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Dipeptydil peptidase-4 inhibitors in type 2 diabetes: A meta-analysis of randomized clinical trials

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KEYWORDS
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Abstract *Background and Aim:* The role of Dipeptidyl Peptidase-4 (DPP-4) inhibitors in the treatment of type 2 diabetes is debated; many recent trials, which were not included in previous meta-analyses, could add relevant information.
Methods and Results: All available randomized controlled trials (RCTs), either published or unpublished, performed in type 2 diabetic patients with DPP-4 inhibitors, with a duration >12 weeks were meta-analyzed for HbA1c, BMI, hypoglycemia, and other adverse events. A total of 41 RCTs (9 of which are unpublished) was retrieved and included in the analysis. Gliptins determine a significant improvement of HbA1c in comparison with a placebo (−0.7 [−0.8:−0.6]), with a low risk of hypoglycemia. DPP-4 inhibitors show a similar efficacy in monotherapy and in combination with other agents. The risk of cardiovascular events and all-cause death with DPP-4 inhibitors is 0.76 [0.46–1.28] and 0.78 [0.40–1.51], respectively.
Conclusions: DPP-4 inhibitors reduce HbA1c, although to a lesser extent than sulphonylureas, with no weight gain and no hypoglycemic risk; further data are needed to assess their long-term safety.

Introduction

Oral Dipeptidyl Peptidase-4 (DPP-4) inhibitors sitagliptin [1] and vildagliptin [2], which increase circulating levels of Glucagon-Like Peptide-1 (GLP-1), have recently been approved for use in type 2 diabetes; other molecules of the same class (such as saxagliptin and alogliptin) are under development.

The role of those new drugs in the treatment of type 2 diabetes is debated. The consensus algorithm of the American Diabetes Association and the European Association for the Study of Diabetes [3,4], in its revised version [4], suggests limiting the use of GLP-1 receptor agonists and DPP-4 inhibitors only in some specific cases, without considering those agents in the mainstream (''Tier 1'') of the algorithm. Conversely, DPP-4 inhibitors are not even included as a second choice, although their use is contemplated in selected patients. The reasons for this

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exclusion are their perceived limited efficacy on HbA1c in comparison with other agents, their poorly defined safety profile, and their cost [3,4].

Efficacy and safety need to be assessed through a comprehensive review of currently available clinical trials. Some detailed reviews of published studies have been recently published [1,2,5]; furthermore, some meta-analyses have been performed [1,6–8]. However, currently available meta-analyses included only published studies, without any attempt at retrieving data from completed and publicly disclosed, although not formally published, clinical trials. Furthermore, several trials have been published in the last few months, increasing in a relevant manner the available data base for the assessment of the clinical profile of DPP-4 inhibitors.

The aim of the present study is to offer a comprehensive and updated synthesis of all available clinical data on the safety and efficacy of DPP-4 inhibitors.

Methods

A meta-analysis was performed including all randomized clinical trials, either with a cross-over or a parallel series design, enrolling patients with type 2 diabetes, with a duration of at least 12 weeks, comparing Dipeptidyl Peptidase-4 (DPP) inhibitors with a placebo or other active drugs (oral hypoglycemic agents and/or insulin). Trials with a shorter duration were excluded, due to the fact that they could not yield relevant information on glycated hemoglobin, which had been chosen as the principal outcome variable. Trials enrolling nondiabetic, or type 1 diabetic, subjects were also excluded.

An extensive Medline search for ''vildagliptin'', ''sitagliptin'', ''saxagliptin'', and ''alogliptin'' was performed, collecting all randomized clinical trials on humans up to November 11th, 2008. The identification of relevant abstracts, the selection of studies based on the criteria described above, and the subsequent data extraction were performed independently by two of the authors (E.M., M.M.), and conflicts resolved by the third investigator (N.M.). The quality of trials was assessed using some of the parameters proposed by Jadad et al. [9]. The score was not used as a criterion for the selection of trials, whereas some items were used only for descriptive purposes.

