be used as a second- or third-line agent for the management of T2DM [101], and then again in the updated guidelines in 2009 [102].

Liraglutide (Victoza®) is the second licensed GLP-1 analog. Liraglutide is synthesized by recombinant DNA technology with only one amino acid substitution, sharing 97% homology with human GLP-1. It has been available in the UK since 2009 and NICE has recently recommended its use in patients with T2DM as an adjunctive therapy [103]. A long-acting formulation, exenatide once-weekly (Ex q.w.) injection, has been developed and tested in Phase III clinical trials, and has recently been approved by the EMA [104].

The purpose of this article is to review the safety and efficacy of using exenatide in the management of T2DM in clinical trials and real-life settings from published data for both the Ex b.i.d. and the Ex q.w. preparation.

## Clinical evidence from randomized controlled trials & real-life studies

### ■ Effect of exenatide on glycemic control & bodyweight

#### Ex b.i.d. as an add-on therapy to a single or combination of OADs

The efficacy of adding exenatide as a glucose-lowering therapy to various OADs is summarized in **Table 1**. In all studies, addition of exenatide unequivocally resulted in a modest but significant reduction in HbA1c of approximately 0.85% and weight loss of 1.5–3 kg [23–26].

The pivotal clinical trials were the three AMIGO studies [23–25], evaluating the effects of adding exenatide to the treatment regimens of subjects with T2DM who were unable to achieve optimal glycemic control using the maximum tolerated doses of either metformin or an SU alone or a combination of both. These studies

**Table 1. Summary of randomized controlled trials comparing twice daily use of exenatide with single or combinations of oral antidiabetic drugs.**

| Study (RCT) | Duration of study (weeks) | Patients (n) | Duration of diabetes (years) | Exenatide-based therapy (10 µg twice daily) | Comparator | Baseline HbA1C (%) ± SD/SE | Change in HbA1C (%) from baseline | p-value | Difference in bodyweight from baseline (if comparator is placebo) or difference between the groups (if both are active comparators) | p-value | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| DeFronzo *et al.* (2005) | 30 | 336 | 6 | Exenatide + metformin | Placebo + metformin | 8.2 ± 1.1 | -0.78 ± 0.10 | <0.002 | -2.8 ± 0.5 | <0.001 | [24] |
| Buse *et al.* (2004) | 30 | 377 | 6 | Exenatide + SU | Placebo + exenatide | 8.6 ± 1.2 | -0.86 ± 0.11 | <0.001 | -1.6 ± 0.3 | <0.05 | [23] |
| Kendall *et al.* (2005) | 30 | 733 | 9 | Exenatide + metformin + SU | Placebo + metformin + SU | 8.5 ± 1.0 | -0.8 ± 0.1 | <0.0001 | -1.6 ± 0.2 | ≤0.01 | [25] |
| Zinman *et al.* (2007) | 16 | 233 | 8 | Exenatide + TZD + metformin | Placebo + TZD + metfromin | 7.9 ± 0.1 | -0.98 (95% CI: -1.21 to -0.74) | <0.001 | -1.51 (CI: -2.15 to -0.88) | <0.001 | [27] |
| Liutkus *et al.* (2010) | 26 | 165 | 6.4 | Exenatide + TZD ± metformin | Placebo + TZD ± metformin | 8.2 ± 0.9 | -0.74 ± 0.16 | <0.001 | -0.6 | NS | [28] |

*NS: Not significant; RCT: Randomized controlled trial; SU: Sulfonylurea; TZD: Thiazolidinedione.*

were placebo-controlled and triple blinded, each conducted over a 30-week period, enrolling a total of 1446 subjects. The results of each study were analyzed on an intention-to-treat basis. In each study, subjects were randomized into one of the three study arms receiving either placebo, exenatide 5 or 10 µg in addition to their existing regimen for 26 weeks following a 4-week lead-in period of taking a placebo injection twice a day. Compared to the placebo arm, the HbA1c decrease from baseline was significant in both groups receiving exenatide 5 and 10 µg, and the reduction was found to be dose dependent. The studies by Buse *et al.* [23] and DeFronzo *et al.* [24] both showed a progressive dose-dependent weight loss of -1.6 kg versus -0.9 kg and -2.8 kg vs -1.6 kg, respectively, in the exenatide treated patients. At week 30, the proportion of patients with baseline HbA1c greater than 7% achieving a target HbA1c of less than 7% was significantly greater in the treatment arms with exenatide than in the placebo arm in all three studies [23–25].

The combination of exenatide with TZDs is found to be effective in a number of studies. In a double-blind, placebo-controlled trial carried out by Zinman *et al.* for 16 weeks, 233 patients with suboptimal glycemic control on TZDs alone or in combination with metformin were randomized to either exenatide (n = 121) or placebo (n = 112) [27]. Addition of exenatide led to a placebo-subtracted reduction in HbA1c of 0.98% and a significant weight loss of 1.51 kg ($p < 0.001$) [27]. Similar findings were reported by Liutkuz *et al.* in a 26-week study **(Table 1)** [28]. Approximately 70% of subjects had improvements in both HbA1c and bodyweight compared with 54% with placebo. However, the former study was limited by a relatively short duration of treatment.

The effect of sustained glycemic control and weight reduction with exenatide was reported by Blonde *et al.* in the open-label extension of the three AMIGO studies where the subjects were followed up to 82 weeks after the conclusion of the initial 30-week treatment period [29]. 668 patients from the exenatide arms of the original study were recruited and received 5 µg exenatide twice daily for 4 weeks followed by 10 µg twice daily for 48 weeks. Only 314 (57%) of the participants completed the study, with 117 (18%) not completing the full 82 weeks of treatment and 237 (43%) withdrawing. By continuing exenatide, reduction in HbA1c from baseline to week 30 was sustained at 82 weeks with the mean reduction of 1.1% and progressive weight reduction of 4.4 kg. At the end of the study period, 48% of patients achieved an HbA1c less than 7%.

