DPP-4 inhibitors: A newer, well-tolerated class of glucose-lowering drugs

Roger Gadsby, GP and Associate Clinical Professor, Warwick Medical School, University of Warwick, Coventry

Dipeptidyl peptidase-4 (DPP-4) inhibitors are the most recent class of glucose-lowering therapies to be launched in the UK. Sitagliptin, the agent in the group to be first licenced, was launched in 2007. A total of four DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin and linagliptin) can now be prescribed. NICE guidelines recommend that DPP-4 inhibitors are considered second to metformin therapy if there is a significant risk of hypoglycaemia with sulphonylurea therapy, or third to metformin plus sulphonylurea or metformin plus pioglitazone in people with T2D (NICE, 2009).

In the recently published report by The NHS Information Centre, Prescribing and Primary Care Services, "Prescribing for Diabetes 2005/6 to 2010/11 in England", DPP-4 inhibitors are listed under "other antidiabetic drugs". Sitagliptin was the most frequently prescribed "other antidiabetic agent" in the UK, accounting for 51.3% of prescriptions. Saxagliptin accounted for 3.0%, vildagliptin 2.0% and linagliptin 0.2% of prescriptions (The NHS Information Centre, Prescribing and Primary Care Services, 2012).

A number of studies have compared the efficacy of DPP-4 inhibitors and other agents in lowering HbA_{1c}. The meta-analysis by Karagiannis et al (2012; summarised on the facing page), included 19 RCTs assessing the glycaemic efficacy of DPP-4 inhibitors. The authors concluded that as a second-line treatment, DPP-4 inhibitors had similar efficacy to GLP-1 agonists and sulphonylureas with a neutral effect on body weight.

I think that the efficacy of DPP-4 in lowering HbA_{1c} is widely accepted by prescribers.

The NICE clinical guideline 87 recommends that DPP-4 inhibitors should only be continued if there has been at least a 5.5 mmol/mol (0.5 percentage points) reduction in HbA_{1c} after 6 months of therapy (NICE, 2009). Prescribers would expect to see at least this level of HbA_{1c} reduction in people with T2D.

The meta-analysis by Gooßen and Gräber (2012; summarised alongside) looks specifically at the safety of DPP-4 inhibitor therapy. The authors analysed data from 67 RCTs that reported DPP-4 safety outcomes in overweight people with T2D. They concluded that the risk of hypoglycaemia whilst taking DPP-4 inhibitor therapy was low and that where it did occur DPP-4 inhibitors were being used in combination therapy with a sulphonylurea or insulin. They also stated that a large body of data supports the long-term safety of DPP-4 inhibitors and refutes an increased risk of infections (which theoretically was thought to be a possibility).

> ***"The authors analysed data from 67 RCTs that reported DPP-4 safety outcomes in overweight people with T2D. They concluded that the risk of hypoglycaemia whilst taking DPP-4 inhibitor therapy was low and that where it did occur DPP-4 inhibitors were being used in combination therapy with a sulphonylurea or insulin."***

Long-term safety studies of DPP-4 inhibitors specifically investigating cardiovascular outcomes are being undertaken. In conclusion, the meta-analysis by Gooßen et al evaluating safety data for DPP-4 inhibitors is reassuring and confirms the clinical impression that these therapies are well tolerated with few side effects in people with T2D.

NICE (2009) *Type 2 diabetes: Newer agents*. NICE clinical guideline 87. Available at: http://www.nice.org.uk/CG87 (accessed 29.08.12)

The NHS Information Centre, Prescribing and Primary Care Services (2011) *Prescribing for diabetes in England: 2005/6 to 2010/11*. Available at: http://bit.ly/zvdfQB (accessed 29.08.12)

DIABETES, OBESITY AND METABOLISM

Long-term safety of DPP-4 inhibitors in treatment of T2D

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓

1 The authors investigated the long-term safety of dipeptidyl peptidase-4 (DPP-4) inhibitors in the long-term treatment of people with T2D.

