

# Dipeptidyl peptidase 4 inhibitors in routine clinical practice: experiences from a Scottish teaching hospital

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## Abstract

**Aims:** This study aimed to assess the effect of dipeptidyl peptidase 4 inhibitors (DPP4i) on glycaemia and weight control and review adherence to renal dosing guidance in routine clinical practice.

**Methods:** A retrospective review of type 2 diabetes patients prescribed a DPP4i was undertaken in a general hospital. Date, type and dose of DPP4i, HbA<sub>1c</sub>, weight and renal function were recorded at initiation of DPP4i therapy and at the first follow-up appointment at least 3 months later.

**Results:** Between March 2008 and June 2012, 335 patients were initiated on DPP4i therapy of whom 263 were eligible for study inclusion (baseline median HbA<sub>1c</sub> 73 mmol/mol (IQR 65-83), median weight 90.8kg (IQR 79.7-104), approximately 74.8% with eGFR >50ml/min/1.73m<sup>2</sup>). Sitagliptin 100mg daily was the most commonly prescribed DPP4i (90.5%). Median time between DPP4i initiation and follow-up was 189 days (IQR 140-239). At follow-up there was a reduction in HbA<sub>1c</sub> (median -8.5 mmol/mol; 95%CI -10, -6.5; p<0.005) and body weight (median -0.45kg; 95% CI -1.15, -0.25, p0.033). At initiation the dose of DPP4i was appropriate for 87.7% of patients.

**Conclusions:** DPP4i are effective in reducing HbA<sub>1c</sub> and body weight in routine specialist secondary care. Inappropriate prescribing in 70% of patients with eGFR <50ml/min/1.73m<sup>2</sup> prompted a review of prescribing practice.

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**Key words:** Dipeptidyl peptidase 4 inhibitors, glycaemic control, type 2 diabetes mellitus, renal dose adjustment, weight control

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## Abbreviations and acronyms

CI	confidence interval
DPP4i	dipeptidyl peptidase 4 inhibitor
eGFR	estimated glomerular filtration rate
GLP1	glucose-like peptide 1
GIP	glucose-dependent insulintropic peptide
HbA <sub>1c</sub>	haemoglobin A1c
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
SPC	summary of product characteristics
SIGN	Scottish Intercollegiate Guidelines Network

## Introduction

DPP4i were first introduced into the UK in 2009. They inhibit the action of the principal enzyme involved in the rapid degradation and inactivation of endogenous GLP1, extending its physiological action by up to three-fold.<sup>1</sup> They also inhibit the degradation of GIP, although its role in the treatment of type 2 diabetes is limited due to an observed down regulation in GIP receptors.<sup>2</sup> Meta-analyses suggest that DPP4i may reduce HbA<sub>1c</sub> by 6.6-8.7mmol/mol and are effective in reducing HbA<sub>1c</sub> in comparison to placebo when used as mono-, dual- or triple therapy.<sup>3-6</sup> The DPP4i class is generally well tolerated clinically and exhibits an overall "weight neutral" effect.<sup>4</sup>

SIGN and NICE guidelines currently recommend DPP4i following or in place of a sulphonylurea for type 2 diabetes in NHS Scotland where metformin alone has failed to achieve glycaemic targets or is not tolerated. Treatment should be continued only if a successful glycaemic response is observed at 3-6 months (>5.5mmol/mol reduction in HbA<sub>1c</sub>).<sup>3,7</sup>

Clinical trial evidence for glycaemic and weight effects of DPP4i are readily available, but there is a lack of observational data pertaining to the "real-life" practical use of these drugs and their effect on glycaemic and weight control. This study assessed the impact of these drugs on glycaemic control and weight of patients attending the Diabetes Centre, Gartnavel General Hospital, Glasgow, UK.

Four DPP4i were available in the UK at the time research was conducted (linagliptin, saxagliptin, sitagliptin and vildagliptin), with the latter three requiring dosage adjustment in renal impairment according to manufacturer prescribing guidance. This study aimed to assess the appropriateness of the dose prescribed in terms of renal function. Alogliptin has since become available but will not be discussed in the context of this research.