In a meta-analysis including 22 published studies of over 24 weeks' duration conducted by Pinelli *et al.* [30], the efficacy and safety of exenatide was compared with that of TZDs as an add-on therapy to other OADs. Both agents have shown beneficial effects on glycemic controlm, but greater HbA1c reduction was observed with TZDs (0.8%) than with exenatide (0.6%). In addition, fasting plasma glucose was significantly reduced from baseline in the cohort treated with TZD-based regimens. However, treatment with exenatide was associated with a greater reduction in mean bodyweight of 2.74 kg whilst treatment with TZDs resulted in an increase of 2.19 kg. Thus, the evidence so far does not indicate that adding exenatide is superior to adding TZDs in subjects with suboptimally controlled T2DM who are receiving other OADs. However, Schwartz in his study concluded that the dual effects of insulin sensitivity by TZDs and stimulation of insulin secretion by exenatide make this combination a rational treatment option [31].

### Ex b.i.d. as an alternative therapy to insulin

When the glycemic target is not met by the optimal combination of dual or triple oral glucose-lowering agents, clinicians are often faced with the dilemma of how to step up treatment, by either adding insulin or a GLP-1 analog as a third-line agent [12]. The efficacy of using exenatide compared with insulin or in combination with insulin is summarized in **Table 2**.

Heine *et al.* [32] compared the safety and efficacy of exenatide with that of long-acting insulin glargine in a head-to-head, randomized open-label study. In this 26-week trial of 551 patients with T2DM suboptimally controlled with maximally tolerated dose of metformin and an SU, both exenatide and insulin glargine were found to reduce HbA1c by 1.11%. However, there was a significant difference of 4.1 kg in weight between the two groups, with a reduction in weight of 2.3 kg with exenatide and an increase of 1.8 kg with insulin glargine. In a 52-week open-label, noninferiority trial by Nauck and colleagues [33], treatment with exenatide compared with biphasic insulin aspart resulted in

**Table 2. Summary of randomized controlled trials comparing twice daily use of exenatide with different insulins.**

| Study (RCT) | Duration of study (weeks) | Patients (n) | Duration of diabetes (years) | Exenatide-based therapy (10 µg twice daily) | Comparator | Baseline HbA1C (%) ± SD/SE | Change in HbA1C (%) from baseline | p-value | Difference in bodyweight from baseline (if comparator is placebo) or difference between the groups (if both are active comparators) | p-value | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Heine *et al.* (2005) | 26 | 551 | 10 | Exenatide + metformin + SU | Glargine + metformin + SU | 8.2 | -1.11 (both groups) | <0.01 | -4.1 (95% CI: -4.6 to -3.5) | <0.0001 | [32] |
| Nauck *et al.* (2007) | 52 | 505 | 10 | Exenatide + metformin + SU | Bisphaisc insulin aspart + metformin + SU | 8.6 ± 1.0 | -1.04 ± 0.07 (exenatide) -0.89 ± 0.06 (biphasic insulin) | <0.001 | -5.4 (95% CI: -5.9 to -5.0) | <0.001 | [33] |
| Barnett *et al.* (2007) | 32 | 138 | 7.4 | Exenatide + glargine + metformin/SU | Glargine+ exenatide+ metformin/SU | 8.9 ± 0.09 | -1.36 ± 0.09 (both groups) | <0.001 | -2.2 (95% CI: -2.8 to -1.7) | <0.001 | [34] |
| Davies *et al.* (2009) | 26 | 356 | 9 | Exenatide + metformin ± SU/TZD | Glargine+ Metformin ± SU/TZD | 8.65 ± 0.68 | -1.25 (exenatide) -1.26 (glargine) | <0.001 | -5.71 (95% CI: -6.58 to -4.84) | <0.001 | [35] |
| Buse *et al.* (2011) | 30 | 261 | 12 | Exentaide + glargine ± metformin/TZD | Placebo + glarine ± metformin/TZD | 8.35 ± 0.85 | -1.74 (exenatide + glargine) -1.04 (placebo + glargine) | <0.001 | -2.74 (95% CI: -3.74 to -1.74) | <0.001 | [38] |
| Levin *et al.* (2011) | 24 | 165 | 8 (Ex b.i.d./ glargine) 11.8 (glargine/ Ex b.i.d.) | Glargine added after exenatide (Ex b.i.d./ glargine) | Exenatide added after glargine (glargine/Ex b.i.d.) | 8.8 ± 1.3 | 0.7 ± 1.6 | <0.0001 | 0.7 ± 8.3 (Ex b.i.d./glargine) -2.5 ± 6.7 (glargine/Ex b.i.d.) | 0.64 0.001 | [43] |

*Ex b.i.d.: Exenatide twice daily; RCT: Randomized controlled trial; SU: Sulfonylurea; TZD: Thiazolidinedione.*

a similar HbA1c reduction. As in the previous study, there was a significant difference in weight of 5.4 kg in favor of exenatide (Table 2).

Similar consistent findings were reported by Barnett *et al*. in a multinational, randomized, open-label, crossover, noninferiority study comparing the effects of exenatide with that of glargine [34]. Patients who had not achieved adequate glucose control with metformin or SU monotherapy were randomized into either treatment with exenatide followed by insulin glargine or *vice versa* for 16 weeks each. Independent of the treatment sequence, glycemic control improved equally in both groups with a reduction in HbA1c of 1.36%. In terms of bodyweight, patients lost weight during exenatide therapy and gained weight during insulin therapy. There was a statistically significant in-between group difference of 2.2 kg. This crossover design provided the opportunity for individual comparison of the response to each treatment.