Completed but still unpublished trials were identified through a search of www.clinicaltrials.gov website. Results of those trials were retrieved, if available, on www.merck.com/mrl/clinical_trials/results.html, www.novartisclinicaltrials.com, or www.clinicalstudyresults.org.

The principal outcome was the effect of DPP-4 inhibitors, compared with other hypoglycemic agents or a placebo, on HbA1c at the end of trial. Secondary outcomes included body mass index (BMI) at the end of the trial. Furthermore, data on the incidence of severe (requiring help from other persons) or any hypoglycemia (number of patients with at least one event) and several adverse events were extracted. The following adverse events were considered: any adverse event, nausea, vomiting, diarrhea, nasopharyngitis, upper respiratory tract infections, lower urinary tract infections and other infections. Furthermore, cases of pancreatitis, angioedema and cardiovascular events (defined as myocardial infarction, angina pectoris, coronary artery revascularization, chronic heart failure, stroke and arteriopathy of lower limbs) reported as serious or severe adverse events were considered, together with death from any cause. The choice of adverse events considered as endpoints was based on reported drug-specific adverse effects of DPP-4 inhibitors and/or other incretin-based therapies [6]. Microvascular complications of diabetes were not considered due to the relatively short duration of the trials included in the meta-analysis.

Separate analyses were performed for trials with different DPP-4 inhibitors, whenever possible.

Heterogeneity was assessed by using I^2 statistics. If a low heterogeneity was detected we applied both a random-effects and a fixed-effects model. We report the results of the random-effects models [10] because the validity of tests of heterogeneity can be limited with a small number of component studies. To estimate possible publication bias caused by the tendency of published studies to be positive, we used funnel plots, the Begg adjusted rank correlation test [11], and the Egger regression approach [12], including only published trials. However, because these tests have low statistical power when the number of trials is small [13], undetected bias may still be present. Weighted mean differences were calculated for HbA1c and BMI and a random effect model was used for the meta-analysis. Mantel–Haenszel odds ratio (MH-OR) with 95% Confidence Interval was calculated for hypoglycemia, and the adverse events defined above, on an intention-to-treat basis, using a random effect model, excluding trials with zero events. All analyses were performed using Comprehensive Meta-analysis Version 2, Biostat (Englewood, NJ, USA) and SPSS 16.0.

Results

The trial flow is summarized in Fig. 1, and the characteristics of the trials included in the meta-analysis are summarized in Table 1. Among the trials included, 32 were described in publications in peer-reviewed journals; results of 9 unpublished trials were disclosed on different websites. Furthermore, 10 unpublished trials, the results of which were undisclosed, could be identified (Table 2). Notably, results could be retrieved for the large majority of trials on currently available DPP-4 inhibitors (sitagliptin and vildagliptin), while only results of preliminary phase II studies were available for products currently under development (saxagliptin).

The Begg adjusted rank correlation test (Kendall tau: −74; $p = 0.13$) and the Egger regression approach (intercept, −2.81 [CI, −6.91–1.27]) suggested no major publication bias.

Efficacy

The metabolic effects of DPP-4 inhibitors observed in clinical trials included in the meta-analysis are summarized in Table 3. I^2 for heterogeneity on HbA1c was 94.6 ($p < 0.01$). Both sitagliptin and vildagliptin produced a significant reduction of HbA1c in placebo-controlled trials (Fig. 2); a separate analysis was not performed for saxagliptin, for