**Table 1** Characteristics of study population\*

Characteristic	Value
Age (years)	59 ± 12.3 (23-87)
Sex male %	55.5
<b>Concomitant glucose lowering therapy (%)*</b>	
Metformin	219 (83)
Sulphonylurea	158 (59.9)
Thiazolidinedione	56 (21.2)
Insulin	40 (15.2)
Others	3 (1.1)
<b>Number of glucose lowering therapies at point of DPP4i initiation (%)*</b>	
No drugs	5 (1.9)
Single drug therapy	69 (26.2)
Dual drug therapy	166 (62.9)
Triple drug therapy	24 (9.1)
Continuous data expressed as mean ± SD (range). * n=264	

## Methods

Ethics and data protection approval were granted by the West of Scotland Research Ethics Service and Caldicott Guardian. A data collection tool was developed and piloted using a sample of 50 patients and amended following peer discussion.

In total 335 patients were identified using the Scottish Care Information – Diabetes Collaborative (SCI-DC) database. Further retrospective review of electronic medical notes via SCI-DC and the NHS Greater Glasgow and Clyde clinical portal was performed to assess eligibility for inclusion. Patients were excluded if they had been commenced on a DPP4i in primary care without a direct recommendation from a diabetes specialist.

A retrospective review of electronic patient notes was performed for eligible patients using the data collection tool. Baseline characteristics were recorded from initiation of DPP4i including concomitant antidiabetic medications, HbA<sub>1c</sub>, weight and eGFR. The latter three measurements were then rechecked at the point of first clinic review of DPP4i therapy, at least three months after initiation.

HbA<sub>1c</sub> and weight at initiation and review were compared separately by calculation of median change, interquartile range and 95% confidence intervals. Due to non-normal distribution of results, a Wilcoxon signed rank test was performed. A p value of <0.05 was used to define statistical significance.

## Results

In total 264 instances of DPP4i initiation were identified between 13th March 2008 and 8th June 2012 (one patient was identified with two distinct episodes of therapy). Patient demographics and use of concomitant glucose lowering therapies are displayed in Table 1. Fifty-five patients were excluded as DPP4i therapy was initiated by a general practitioner in a primary care clinic and clinical measurements were not available. Seventeen patients were

**Table 2** Frequency of initiation of individual DPP4i.

Drug/Dose	Total n=264 (%)
Linagliptin 5mg od	1 (0.4)
Saxagliptin 2.5mg od	11 (4.2)
Saxagliptin 5mg od	7 (2.7)
Sitagliptin 25mg od	0
Sitagliptin 50mg od	4 (1.5)
Sitagliptin 100mg od	239 (90.5)
Vildagliptin 50mg od	0
Vildagliptin 50mg bd	2 (0.8)

**Table 3** Glycaemic response to DPP4i therapy

	Patients included n=264 (%)	Median HbA <sub>1c</sub> (mmol/mol) (IQR)	Median change in HbA <sub>1c</sub> (mmol/mol)	CI	P value
HbA <sub>1c</sub> at initiation	263 (99.6)	73 (65-83)			
HbA <sub>1c</sub> at follow-up (all patients)	215 (81.4)	64 (55-78)	-8.5	-10, -6.5	<0.005
HbA <sub>1c</sub> at follow-up (DPP4i addition only)	192 (72.7)	64 (54-76)	-9.5	-12, -6.5	<0.005

deceased at the time of data collection and medical records were inaccessible via the SCI-DC store. Median time between initiation of DPP4i and follow-up review was 189 days (IQR 140-239); 90.5% of patients were initiated on sitagliptin 100mg daily with the full range of DPP4i and doses prescribed shown in Table 2.