Another head-to-head trial comparing the efficacy and safety of exenatide versus insulin glargine was the HEELA study [35]. This was a multicenter, randomized, open-label, parallel-arm comparator study undertaken over 26 weeks. The findings were comparable to the above studies (Table 2). Both insulin glargine and exenatide showed equal improvement in glycemic control with weight reduction in the group treated with exenatide (-2.73 kg) compared with weight gain in the glargine-treated group (+2.98 kg). The scatter plot clearly demonstrated that the majority of the responders who lie in the quadrant where both weight loss and improvement in glycemic control occurred were those treated with exenatide rather than with glargine.

However, there are important differences from the other studies. This study included T2DM patients with increased cardiovascular risk factors whose diabetes control was inadequate on two or three OADs. The outcomes with respect to cardiovascular risk factors will be discussed in the 'Effect on cardiometabolic parameters' section. In addition, the baseline BMI was higher (34.1 vs 31.3 kg/m$^2$) than in previous studies. Finally, it is of particular relevance to the UK population as the study was carried out in the UK.

In all the above studies, reduction in HbA1c was more marked in the first 12 weeks with maintenance of reduction for the rest of the study period. Furthermore, although both treatment modalities lowered the fasting glucose level, insulin glargine reduced it more than exenatide [32,34,35], whilst exenatide reduced the post-prandial glucose excursion more than insulin glargine or biphasic insulin aspart [32–35]. There was no difference in overall hypoglycemic events and fewer episodes of nocturnal hypoglycemia were reported with exenatide. Moreover, a higher proportion of patients treated with exenatide achieved HbA1c less than 7% in all the above studies ranging from 40 to 60% [32–35].

The mean insulin glargine dose (38.7 U/day) was higher in the HEELA study compared with the studies reported by Heine and Barnett, but was comparable to the insulin dose used in the study by Nauck [33]. At least 25% of the patients in the HEELA study received more than 50 U/day of insulin, providing more robust comparative data on the use of exenatide or glargine. The higher dose may be explained by the higher HbA1c and BMI at baseline, although a stepwise titration approach was adopted in all three studies.

All these studies confirmed that glycemic control achieved with exenatide was noninferior to either long-acting insulin glargine or biphasic insulin aspart with no increased risk of hypoglycemia. The advantage of exenatide therapy is that it invariably results in significant weight loss, a desired effect that neither SU, TZD, DDP-4 inhibitors nor insulin can offer.

### Ex b.i.d. as an add-on therapy to insulin

At present, exenatide is not licensed to be used with insulin and there is limited randomized clinical data on the combined use of exenatide and insulin. In a small proof-of-concept study including 24 subjects of whom six were receiving insulin, Kolterman and associates [21] demonstrated the effect of exenatide on the postprandial glucose level. Arnolds and colleagues [36] also showed in their study that adding Ex b.i.d. to a combination of basal insulin glargine and metformin substantially reduced postprandial glucose excursion. The rationale for combining exenatide with basal insulin is based on complementary pharmacological effects on prandial and fasting glucose levels [37], and hence combination therapy offers a potential option to improve glycemic control with the added benefit of weight loss.

Buse *et al*. studied the outcome of adding

twice-daily injections of exenatide to insulin glargine in a 30-week, parallel, randomized, placebo-control trial in subjects with poor glycemic control on insulin glargine alone or in combination with metformin or pioglitazone or both [38]. There was a significant difference in HbA1c reduction of 1.74% with exenatide compared with 1.04% with placebo, with a significant between-group difference of 0.69% ($p < 0.001$). Mean weight decreased by 1.8 kg with exenatide and increased by 1 kg with placebo, a significant difference of 2.7 kg **(Table 2)**.

The findings of these prospective clinical trials are reflected in the observational studies as summarized in **Table 3**. In a retrospective analysis of patients taking both exenatide and insulin carried out by Yoon and colleagues followed up over 27 months (n = 188), the greatest HbA1c reduction was observed at the end of the first 6 months (0.66%), which was subsequently maintained at a lesser reduction of 0.54% in the remaining months. Meanwhile, bodyweight declined with increasing treatment duration, with the greatest reduction of -5.5 kg observed at 18–27 months **(Table 3)** [39]. In another retrospective study of 124 obese subjects with poor control of diabetes by Sheffield and colleagues, addition of exenatide to insulin was shown to effectively reduce HbA1c by 0.87% ($p < 0.001$) and bodyweight by 5.2 kg ($p < 0.001$) over 1 year duration [40]. In the largest nationwide observational study in the UK, Ryder and associates examined the effects of exenatide in real clinical practice. Data from 4857 subjects, of whom 39.5% (1921) were on insulin, with a median follow-up of approximately 6 months were analyzed. The audit confirmed the effectiveness of exenatide in reducing HbA1c and mean bodyweight by 0.73% and 5.9 kg, respectively. On further subgroup analysis, there was also a modest but significant improvement in glycemic control in the cohort treated with a combination of exenatide and insulin (0.51 ± 0.06%), although the reduction was less compared with the noninsulin and exenatide-treated patients, (0.94 ± 0.04%), $p < 0.001$ for the difference. Weight reduction occurred in both groups, although the in-between group difference was insignificant [41,42].