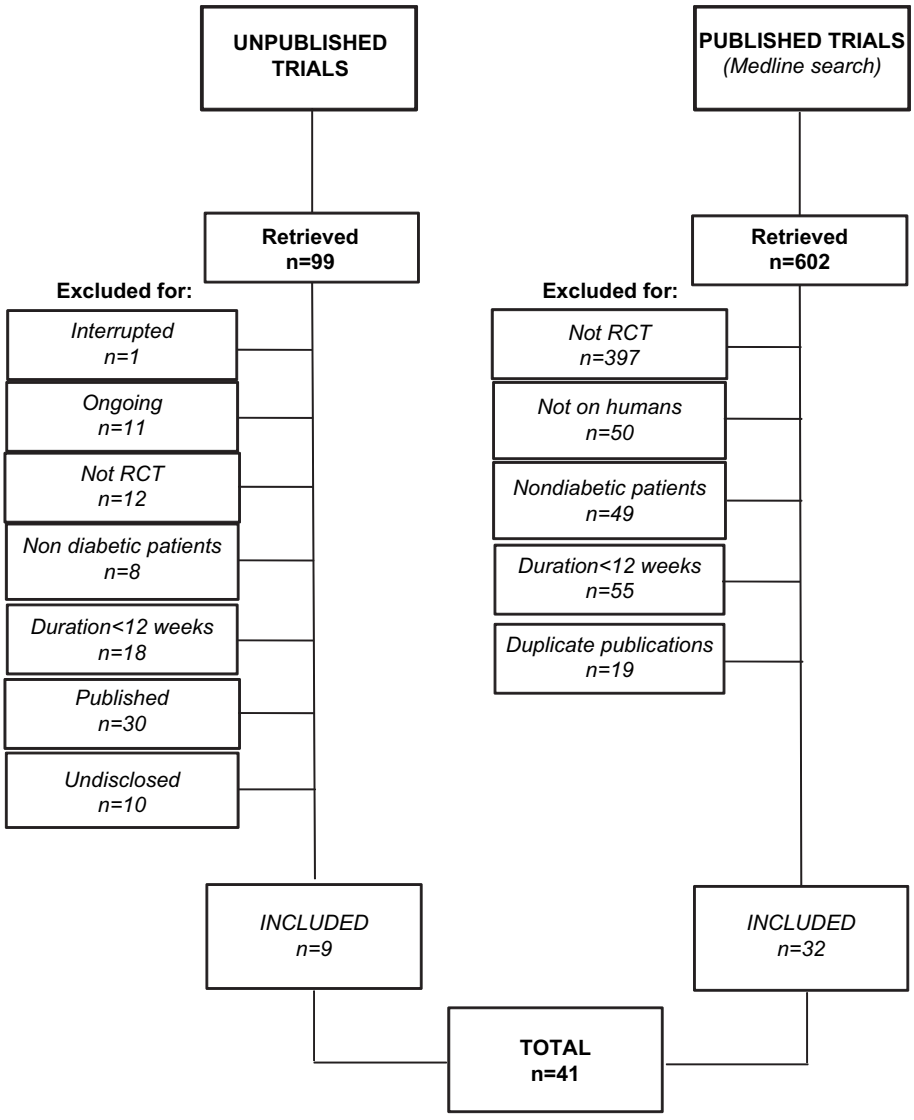

Figure 1 Trial flow diagram. RCT: randomized clinical trial.

which only one trial was available. Similar reductions of HbA1c, in comparison with a placebo, were observed in monotherapy and in combination with other hypoglycemic agents. The extent of HbA1c reduction was similar in shorter and longer-term trials; similar effects of HbA1c reduction were observed in placebo-controlled studies enrolling patients with a different duration of diabetes or baseline HbA1c (Fig. 2). The reduction of HbA1c in unpublished trials (−0.68 [−1.57; 0.21]; $p = 0.13$) was similar to that obtained in published trials (−0.70 [−0.80; −0.59]; $p < 0.001$), although it did not reach statistical significance due to the small number of unpublished studies ($N = 4$). A nonsignificant trend toward a greater placebo-subtracted effect on HbA1c was observed in trials enrolling patients with a mean baseline HbA1c lower than 8%, in comparison with trials on subjects with a greater degree of hyperglycemia (Fig. 2). In active-comparator studies, DPP-4 inhibitors showed a similar effect to that of thiazolidinediones; conversely, in the two available direct comparison studies, endpoint HbA1c with DPP-4 inhibitors (sitagliptin in both cases) were higher than with sulfonylureas; similarly, metformin appeared to be more effective than DPP-4 inhibitors (Fig. 2). A meta-analysis of trials versus acarbose could not be performed because only one trial was available. None of the trials with DPP-4 inhibitors reported 2-h post-prandial glucose from home self-monitoring.