## Glycaemic response

Median HbA<sub>1c</sub> at initiation and at clinic review after at least three months and median change in HbA<sub>1c</sub> are shown in Table 3. Analysis of all patients with HbA<sub>1c</sub> measurements at initiation and follow up yielded a median reduction in HbA<sub>1c</sub> of 8.5mmol/mol (n=215). Refining this to include patients where DPP4i initiation was the only therapeutic adjustment ("DPP4i initiation only") at the initial visit showed a median reduction of 9.5mmol/mol (n=192). Both reductions were noted to be statistically significant.

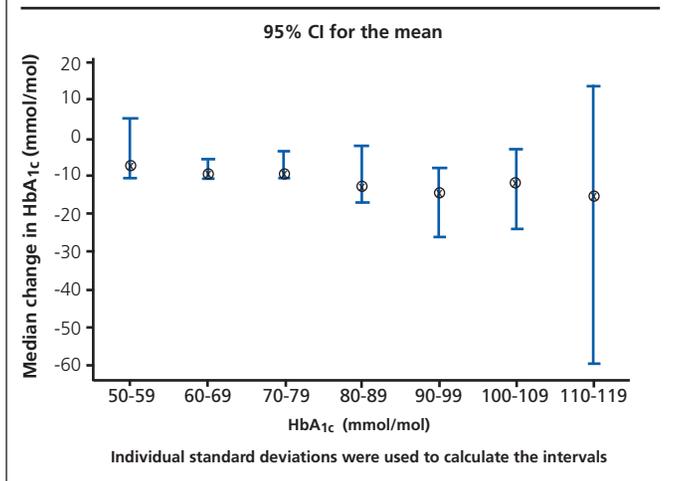
Of the 192 patients with HbA<sub>1c</sub> results at follow-up, 149 (77.6%) exhibited a reduction in HbA<sub>1c</sub> between initiation and follow-up after at least three months (Table 4). One hundred and thirty-three (69.3%) exhibited a reduction in HbA<sub>1c</sub> of ≥5mmol/mol which indicates a successful response to DPP4i therapy according to national prescribing guidance.<sup>3,7</sup>

Comparison of HbA<sub>1c</sub> concentration at initiation and glycaemic response to DPP4i initiation, where DPP4i initiation was the only therapeutic intervention, can be seen in Figure 1. Patients in the higher groupings of initial HbA<sub>1c</sub> appeared to have a larger glycaemic response to therapy.

**Table 4** Subsets of glycaemic response to DPP4i therapy

Change in HbA <sub>1c</sub>	Reduction in HbA <sub>1c</sub> (≥5mmol/mol)	Reduction in HbA <sub>1c</sub> (≤5mmol/mol)	No Response	Increase in HbA <sub>1c</sub> *
Total Patients (%) n = 192	133 (69.3)	16 (8.3)	3 (1.6)	40 (20.8)

\*Increase in HbA<sub>1c</sub>: Mean 11.4, Range 1-36.

**Figure 1.** Median change in HbA<sub>1c</sub> according to groupings of HbA<sub>1c</sub> concentration at initiation.**Table 5** Weight response to DPP4i therapy

	Patients included n=264 (%)	Median weight (kg) (IQR)	Median change in weight	95% CI	P value
DPP4i initiation	261 (98.9)	90.8 (79.7-104)	(n = 181) -0.45 (3.35)	-1.15, -0.25	0.033
Clinic review after at least three months	189 (72.3)	88.4 (79.3-103)			

### Weight response

Change in weight between initiation and follow-up in all patients is detailed in Table 5. A small median reduction in weight was observed and was noted to be statistically significant ( $p < 0.05$ ).