Furthermore, in a retrospective review of 164 patients (glargine added after exenatide, n = 44, exenatide added after glargine, n = 121), long-term therapy with the combination of glargine and exenatide up to 24 months resulted in reduction in HbA1c in both treatment groups

**Table 3. Summary of observational studies of the use of twice daily use of exenatide with insulin.**

| Study | Duration of study | Patients (n) | Duration of diabetes (years) | Exenatide-based therapy (10 µg twice daily) | Comparator | Baseline HbA1C (%) | Change in HbA1C (%) from baseline | p-value | Change in bodyweight from baseline (kg) | p-value | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Yoon *et al.* (2009) (retrospective study) | 27 months | 188 | 11 | Exenatide + OAD ± insulin | Nil | 8.05 ± 1.47 | -0.66 (at 0–6 months interval)<br>-0.54 (at 12–27 months interval) | <0.001<br>0.02 | -2.4 (at 0–6 months interval)<br>-4.3 (at 6–12 months interval)<br>-6.2 (at 12–18 months interval)<br>-5.5 (at 18–27 months interval) | <0.001<br><0.001<br><0.001<br><0.001 | [39] |
| Ryder *et al.* (2010) (ABCD Nationwide audit) | 26 weeks | 4551 (for HbA1c)<br>4395 (for bodyweight) | 8 | Exenatide + OAD ± insulin | Nil | 9.45 ± 1.69 | -0.73 ± 0.03 | <0.001 | -5.9 ± 0.1 | <0.001 | [59] |
| Thong *et al.* (2011) (ABCD Nationwide audit) | 26 weeks | 4857 | 8 | Exenatide + insulin | Exenatide + noninsulin therapy | 9.45 ± 1.69 | -0.51 ± 0.06 (insulin-treated group)<br>-0.94 ± 0.04 (noninsulin-treated group) | <0.001 | -5.8 ± 0.2 (insulin-treated group)<br>-5.5 ± 0.1 (noninsulin-treated group) | 0.278 | [42] |

*Ex b.i.d.: Exenatide twice daily; OAD: Oral antidiabetic drug; SU: Sulfonylurea; TZD: Thiazolidinediones.*

(0.7 ± 1.6%, p < 0.0001) without significant weight gain regardless of the order in which either exenatide or insuin glargine was added. Bodyweight remained unchanged in the exentaide/glargine group (0.7 ± 8.3 kg, p = 0.64), whereas it decreased in the glargine/exenatide group (-2.5 ± 6.7 kg, p = 0.001) [43].

In the study by Yoon and colleagues, mean total daily dose of insulin decreased by -18 and -14.8 U/day (p < 0.001) at 6 and 12 months, respectively, with treatment of exenatide. Changes in TDD at 18 and 27 months, were insignificant [39]. The percentage change of prandial insulin dose from baseline was -33.5% (p < 0.001) at 6 months, -25.9% (p = 0.002) at 12 months, -29.7% (p = 0.02) at 18 months and -55.7% (p = 0.005) at 27 months although the change in basal insulin dose was insignificant. Of note, only 14% of patients were on premixed insulin, whilst the remainder were either on basal insulin alone or basal and prandial insulin. Moreover, 45% of the patients in the report published by Sheffield [40] managed to discontinue premeal insulin (p < 0.001). In the ABCD nationwide audit, approximately 17% of the patients were able to discontinue insulin with HbA1c reduction, and insulin dose was significantly reduced from 1.0 ± 0.8 to 0.7 ± 0.7 U/kg/day (p < 0.001).

In the study by Buse *et al.* [38] the dose of insulin was adjusted to achieve a target fasting glucose level. At randomization, patients continued to receive the same dose of glargine if their HbA1c was more than 8%, whereas it was reduced by 20% if their HbA1c was less than 8% for 5 weeks. Subsequently, the insulin dose was adjusted on a weekly basis for another 5 weeks and every 2 weeks thereafter to achieve a fasting glucose level of less than 5.6 mmol/l according to the treat-to-target algorithm [44]. By nature of the study design, mean insulin dose was found to increase from baseline. It was significantly higher in the group treated with placebo and insulin glargine (20 U/day) compared with those taking exenatide and glargine (13 U/day) with an in-between group difference of -6.5 U/day (95% CI: -12.3 to -0.8 U/day).

The greater improvement in glycemic control seen in the randomized controlled trial by Buse [38] compared with that in the observational studies [39,41] appears to be due to the use of the treat-to-target algorithm with systematic uptitration of insulin dose. On the other hand, an increase in insulin dose could have contributed to the smaller reduction in weight observed.

A modest but significant reduction in HbA1c, bodyweight and prandial insulin requirement seen in observational studies offers a potential justification for combination therapy although long-term data are needed to establish the safety of this regimen. In addition, the evidence thus far from randomized clinical trials proves that combination of exenatide with structured titration of basal insulin therapy could achieve an overall improvement in glycemic control, which is superior to adjusting basal insulin alone [38]. In conclusion, in both prospective clinical trials and observational studies, addition of exenatide to insulin therapy showed beneficial effects without increased hypoglycemia. This would appear to be an attractive therapeutic option. However, combination therapy is yet to be licensed by the drug regulatory bodies.

## Exenatide compared with other GLP-1 analogs & DPP-4 inhibitors

### *Ex b.i.d. versus liraglutide therapy: LEAD 6*

The LEAD 6 study directly compared the efficacy and safety of exenatide (Ex b.i.d.) with the other commercially available GLP-1 analog, liraglutide. This is a synthetic compound that also interacts with the GLP-1 receptor but differs from exenatide (Ex b.i.d.) in amino acid sequence. It is longer acting and therefore only requires once daily administration [45]. The results are summarized in **Table 4**. Liraglutide was found to be more effective in improving overall glycemic control with greater reduction in HbA1c and fasting glucose level. More patients achieved HbA1c less than 7% with liraglutide (54 vs 43%; odds ratio: 2.02; p = 0.0015) compared with Ex b.i.d. Both drugs promoted similar weight loss. Although nausea was the most frequent adverse event, it resolved more quickly (2.5 vs 8.6% at 26 weeks) with liraglutide. Furthermore, minor hypoglycemic episodes were less frequent (1.93 vs 2.60 events per patient per year; rate ratio: 0.55; 95% CI: 0.34–0.88; p = 0.0131) despite greater reductions in fasting glucose levels in patients treated with liraglutide than Ex b.i.d.