Body weight

DPP-4 inhibitors showed no significant effect on BMI in placebo-controlled trials (+0.2 [−0.1; 0.6] kg/m^2; $p = 0.11$; 13 trials), while a modest, although significant, difference was detected in comparison with thiazolidinediones (−0.2 [−0.3; −0.1] kg/m^2; $p = 0.008$). Comparisons with other classes of hypoglycemic agents could not be meta-analyzed due to the fact that BMI at endpoint was reported only in one trial versus acarbose, sulfonylureas or metformin.

Safety: hypoglycemia

Information on hypoglycemia could be retrieved for 15 out of 18 trials with sitagliptin, and 19 out of 21 with

Table 1 Characteristics of the studies included in the meta-analysis.

Study (Ref.)	Dose (mg/die)	Comparator	Add-on to	Description of randomization	Description of blinding	Reporting of drop-out	Intention-to-treat
Vildagliptin							
Pan [33]	100	Acarbose	None	NA	NA	A	Yes
Schweizer [28]	100	Metformin	None	NA	NA	A	Yes
Rosenstock [34]	50—100	Rosiglitazone	None	NA	NA	A	Yes
2329 [14]	50—100	Pioglitazone	None	NR	NR	NR	Yes
Bolli [21]	100	Pioglitazone	Metformin	NA	NA	A	No
Rosenstock [35]	100	Pioglitazone	None	NA	A	A	Yes
	50—100	Placebo	Pioglitazone	NA	A	A	Yes
Dejager [36]	50—100	Placebo	None	NA	NA	A	Yes
Scherbaum [37]	50	Placebo	None	NA	NA	A	Yes
Mari [38]	50	Placebo	None	NA	NA	A	NR
Scherbaum [39]	50	Placebo	None	NA	NA	A	Yes
Pratley [27]	50	Placebo	None	NA	A	A	Yes
Pi-Sunyer [40]	50—100	Placebo	None	NA	NA	A	Yes
Ristic [41]	25—100	Placebo	None	NA	NA	NA	Yes
1202 [14]	20—100	Placebo	None	NR	NR	NR	Yes
Ahren [42]	50	Placebo	Metformin	NA	NA	A	NR
Bosi [22]	50—100	Placebo	Metformin	NA	NA	A	Yes
Garber [43]	50—100	Placebo	Pioglitazone	NA	NA	A	Yes
Garber [19]	50—100	Placebo	Glimepiride	A	NA	A	Yes
1302 [14]	100	Placebo	Glimepiride	NR	NR	NR	Yes
Fonseca [20]	100	Placebo	Insulin	NA	NA	A	Yes
1303 [14]	50—100	Placebo	NR	NR	NR	NR	Yes
D'Alessio [44]	100	Placebo	Metf./None	NA	NA	A	Yes
Sitagliptin							
PN-036 [15]	50—100	Metformin	None	NA	A	A	Yes
Scott [45]	100	Rosiglitazone	Metformin	NA	NA	A	Yes
	100	Placebo	Metformin	NA	NA	A	Yes
PN-035 [15]	100	Pioglitazone	Glim ± Met	NA	NA	A	Yes
Nauck [17]	100	Glipizide	Metformin	NA	NA	A	Yes
PN-028 [15]	25—50	Placebo/Glip.	OAD/Insulin	NR	NR	NR	Yes
Scott [18]	10—100	Glipizide	None	A	A	A	Yes
	10—100	Placebo	None	A	A	A	Yes
Nonaka [46]	100	Placebo	None	NA	NA	A	Yes
Hanefeld [16]	25—100	Placebo	None	NA	A	A	No
Raz [47]	100—200	Placebo	None	NA	NA	A	Yes
Goldstein [23]	50—100	Placebo	None	NA	A	A	Yes
Rosenstock [35]	100	Placebo	Pioglitazone	NA	NA	A	Yes
Hermansen [24]	100	Placebo	Glim ± Metf	NA	NA	A	Yes
Goldstein [23]	50—100	Placebo	Metformin	NA	A	A	Yes
Charbonnel [48]	100	Placebo	Metformin	NA	NA	A	Yes
Aschner [49]	100—200	Placebo	None	NA	NA	A	Yes
Raz [50]	100	Placebo	Metformin	A	NA	A	Yes
PN-040 [15]	100	Placebo	OAD/None	NR	NR	NR	Yes
PN-044 [15]	25—200	Placebo	OAD/None	NR	NR	NR	Yes
Saxagliptin							
Rosenstock [51]	2.5—40	Placebo	None	NA	NA	A	Yes

