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Controversy about the relative efficacy of dipeptidyl peptidase IV inhibitors

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Abbreviation

DPP-4 Dipeptidyl peptidase IV

To the Editor: The position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recently published an updated algorithm for the initiation and adjustment of therapy for the management of hyperglycaemia in type 2 diabetes [1]. Interestingly, from a clinical point of view, the paper recommends a patient-centred strategy and gives some key properties for each medication to help physicians choose the best option for an individual patient. This personalised approach should take into account the efficacy and safety profile of the glucose-lowering compound, its cost and some clinical characteristics of the diabetic patient. In contrast to the previous version [2] and taking into account previous criticism [3], dipeptidyl peptidase IV (DPP-4) inhibitors (also called gliptins) [4] are now considered a possible valuable alternative to other pharmacological options after failure to respond to metformin monotherapy.

Considering the comparative efficacy of the various glucose-lowering agents combined with metformin, the remarkable Fig. 2 of the position statement, summarising general recommendations, indicates that the reduction in HbA_{1c} is 'high' with sulfonylureas and with thiazolidinediones, whereas it is considered as 'intermediate' with DPP-4 inhibitors [1]. This discrimination is difficult to understand and does not reflect the currently available data. Moreover, it is partially in contradiction with the text of the position statement paper itself, which is much more nuanced:

> 'The glucose-lowering effectiveness of non-insulin pharmacological agents is said to be high for metformin, sulfonylureas, TZDs and GLP-1 agonists ... and generally lower for ... DPP-4 inhibitors ... However, older drugs have typically been tested in clinical trial participants with higher baseline HbA_{1c}, which is itself associated with greater treatment emergent glycaemic reductions, irrespective of therapy type. In head-to-head studies, any differential effects on glucose control are small.'

Furthermore, in the chapter with the subtitle 'Advancing to dual combination therapy', the position statement continues as follows: 'On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of ~1%', and concludes 'With a distinct paucity of long-term comparative-effectiveness trials available, uniform recommendations on the best agent to be combined with metformin cannot be made.' I agree that the text objectively reflects available data from the literature, but regret that Fig. 2, which provides a synthetic summary, does not! As in the previous consensus statement [2], the discrimination between the efficacy of oral glucose-lowering agents seems to rely more on opinion than on evidence [3]. I fear, however, that most physicians will just refer to the concise figure and, even if they read the more balanced information written in the core of the manuscript, they may not recall it later.

As add-on therapy to metformin, all available data from the literature indicate that the efficacy of DPP-4 inhibitors is similar to that of either sulfonylureas or thiazolidinediones [5-7]. This conclusion is supported not only by indirect comparisons [5, 6], but also by head-to-head trials comparing a DPP-4 inhibitor (for instance sitagliptin, vildagliptin or saxagliptin) and a sulfonylurea or a thiazolidinedione in patients not well controlled with metformin alone [7]. Several meta-analyses have confirmed the similar reduction in HbA_{1c} with a DPP-4 inhibitor and with a sulfonylurea or a thiazolidinedione in these conditions [5, 6]. For instance, in patients

specifically treated with metformin, an overall HbA_{1c} reduction of -0.78% (95% CI -0.93, -0.64) was reported with DPP-4 inhibitors, which was not different from the -0.79% (-0.97, -0.62) with sulfonylureas and the -0.85% (-1.08, -0.66) with thiazolidinediones [5]. Head-to-head trials in metformin-treated patients confirmed a similar efficacy in reducing HbA_{1c} between DPP-4 inhibitors and sulfonylureas (uptitrated glipizide or glimepiride; eight trials; change -0.56% vs -0.61%; NS) or between DPP-4 inhibitors and thiazolidinediones (rosiglitazone or pioglitazone; five trials; change -0.76% vs -0.83%; NS) [7].

Perhaps the inappropriate statement that DPP-4 inhibitors are less effective at reducing HbA_{1c} levels comes from indirect comparisons, with early trials having tested the efficacy of glitazones (and sulfonylureas) in patients with poorly controlled diabetes (the higher the baseline HbA_{1c}, the greater the reduction achieved irrespective of the pharmacological agent prescribed) [8]. Although this possibility is mentioned in the text by Inzucchi and colleagues, it is forgotten in the general recommendations provided in Fig. 2 [1]. Furthermore, concerning sulfonylureas, while the initial HbA_{1c} reduction may be impressive, this favourable response is commonly followed by a progressive deterioration of glucose control (as recognised and briefly mentioned in the text of the position statement).

It therefore does not seem justified, based on the available evidence, to state that the reduction in HbA_{1c} is 'intermediate' with DPP-4 inhibitors whereas it is qualified as 'high' with sulfonylureas or thiazolidinediones. Such a strong distinction in the general recommendations (the key figure of the position statement) may influence the prescription of physicians because a reduction in HbA_{1c} is generally considered the most important surrogate endpoint in the management of type 2 diabetes. This distinction between DPP-4 inhibitors on the one hand and sulfonylureas and thiazolidinediones on the other can only be justified if the authors adjust the reduction in HbA_{1c} according to the cost of the agent used. This is not the case because cost is considered as a separate item in the box summarising the overall evaluation for each pharmacological compound as provided in the otherwise nice algorithm of this position statement [1].

Duality of interest

A.J. Scheen has received lecture/advisor fees from AstraZeneca/BMS, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, NovoNordisk, sanofi-aventis and Servier

Contribution statement

The author was solely responsible for the conception, design and drafting of the manuscript, and approved the final version for publication.

References

1. Inzucchi SE, Bergenstal RM, Buse JB et al (2012) Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 55:1577-1596

2. Nathan DM, Buse JB, Davidson MB et al, American Diabetes Association; European Association for the Study of Diabetes (2009) Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 52:17-30

3. Schernthaner G, Barnett AH, Betteridge DJ et al (2010) Is the ADA/ EASD algorithm for the management of type 2 diabetes (January 2009) based on evidence or opinion? A critical analysis. Diabetologia 53:1258-1269

4. Scheen AJ (2012) A review of gliptins in 2011. Expert Opin Pharmacother 13:81-99

5. Phung OJ, Scholle JM, Talwar M, Coleman CI (2010) Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. JAMA 303:1410-1418

6. Karagiannis T, Paschos P, Paletas K, Matthews DR, Tsapas A (2012) Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. BMJ 344:el369

7. Scheen AJ (2012) DPP-4 inhibitors in the management of type 2 diabetes: a critical review of head-to-head trials. Diabetes Metab 38:89-101

8. DeFronzo RA, Stonehouse AH, Han J, Wintle ME (2010) Relationship of baseline HbA_{1c} and efficacy of current glucose-lowering therapies: a meta-analysis of randomized clinical trials. Diabet Med 27:309-317