2 A total of 67 eligible RCTs reporting safety outcomes in overweight or obese people with T2D taking DPP-4 inhibitors were identified from MEDLINE, CENTRAL, manufacturer and prescriber database searches. Trials were double-blinded, randomised-, placebo- or active-controlled, and lasted ≥18 weeks.

3 Measured outcomes included the sum of adverse events by system organ class, general safety outcomes and hypoglycaemic episodes. Risk ratios were computed using the Mantel–Haenszel fixed-effects model. Separate meta-analyses were conducted for trials comparing DPP-4 inhibitors with other gliptins, other antidiabetes medicines and placebo.

4 DPP-4 inhibitors did not differ to placebo in terms of adverse events (relative risk, 1.02 [95% confidence interval, 0.99–1.04]), nor were they associated with an increased risk of infection compared with placebo or other antidiabetes medications.

5 Hypoglycaemia rates were comparable for gliptin monotherapy and placebo but co-therapy with insulin or a sulphonylurea was associated with an increased risk of hypoglycaemia compared with placebo.

6 The authors concluded that the data indicate that DPP-4 inhibitors are well tolerated in the treatment of T2D and that careful choice of co-therapy with insulin sulphonylurea may limit hypoglycaemia in these individuals.

Gooßen K, Gräber S (2012) Longer term safety of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus: *Diabetes Obes Metab* 20 Apr [Epub ahead of print]

DIABETES CARE

Genetic testing for MODY: New criteria are needed

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 Many people with maturity-onset diabetes of the young (MODY) are misdiagnosed as having T1D or T2D.

2 The authors of the Young Diabetes in Oxford (YDX) study investigated the prevalence of MODY in people with clinically defined T1D (*n*=247) or T2D (*n*=322) displaying atypical characteristics, from 12 GP surgeries.

3 Individuals underwent diagnostic testing for *HNF1A*, *HNF4A*, and *GCK* mutations if they had clinically labelled T1D or T2D, met the testing guidelines criteria and had not undergone prior genetic testing for MODY. Extended testing criteria included residual beta-cell function three or more years from diagnosis in T1D and, in people with T2D, age of diagnosis ≤30 years and/or absence of metabolic syndrome.

4 In the T1D group, two people were found to have *HNF1A* mutations. Ten *HNF1A*, two *HNF4A* and one *GCK* mutation were found in the T2D group. Only 47% of people with MODY met the current national diagnostic sequencing guidelines.

5 The authors concluded that the study findings confirm that MODY is often misdiagnosed as either T1D or T2D and that the selection criteria for genetic testing for MODY should be widened to take into account clinical features indicative of being at a higher risk of MODY.

6 The authors suggest that *HNF1A* and *HNF4A* resequencing should be considered in people with C-peptide-positive diabetes diagnosed up to 30 years of age, regardless of risk factors.

Thanabalasingham G, Pal A, Selwood MP et al (2012) Systematic assessment of etiology in adults with a clinical diagnosis of young-onset type 2 diabetes is a successful strategy for identifying maturity-onset diabetes of the young. *Diabetes Care* **35**:1206–12

DIABETIC MEDICINE

Blood glucose self-monitoring strips: Usage increasing

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 The authors evaluated blood glucose self-monitoring strip usage amongst people with T2D in Tayside, Scotland using electronic prescribing record data.

2 The number of dispensed strips was stratified against diabetes treatment (in insulin-, oral-, or diet-treated people), age, sex and socio-economic factors in 1993, 1999 and before 1 January 2009.

3 Over 15 years, strip usage increased across all treatment groups: 15.5% (1993), 24.2% (1999) to 29.8% (2009). People treated with oral agents showed the largest increase in usage over time. Non-insulin-treated women and less deprived individuals were most likely to self-monitor.

4 The authors concluded that, as national guidelines recommend, individuals who will not benefit from blood glucose self-monitoring should be dissuaded from doing so.