NA: not adequate or not adequately reported; A: adequate; NR: not reported; glip.: glipizide; glim ± metf: glimepiride and/or metformin; metf.: metformin; OAD: oral antidiabetic drugs; and SU/metf: sulfonylureas or metformin.

vildagliptin. In some trials (1302 [14], 1303 [14], PN-035 [15], PN-036 [15], and PN-044 [15]), the overall number of hypoglycemic episodes was not reported. Of the remaining 34 studies, 5 (2 with sitagliptin and 3 with vildagliptin) reported that no hypoglycemic event had occurred during the trial. In the remaining studies, hypoglycemia was observed in 184 of 9944 patients treated with DPP-4 inhibitors (103 of 4573, 81 of 5100, and 0 of 271 with sitagliptin, vildagliptin and saxagliptin, respectively) and 293 of 5698 in comparator groups. The incidence of hypoglycemia with DPP-4 inhibitors (both sitagliptin and vildagliptin) was not significantly different from that observed with a placebo, even when those agents were used in combination with sulphonylureas or insulin (Fig. 3). In

Table 2 Characteristics of the unpublished and undisclosed studies.

Study	# Patients planned	Comparator	Add-on to	Trial duration (weeks)	Design	Randomization	Study end date[a]
DPP-4 inhibitors							
Vildagliptin							
NCT00368134 [52]	370	Voglibose	None	12	PS	Double blind	June 2007
NCT00396227 [52]	2665	Glitazones	Metformin	12	PS	Open label	October 2007
Sitagliptin							
NCT00411554 [52]	310	Voglibose	None	12	PS	Double blind	August 2007
Saxagliptin							
NCT00327015 [52]	1396	Placebo	Metformin	52	PS	Double blind	November 2007
		Metformin	None	52	PS	Double blind	
NCT00121641 [52]	460	Placebo	None	24	PS	Double blind	August 2007
NCT00374907 [52]	36	Placebo	None	12	PS	Double blind	October 2007
NCT00295633 [52]	555	Placebo	Glitazones	24	PS	Double blind	October 2007
NCT00121667 [52]	720	Placebo	Metformin	24	PS	Double blind	August 2006
NCT00313313 [52]	780	Placebo	Glyburide	24	PS	Double blind	September 2007
NCT00316082 [52]	365	Placebo	None	24	PS	Double blind	November 2007

PS: parallel series.
[a] Final data collection date for primary outcome measure.

direct comparison, DPP-4 inhibitors were associated with a significantly lower hypoglycemic risk than sulphonylureas, whereas no significant differences were detected with respect to thiazolidinediones (Fig. 3). The number needed to harm (NNH) for sulphonylureas in comparison with DPP-4 inhibitors, with respect to hypoglycemia, on an yearly basis, was 128.

All trials with DPP-4 inhibitors reported information on severe hypoglycemia, except 10 (6 with sitagliptin, 4 with vildagliptin). In three distinct trials [16–18], severe hypoglycemia was reported by 5 patients treated with sitagliptin, in monotherapy ($N = 4$) or in combination with metformin ($N = 1$), versus 9 cases in comparator groups (all treated with sulphonylureas). No case of severe hypoglycemia was reported in patients treated with vildagliptin, versus 5 with comparator (placebo in all cases); the severe hypoglycemic episodes detected in vildagliptin trials occurred in combination studies with sulphonylureas [19] or insulin [20].