### Dose adjustment in renal impairment

Two hundred and sixty patients at initiation and 193 patients at follow-up had eGFR values available for assessment. Degree of renal impairment amongst the study population is shown in Table 6. Most patients had an eGFR  $>50\text{ml}/\text{min}/1.73\text{m}^2$  and thus would not require any dosage adjustment of any of the currently available DPP4i according to manufacturer's guidance. In patients with moderate renal impairment (eGFR  $30\text{--}50\text{ml}/\text{min}/1.73\text{m}^2$ ) approximately 25% at initiation and 90% at review were prescribed unlicensed doses of DPP4i. Similarly, in

**Table 6** Renal function and DPP4i dose

	Total at initiation (Total [%] prescribed licensed dose*) n = 260	Total at follow-up (Total [%] prescribed licensed dose*) n = 193
eGFR		
$>50\text{ml}/\text{min}/1.73\text{m}^2$	217 (215 [99.1])	155 (155 [100])
$30\text{--}50\text{ml}/\text{min}/1.73\text{m}^2$	35 (9 [25.7])	28 (3 [10.7])
$15\text{--}30\text{ml}/\text{min}/1.73\text{m}^2$	8 (4 [50])	10 (4 [40])
$<15\text{ml}/\text{min}/1.73\text{m}^2$	0	0

\*Licensed dose in accordance with manufacturer's SPC.<sup>8-11</sup>

patients with severe renal impairment (eGFR  $15\text{--}30\text{ml}/\text{min}/1.73\text{m}^2$ ) 50% at initiation and 60% at review were prescribed unlicensed doses.

### Discussion

#### Glycaemic control

In our study, patients with type 2 diabetes mellitus treated with DPP4i had significantly lower HbA<sub>1c</sub> levels after at least three months. This is consistent with results observed in clinical trials.<sup>3-6</sup> When all patients were included there was a significant reduction in HbA<sub>1c</sub>, and this may have been a greater reduction had some of this group not had other medication stopped at the same time. A significant reduction in HbA<sub>1c</sub> was also observed in patients where addition of DPP4i was the only therapeutic intervention at initiation. This confirmation of real world glycaemic lowering efficacy of the class is reassuring. Patients with higher initial HbA<sub>1c</sub> seem to have a greater glycaemic response.

#### Effect on weight

A small reduction in weight was observed amongst the patient population studied. An increase in weight of 1kg has been said to confer a 2% increase in risk of disease progression in early type 2 diabetes.<sup>12</sup> Glucose lowering therapy conferring weight neutrality or reduction is therefore likely to be beneficial in the management of type 2 diabetes, especially when compared to alternatives such as thiazolidinediones or sulphonylureas, well known to cause weight gain.

#### Dose adjustment in renal impairment

Adjustment of DPP4i dose for renal impairment was infrequent, suggesting a lack of prescriber awareness of recommendations for prescribing in patients with renal impairment. Exposure to sitagliptin and saxagliptin increases proportionately with reducing renal function but has not been associated with an increased incidence of adverse effects.<sup>13,14</sup> Use of doses outwith the product licence also has potential medicolegal implications for prescribers. In a patient population where renal function tends to decline, prescribers should be aware of the potential risks



### Key messages

- In the 'real life' clinical setting DPP4i:
  - reduce HbA<sub>1c</sub> similarly to randomised controlled trials
  - have no effect or marginally reduce weight
- There is inadequate awareness of the need for dose adjustments of DPP4i in impaired renal function

involved in failing to adjust the dose. These results have prompted a review of clinical governance practices surrounding the use of DPP4i with a clearer focus on evaluation of renal function and drug selection or dosage adjustment.

National guidelines recommend that DPP4i be discontinued if patients fail to achieve at least a 5.5mmol/mol reduction in HbA<sub>1c</sub>. As results from the local laboratory were not reported as decimals it was not possible to detect changes with such precision, so a lower reduction of 5mmol/mol was used. Therefore the reported patients achieving this goal in glycaemic control may not fully reflect guidelines recommendations.

Ultimately, our experience shows that DPP4i are effective in reducing HbA<sub>1c</sub> and body weight in routine specialist secondary care. Inappropriate prescribing in 70% of patients with eGFR <50ml/min/1.73m<sup>2</sup> indicates that there should be a review of prescribing practice.

**Conflict of interest** ALB has received travel grants from Boehringer Ingelheim and speakers fees from Eli Lilly. GCJ has contributed to advisory boards, received travel grants and speakers fees from Boehringer Ingelheim/Lilly/MSD/Bristol Meyers-Squibb.

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