Thus, liraglutide offers a further treatment option for T2DM, especially when weight loss and risk of hypoglycemia are major considerations. The fact that it requires once-daily administration whilst providing significantly

greater improvement in glycemic control, less frequent episodes of hypoglycemia and better GI tolerance, liraglutide offers an advantage over Ex b.i.d. However, the liraglutide dose used in this study is higher (1.8 mg) than the dose approved by NICE (1.2 mg) and there are no data comparing liraglutide (1.2 mg) and exenatide (Ex b.i.d.).

### *Ex b.i.d. versus long-acting Ex q.w.: DURATION 1 & DURATION 5*

Since GLP-1 is mainly secreted postprandially, administration of GLP-1 analogs with meals results in reduction of postprandial glucose levels. However, the rationale for further exploration of long-acting preparations stems from observational findings of better glucose control with continuous 24 h GLP-1 infusions compared with 16 h infusions [46]. There is also a reduction in both nocturnal [46] and fasting glucose level with continuous infusions [46,47]. This demonstrates the role of basal concentrations of GLP-1 in the control of fasting glucose. Thus, it is expected that a longer-acting preparation (Ex q.w.) would improve overall glycemic control by having effects on both fasting and postprandial glucose levels due to continuous exposure, whereas the normal preparation (Ex b.i.d.) would reduce the postprandial glucose more.

In a 30-week randomized, noninferiority (DURATION 1) study, Ex q.w. 2 mg (subcutaneous) administered once weekly demonstrated significantly greater reductions in HbA1c (-1.9 vs -1.5%) compared with Ex b.i.d. 10 µg twice a day [48]. Both treatment regimes resulted in reductions in fasting and postprandial glucose levels although the change in fasting plasma glucose was significantly greater with Ex q.w. (-2.3 vs -1.4 mmol/l; $p < 0.001$). Similarly, in the DURATION 5 study, Ex q.w. produced a significantly greater reduction in HbA1c from baseline with a between-group difference of -0.7% ($p < 0.0001$) and a reduction in fasting glucose of -1.28 mmol/l ($p = 0.0008$) [49]. This may be explained by greater suppression in fasting glucagon level with corresponding reduction in glucose level from continuous exposure to exenatide with Ex q.w. therapy. Moreover, a greater proportion of patients receiving Ex q.w. achieved a target HbA1c less than 7% [48,49]. Weight reduction was similar between Ex q.w. and Ex b.i.d. and there was no increased risk of hypoglycemia in both studies [48,49]. Both treatment modalities were well tolerated, although the most frequent adverse effect, nausea was less frequent with Ex q.w. [48,49]. Hence, treatment with long-acting Ex q.w. proved to be superior to Ex b.i.d. injection and offers a promising alternative therapy with the favorable added benefit of potentially greater adherence to treatment.

### *Ex b.i.d. versus the DPP-4 inhibitor: sitaglitpin*

DPP-4 inhibitors are commonly used incretin-based glucose-lowering agents that inhibit the DPP-4 enzyme to prolong the action of GLP-1. They have been shown to produce a modest reduction of HbA1c with a neutral effect on bodyweight. The effects of a GLP-1 analog (exenatide, Ex b.i.d.) and DDP-4 inhibitor (sitagliptin) were compared in a double blind, randomized, crossover study. Patients received exenatide (5 µg b.i.d. for 1 week, then 10 µg b.i.d. for 1 week) or sitagliptin (100 mg once a day) for 2 weeks. After 2 weeks, patients crossed-over to the alternate therapy. Ex b.i.d. significantly lowered postprandial glucose levels compared with sitagliptin and postprandial glucose levels increased after switching from exenatide to sitagliptin. Reduction in fasting glucose level was similar. Compared to sitagliptin, exenatide also significantly slowed gastric emptying and reduced caloric intake [50]. Thus, it can be inferred and expected that having reduced both fasting plasma glucose and 2 h postprandial glucose levels, Ex b.i.d. potentially offers superior glycemic control with the added benefit of weight loss when compared with the DPP-4 inhibitors. Although this study was limited by a very short duration, it demonstrated that treatment with Ex b.i.d. in terms of glycemic efficacy and weight loss may be superior to sitagliptin.

### *Long-acting exenatide (Ex q.w.) versus other glucose-lowering therapies*

Clinical trials comparing the efficacy of Ex q.w. versus Ex b.i.d. injections (DURATION 1 and 5 studies), sitagliptin or pioglitazone (DURATION 2 study) and glargine (DURATION 3 study) are summarized in **Table 4**. When compared with placebo in patients receiving metformin [51], Ex q.w. therapy resulted in significant reductions in HbA1c of -1.7% ($p < 0.0001$) with weight reduction of -3.8 kg ($p < 0.05$) [51]. The findings