Safety: other adverse events

The proportion of patients experiencing any adverse event was retrieved for 29 placebo-controlled trials and 11 active-comparator study. Treatment with DPP-4 was not associated with any increase in the overall risk of adverse events in comparison with placebo (MH-OR 1.03 [0.93; 1.13]; $p = 0.51$) or thiazolidinediones (0.97 [0.81; 1.17]; $p = 0.75$, $N = 5$ trials), whereas the incidence was significantly lower than with sulphonylureas (0.64 [0.51; 0.80]; $p < 0.001$, $N = 2$ trials), metformin (0.78 [0.61; 1.00]; $p = 0.050$, $N = 2$ trials), and α-glucosidase inhibitors (0.51 [0.39; 0.67]; $p < 0.001$, $N = 2$ trials).

Information on mortality was unavailable for two vildagliptin trials; at least one death was observed in 17 of the remaining 39 trials with DPP-4 inhibitors. In those, 18 and 13 deaths were recorded in patients treated with the investigational drug or with comparators, respectively (Table 4). The risk of death with DPP-4 inhibitors, compared with control groups, was 0.78 [0.40; 1.51]; $p = 0.47$.

Forty-one patients reported a cardiovascular event in trials with DPP-4 inhibitors (Table 4). The MH-OR for cardiovascular events, in comparison with control groups, was 0.76 [0.46–1.28], $p = 0.30$, for DPP-4 inhibitors; the corresponding figure for placebo-controlled trials was 0.86 [0.47–1.59], $p = 0.63$.

The other serious/severe adverse events considered occurred in only a few cases, preventing any statistical analysis. In all the trials included, two cases of pancreatitis were reported (1 during vildagliptin and 1 with placebo), along with 6 cases of angioedema (3 with vildagliptin, 1 with sitagliptin, and 2 with placebo).

Other adverse events are reported in Table 4. No increase of gastrointestinal adverse events was detected with DPP-4 inhibitors. A significant increase in the risk of nasopharyngitis was observed with sitagliptin (NNH = 98), but not with vildagliptin, while a nonsignificant trend toward the increase of risk of urinary tract infection was observed with vildagliptin only. Treatment with DPP-4 inhibitors was not associated with any increase in the risk of upper respiratory tract infections, different from nasopharyngitis, whereas the actual incidence of other infections was lower than in comparator groups (Table 5).

Discussion

DPP-4 inhibitors have been proposed as an alternative to currently available therapies (sulphonylureas, thiazolidinediones or insulin), mainly as an add-on treatment in patients failing with metformin monotherapy. However, even the most recent version of the ADA–EASD consensus algorithm does not consider these drugs a viable option, except for selected cases [4]. The reasons for exclusion from the main treatment algorithm are scarce efficacy, limited amount of available evidence and high cost. With respect to available evidence, it should be recognized that several trials, which had not been included in previous meta-analyses [6], have been recently published [19,21–25]. Furthermore, there are a relevant number of

Table 3 Moderators and outcome variables in individual studies included in the meta-analysis.