Evans JM, Mackison D, Emslie-Smith A et al (2012) Self-monitoring of blood glucose in Type 2 diabetes: cross-sectional analyses in 1993, 1999 and 2009. *Diabet Med* **29**: 792–5

BMJ

DPP-4 inhibitors: Safety and efficacy in treatment of T2D

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓

1 The authors set out to determine the efficacy and safety of dipeptidyl peptidase-4 (DPP-4) inhibitors compared with other oral hypoglycaemic medications in people with T2D.

2 Database searches yielded 19 RCTs. The authors assessed the glycaemic efficacy by the change in HbA_{1c} and further secondary outcomes, including hypoglycaemia, change in body weight, and adverse events.

3 DPP-4 inhibitor monotherapy resulted in a smaller reduction in HbA_{1c} compared with metformin. As a second-line treatment, DPP-4 inhibitors had similar efficacy to GLP-1 agonists and sulphonylureas, with neutral effects on body weight but at an increased unit cost.

Karagiannis T, Paschos P, Paletas K et al (2012) Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting. *BMJ* **344**: e1369

DIABETES, OBESITY AND METABOLISM

Efficacy of second-line therapies added to metformin in T2D

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 The authors compared the efficacy of second-line antidiabetes drugs in people with T2D taking metformin.

2 A total of 39 RCTs were identified from database searches and included in the meta-analysis. Measured outcomes, including change in HbA_{1c}, risk of hypoglycaemia and change in body weight, were compared using Bayesian mixed treatment comparison.

3 HbA_{1c} reduction was similar across all analysed second-line therapies but greatest with basal and biphasic insulin and GLP-1 analogues. GLP-1 analogues were superior to other therapies in terms of hypoglycaemic risk and reduction in body weight.

4 The authors concluded that further research is needed into second-line treatment outcomes in T2D, and that decisions about second-line antidiabetes therapies added to metformin needs to take into account factors such as long-term safety, cost-effectiveness and durability of the agent.

Liu SC, Tu YK, Chien MN et al (2012) Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: A network meta-analysis. *Diabetes Obes Metab* **14**: 810–20

"People treated with oral antidiabetes agents showed the largest increase in glucose self-monitoring strip usage over time."

"TAK-875 treatment improved glycaemic control in a dose-dependent manner with significant HbA_{1c} reductions occuring at all doses compared with placebo."

LANCET

FFAR1 found to be a viable therapeutic target in the treatment of T2D

Readability	✓✓✓
Applicability to practice	✓
WOW! factor	✓✓

1 The authors set out to investigate the effect of TAK-875 on free fatty acid receptor 1 (FFAR1) activation and subsequent glycaemic control compared with placebo or glimepiride in people with uncontrolled T2D.

2 A total of 426 people with T2D who had not responded to metformin or diet treatment were randomly assigned to one of five daily doses (6.25–200 mg) of TAK-875 (n=303), glimepiride (4 mg; n=62) or placebo (n=61) for 12 weeks. Measured outcomes included change in HbA_{1c}, blood glucose, hypoglycaemia incidence and change in body weight. The people receiving treatment and the study investigators were both masked to treatment assignment.

3 TAK-875 treatment improved glycaemic control in a dose-dependent manner with significant least square mean HbA_{1c} reductions occurring at all doses compared with placebo (-1.12% [SE 0.113] to -0.65% [SE 0.114], ranging from 50 mg to 6.25 mg).

4 Hypoglycaemia event incidence was significantly higher in the glimepiride treatment group (19% [n=12], P=0.010–0.002) but was similar across all TAK-875 groups and the placebo group (2% [n=7] versus 3% [n=2], respectively).

5 In the placebo group there was significant weight reduction over time (P=0.017). TAK-875 was not associated with weight gain but glimepiride resulted in a significant weight gain compared with placebo and also with baseline measurements.

6 The authors concluded that FFAR1 may be a viable therapeutic target for the treatment of T2D.

Burant CF, Viswanathan P, Marcinak J et al (2012) TAK-875 versus placebo or glimepiride in type 2 diabetes mellitus: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* **379**: 1403–11

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