**Table 4. Summary of randomized controlled trials of twice daily use of exenatide compared with other glucagon-like peptide-1 analogs (liraglutide, exenatide once weekly) and dipeptidyl peptidase-4 inhibitors.**

| Study (RCT) | Duration of study (weeks) | Patients (n) | Duration of diabetes (years) | Exenatide-based therapy | Comparator | Baseline HbA1C (%) ± SD/SE | Change in HbA1C (%) from baseline | p-value (between-group difference) | Difference in bodyweight from baseline (kg) | p-value (between-group difference) | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| LEAD 6 study (Buse *et al.* 2009) | 26 | 464 | 12 | Ex b.i.d. (10 µg twice daily) + metformin ± SU | Liraglutide (1.8 mg once daily) + metformin ± SU | 8.2 ± 1.0 | -0.79 (Ex b.i.d.)<br>-1.12 (liraglutide) | <0.0001 | -2.87 (Ex b.i.d.)<br>-3.24 (liraglutide) | NS | [45] |
| DURATION 1 study (Drucker *et al.* 2008) | 30 | 259 | 7 | Ex b.i.d. (10 µg twice daily) | Ex q.w. (2 mg once a week) | 8.3 ± 1.0 | -1.5 (Ex b.i.d.)<br>-1.9 (Ex q.w.) | 0.0023 | Similar | NS | [48] |
| DURATION 2 study (Bergenstal *et al.* 2010) | 26 | 491 | 6 | Ex q.w. (2 mg once weekly) + placebo oral once daily | Sitagliptin (100 mg daily) or pioglitazone (45 mg daily) + placebo injection once weekly | 8.5 ± 1.1 | -1.5% (Ex q.w.)<br>-0.9% (sitaglitpin)<br>-1.2% (pioglitazone) | <0.0001<br>0.0165 | -2.3 kg (Ex q.w.)<br>-0.8 kg (sitagliptin)<br>+2.8 kg (pioglitazone) | 0.0002 (sitagliptin)<br><0.0001 (pioglitazone) | [52] |
| DURATION 3 study (Diamant *et al.* 2010) | 26 | 456 | 8 | Ex q.w. (2 mg once weekly) + metformin ± SU | Glargine once daily + metformin ± SU | 8.3 ± 1.1 | -1.5% (Ex q.w.)<br>-1.3% (glargine) | 0.017 | -2.6 kg (Ex q.w.)<br>+1.4 kg (glargine) | <0.0001 | [53] |
| DURATION 5 study (Blevins *et al.* 2011) | 24 | 252 | 7 | Ex q.w. (2 mg once weekly) + metformin ± SU ± TZD | Ex b.i.d. (10 µg twice daily) + metformin ± SU ± TZD | 8.4 ± 1.2 | -1.6% (Ex q.w.)<br>-0.9 (Ex b.i.d.) | <0.0001 | -2.3 kg (Ex q.w.)<br>-1.4 kg (Ex b.i.d.) | NS | [49] |

*Ex b.i.d.: Exenatide twice daily; Ex q.w.: Exenatide once weekly; NS: Not significant; RCT: Randomized controlled trial; SU: Sulfonylurea; TZD: Thiazolidinedione.*

of the DURATION 1 and DURATION 5 studies have already been discussed in the 'Ex b.i.d. versus long-acting Ex q.w.: DURATION 1 & DURATION 5' section.

In the DURATION 2 study, the safety and efficacy of Ex q.w. was assessed against the maximum approved dose of the DPP-4 inhibitor, sitagliptin (100 mg) or the TZD, pioglitazone (45 mg) in patients treated with metformin [52]. Treatment with Ex q.w. was shown to be superior to either sitagliptin or pioglitazone with a treatment differences in HbA1c reduction of -0.6 and -0.3%, respectively. Similarly, treatment with Ex q.w. resulted in a significantly greater reduction in bodyweight with a treatment difference of -1.5 kg with sitagliptin and -5.1 kg with pioglitazone. The percentage of patients who achieved target HbA1c was significantly greater with Ex q.w. treatment (60%) than that with sitagliptin (35%) and was similar to pioglitazone (52%). Fasting glucose was reduced in all treatment arms with Ex q.w. providing the greatest reduction (-1.8 mmol/l) followed by pioglitazone (-1.5 mmol/l) and then sitagliptin (-0.9 mmol/l). No episodes of major hypoglycemia occurred. The most frequent adverse events were nausea and diarrhea with Ex q.w. and sitagliptin, whereas upper respiratory tract infections and peripheral edema were the most frequent events observed with pioglitazone. In clinical practice the ultimate goal is to achieve optimum glycemic control with weight loss and minimum hypoglycemia. The DURATION 2 study proved that addition of Ex q.w. to metformin comes closer to achieving this goal than treatment with either sitagliptin or pioglitazone.

In the previous head-to-head studies by Heine and Davies, treatment with exenatide twice daily demonstrated comparable improvement in glycemic control with significant weight loss in contrast to weight gain with insulin glargine [32,35]. In the DURATION 3 study, the effect of Ex q.w. was compared with that of insulin glargine [53]. Ex q.w. resulted in greater HbA1c reduction of -0.16% with a progressive decrease in weight of -4.0 kg than insulin glargine titrated to target. Both treatments reduced mean fasting glucose and postprandial glucose level, although greater reductions of fasting glucose were observed with insulin glargine and postprandial glucose with Ex q.w. The mean dose of insulin increased from baseline 10 IU per day to 31 IU per day at the end

point. There were fewer hypoglycemic episodes in the Ex q.w.-treated group compared with the glargine treated group. More hypoglycemic episodes were observed in both groups in those treated with concomitant SUs.

In conclusion, all the above studies showed that treatment with Ex q.w. is either noninferior or superior to other commonly used glucose-lowering agents in improving glycemic control with no increased risk of hypoglycemia and the additional desired effect of weight loss. Thus, it offers an important therapeutic option for obese patients with T2DM, for whom risk of hypoglycemia, weight gain and treatment adherence are of particular concern.

### Effect on cardiometabolic parameters

T2DM patients have four- to five-times the risk of cardiovascular complications compared with the general population, which accounts for 80% of mortality [54]. It is well established that improvement in glycemic control significantly reduces microvascular complications while macrovascular complications are reduced to a lesser degree [9]. Intentional weight loss in diabetes patients is associated with a 28% reduction in cardiovascular disease and diabetes mortality [55]. Moreover, moderate weight loss significantly improves fasting glucose level, HbA1c, blood pressure (BP) and lipid profile [56]. The effect of exenatide on glycemic control and weight loss has already been discussed in the section 'Effect of exenatide on glycemic control and bodyweight' section. The effects on other surrogate cardiovascular parameters (i.e., BP and lipid profile will be discussed in this section).

In the three AMIGO studies, addition of Ex b.i.d. to metformin, SU or combination did not demonstrate changes in heart rate, BP or lipid profile [23–25] except for a small reduction in low-density lipoprotein (LDL) in patients treated with exenatide and SU [23]. The 3-year open-label extension of the above studies showed a significant improvement of surrogate cardiometabolic parameters, with a reduction in systolic BP of -3.5 mmHg, diastolic BP of -3.3 mmHg, while total cholesterol was reduced by 5%, triglyceride by 12%, LDL by 6% and high-density lipoprotein (HDL) increased by 24% [57]. Comparable reductions were reported by both Brixner and Ryder [58,59] in observational studies with 6 months' follow-up.

Similarly, significant reductions in total cholesterol (-0.36 mmol/l), triglyceride (-0.33 mmol/l) and LDL (-0.25 mmol/l) and systolic BP without significant change in HDL or diastolic BP occurred with Ex b.i.d. treatment compared with insulin glargine over 26 weeks of treatment [35]. Combination of Ex b.i.d. and glargine treatment resulted in a significant reduction of both systolic BP and diastolic BP [38]. However, heart rate was noted to increase in the Ex b.i.d. group with a mean difference of 3 bpm ($p < 0.01$).

Although 25% of subjects who lost the most weight had the greatest improvements in triglyceride, HDL-C and blood pressure, there was minimal correlation between bodyweight change and serum lipid in Klonoff's study [57], implying that exenatide may have an independent effect on improving these cardiovascular markers and hence lead to reduction in cardiovascular events independent of weight loss.

A significantly greater reduction in total and LDL cholesterol was observed with Ex q.w. compared with Ex b.i.d. preparation, whilst the reduction in fasting triglyceride was similar with both treatment modalities. Patients in both groups had similar but significant improvements in systolic BP and diastolic BP [48]. In the DURATION 2 study [52], reduction in systolic BP was significantly greater with Ex q.w. treatment than with sitagliptin, but the difference was not significant when compared with pioglitazone. Significant improvement in HDL cholesterol was found with all treatments, although improvement was greater with pioglitazone than with Ex q.w. When compared with insulin glargine, there was no difference in cardiovascular parameters other than higher mean heart rate observed with Ex q.w., but not with insulin ($p < 0.0001$). There was no association between changes in heart rate and changes in BP [53]. Although reduction in systolic BP, total cholesterol, triglyceride and LDL were greater with liraglutide treatment, the difference was insignificant when compared with Ex b.i.d. [45].

Moreover, it was found that Ex b.i.d.-treated patients were 19% less likely to have CVD event than nonexenatide-treated patients with a hazard ratio of 0.81 (CI: 0.68–0.95; $p = 0.01$) and less CVD-related hospitalization with a hazard ratio of 0.94 (CI: 0.91–0.97; $p < 0.001$) [60]. Similarly, in a retrospective analysis of the pooled data from 12 randomized controlled

trials, treatment with exenatide (Ex b.i.d.) did not increase the risk of cardiovascular events (RR: 0.7; 95% CI: 0.38–1.31) [61]. There was a suggestion that it may improve cardiovascular outcome although it did not reach statistical significance. Both studies are thus in favor of treatment with exenatide in improving cardiovascular outcomes.

In addition, there are emerging evidences that exenatide, beyond weight loss and improvement in glycemic control, may have an independent effect in improving cardiovascular outcomes. GLP-1 receptors (GLP-1R) are widely expressed in cardiac myocytes, endocardium, vascular endothelium and coronary smooth muscles and the cardioprotective effect is mediated through both GLP-1R-dependent and -independent pathways. In animal models, GLP-1 improved left ventricular function in heart failure, infarct size after myocardial ischemia and improved glucose uptake in myocardium and vasodilatation of endothelium [62–64]. In small-scale human studies, GLP-1 infusion improved left ventricular function in patients with chronic heart failure of ischemic origin, patients having angioplasty or CABG after myocardial ischemia [65–67]. Moreover, GLP-1 improves coronary blood flow and protects reperfusion injury and helps in left ventricular remodeling following postmyocardial ischemia [68]. Furthermore, administration of exenatide was found to be associated with reduction of inflammatory mediators, such as hs-CRP, accumulation of monocyte and macrophages associated with atherosclerosis and hence coronary artery disease [69–71].

## Place in therapy

### ■ Dosage, administration & patient selection

Ex b.i.d. is administered at a fixed dose of 10 µg b.i.d as a subcutaneous injection within 60 min before the meal following a 4-week initiation period of 5 µg twice a day. It is contraindicated in patients with a creatinine clearance less than 30 ml/min. With the advent of new hypoglycemic agents, clear guidance is needed to indicate when to introduce these agents as the disease progresses.

NICE guidance advocates the use of Ex b.i.d. as an alternative adjunctive therapy to oral hypoglycemic agents in triple therapy with metformin and either SU or TZD in people with T2DM when glycemic control remains or becomes inadequate (i.e., HbA1c ≥7.5%) with a BMI of at least 35 kg/m$^2$ in people of European descent (with appropriate adjustment for other ethnic groups) or a BMI less than 35 kg/m$^2$ if insulin therapy would have significant occupational implications or weight loss would benefit significant obesity-related comorbidities, for example obstructive sleep apnea [105]. It is contraindicated to be used in combination with DPP-4 inhibitors. The consensus statement from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) advocates the use of Ex b.i.d. when hypoglycemia and weight gain are the impediments in stepping up the treatment to improve glycemic control, especially when HbA1c less than 8% [2]. NICE also recommends continuing treatment with exenatide only if there is a beneficial response (i.e., reduction of HbA1c by 1% and a weight loss by 3% of initial bodyweight at 6 months) [105].

In an observational study by Ryder and colleagues in the UK, Ex b.i.d. was found to be commonly used outside that of NICE guidelines with considerable benefits to patients in terms of glycemic control and weight loss [41]. Only 21.7% of the study population fulfilled the NICE criteria on initiation of Ex b.i.d. and 33.9% were concomitantly treated with insulin. However, at the end of 6 months' duration of Ex b.i.d. therapy, approximately 60% of patients started on Ex b.i.d. achieved both HbA1c and weight reduction, but less than 30% achieved NICE criteria for a metabolic success to continue the treatment. Among the responders, approximately 45% showed improvement in glycemic control by at least 1% with loss of less than 3% of bodyweight and 68% lost at least 3% of the bodyweight, but with less than 1% improvement in glycemic control. Thus, many patients achieved significant HbA1c or weight response, but not both at the same time [41]. In practice, clinical judgment needs to be applied when deciding the clinical response of individual patients as other alternative therapies may be less efficacious.

### ■ Tolerability & adverse effects

The most common treatment-emergent adverse event reported was GI intolerance, which was predominantly dose dependent. Nausea accounted for more than 20–57% of adverse events followed by vomiting and diarrhea [23–25,28,32–34,37–39]. In the majority of patients

who discontinued exenatide, it was mainly due to GI intolerance. Gradual dose escalation, in one study, successfully reduced the dose-limiting nausea and vomiting without compromising glycemic control [72]. Although injection can be delayed up to 1 h before having a meal, Schwartz, from his experience, suggested patients should inject exenatide with their first bite and stop eating when they feel full rather than continuing to eat in order to prevent bloating, which eventually leads to nausea and vomiting [73]. In the observational retrospective analysis by Sheffield [40], 36% of the patients discontinued within the first year of treatment. The risk ratio was 2.9 (95% CI: 2–4.2) for nausea and 3.3 (95% CI: 2.5–4.4) for vomiting [74]. None of the studies reported treatment-emergent pancreatitis.

In the meta-analysis carried out by Amori *et al*. [74], mild-to-moderate hypoglycemia was more commonly reported with exenatide than with placebo (16 vs 7%, respectively; risk ratio: 2.3; 95% CI: 1.1–4.9), especially when co-administered with SU [74]. The overall hypoglycemia rate was decreased after reduction of the SU dose in exenatide-treated patients [33]. Severe hypoglycemia was rare and reported in only 5 out of 2781 patients treated with exenatide [74]. However, compared with treatment with long-acting insulin glargine or biphasic insulin, there was no significant difference in overall incidence of symptomatic hypoglycemia and in fact, the incidence of nocturnal hypoglycemic episodes was significantly lower in the exenatide than insulin-treated patients [74]. The risk of hypoglycemia was approximately 2% in both Ex b.i.d. and insulin-treated groups with the risk ratio of 1.0 (95% CI: 0.5–2.3 [74]. Furthermore, addition of Ex b.i.d. to basal insulin glargine did not increase the incidence of hypoglycemia compared with placebo (1.4 vs 1.2 events per participant per year). The proportion of patients who had minor hypoglycemia was also similar between the exenatide and placebo groups [74]and there were no major hypoglycemic episodes in the exenatide-treated cohort [33,34,38]. No evidence of safety concern was reported in the observational study by Ryder and colleagues, despite statistically higher rates of hypoglycemia from background insulin [42].

## Conclusion

Exenatide, particularly Ex b.i.d., offers a promising alternative option in managing overweight and obese patients with T2DM inadequately controlled with combination therapy of oral agents or insulin. It also compliments other existing therapies through its alternative mode of action. It is found to be generally well tolerated with improvement in glycemic control.

Generally, treatment with exenatide, either Ex b.i.d. or Ex q.w., also results in sustained weight loss in contrast to the weight gain ordinarily seen with most other glucose-lowering agents as glycemic control improves. Furthermore, cardiovascular biomarkers improve after treatment with exenatide. Improvement in BP control and lipid parameters have the potential to further reduce the cardiovascular complications caused by T2DM. However, further long-term data are needed before we could definitely conclude that either Ex b.i.d. or Ex q.w. has a specific indication to reduce cardiovascular risk in patients with T2DM.

Of note, exenatide is currently not licensed to be used in combination with insulin, although it is being used in many real-life clinical situations. Moreover, exenatide is relatively young in evolution among other well-established therapeutic agents. Hence, it needs further continued and robust evaluation in both long-term randomized controlled trials and observational studies to assess its efficacy and safety to determine its role among many other available therapies for T2DM.

### Financial & competing interests disclosure

*K Khunti has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme. He has received grants in support of investigator and investigator initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Boehringer Ingelheim and Merck Sharp & Dohme. M Davies has acted as a consultant, advisory board member and speaker for Novartis Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp, and Dohme and Roche, and as a speaker for Servier. M Davies has received grants in support of investigator and investigator-initiated trials from Novartis Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Merck Sharp and Dohme, GlaxoSmithKline and Servier. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

*No writing assistance was utilized in the production of this manuscript.*

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