Study (Ref.)	# Patients (ID/C)	Comparator	Trial duration (weeks)	>Age[a] (years)	Duration of DM[a] (years)	HbA1c baseline[a] (%)	HbA1c endpoint (%, ID/C)	BMI baseline[a] (Kg/m^2)	BMI endpoint (Kg/m^2)
DPP-4 inhibitors									
Vildagliptin									
Pan [33]	440/220	Acarbose	24	52	1.2	8.6	7.2/7.3	26.1	26.3/25.2
Schweizer [28]	526/254	Metformin	52	53	1.0	8.7	7.7/7.3	32.4	32.5/31.8
Rosenstock [34]	459/238	Rosiglitazone	24	54	2.5	8.7	7.6/7.4	32.5	32.1/33.5
2329 [14]	218/55	Pioglitazone	12	52	2.0	10.0	NR	NR	NR
Bolli [21]	295/280	Pioglitazone	24	56	6.4	8.4	7.5/7.5	32.1	32.1/32.8
Rosenstock [35]	154/161	Pioglitazone	24	51	2.0	8.7	7.0/7.3	29.4	29.9/29.4
	292/161	Placebo	24	52	2.0	8.7	7.5/7.3	29.3	29.5/29.4
Dejager [36]	472/160	Placebo	24	54	2.1	8.4	7.6/8.1	32.9	NR
Scherbaum [37]	67/61	Placebo	52	64	3.3	6.6	6.6/7.1	30.2	NR
Mari [38]	156/150	Placebo	52	63	2.6	6.7	6.5/6.9	30.2	NR
Scherbaum [39]	156/150	Placebo	52	63	2.5	6.7	6.5/6.9	30.2	30.2/29.9
Pratley [27]	70/28	Placebo	12	55	4.0	8.0	7.4/8.1	29.9	NR
Pi-Sunyer [40]	262/92	Placebo	24	51	2.1	8.4	7.7/8.4	32.2	31.9/32.2
Ristic [41]	221/58	Placebo	12	56	3.0	7.7	7.2/7.7	31.1	31.0/31.4
1202 [14]	219/72	Placebo	12	59	NR	7.4	6.7/7.	24.0	NR
Ahren [42]	56/51	Placebo	12	57	5.5	7.8	7.1/7.8	29.7	NR
Bosi [22]	349/171	Placebo	24	54	6.2	8.4	7.5/8.4	32.7	32.5/31.7
Garber [43]	260/138	Placebo	24	54	4.7	8.7	7.6/8.1	32.4	NR
Garber [19]	264/144	Placebo	16	58	7.1	8.5	7.9/8.6	31.4	31.8/31.2
1302	102/100	Placebo	12	60	9.0	7.9	6.8/7.9	NR	NR
Fonseca [20]	144/152	Placebo	24	59	14.7	8.4	7.9/8.2	33.1	33.8/33.1
1303 [14]	178/61	Placebo	12	60	6.5	7.4	6.5/7.7	NR	NR
D'Alessio [44]	20/19	Placebo	12	55	3.5	6.7	6.3/6.3	32.3	NR
Sitagliptin									
PN-036 [15]	179/176	Metformin	30	53	4.5	8.9	8.1/7.6	31.9	NR
Scott [45]	94/87	Rosiglitazone	18	55	5.0	7.7	7.0/6.9	30.2	30.1/30.9
	94/92	Placebo	18	55	5.0	7.7	7.0/7.5	30.1	30.1/29.8
PN-035 [15]	91/68	Pioglitazone	30	56	8.7	8.2	7.6/8.0	31.2	NR
Nauck [17]	576/559	Glipizide	52	57	6.3	7.7	7.2/7.0	31.2	30.7/31.7
PN-028 [15]	65/26	Placebo/Glip	54	68	13.5	7.7	7.0/7.6	NR	NR
Scott [18]	595/123	Glipizide	12	55	5.0	7.9	7.5/7.1	30.8	NR
	595/125	Placebo	12	55	5.0	7.9	7.5/8.1	31.0	NR
Nonaka [46]	75/76	Placebo	12	55	4.0	7.6	6.9/8.1	25.2	NR
Hanefeld [16]	444/111	Placebo	12	56	3.7	7.7	7.4/7.8	31.7	NR
Raz [47]	411/110	Placebo	18	55	4.6	8.0	7.7/8.2	32.1	31.8/32.3
Goldstein [23]	179/176	Placebo	24	53	4.5	8.7	8.2/8.9	31.9	NR
Rosenstock [35]	175/178	Placebo	24	56	6.1	8.1	7.2/7.8	31.5	32.6/31.5
Hermansen [24]	222/219	Placebo	24	56	8.7	8.3	7.8/8.6	31.0	31.5/31.2
Goldstein [23]	372/364	Placebo	54	53	4.4	8.8	7.1/7.8	32.2	NR
Charbonnel [48]	429/206	Placebo	24	54	6.3	8.0	7.3/7.9	31.3	NR
Aschner [49]	488/253	Placebo	24	54	4.4	8.0	7.3/8.2	30.5	30.3/30.5
Raz [50]	96/94	Placebo	30	55	8.0	9.2	8.3/9.1	30.2	NR
PN-040 [15]	352/178	Placebo	18	NR	NR	8.7	NR	NR	NR
PN-044 [15]	290/73	Placebo	12	NR	NR	7.6	NR	NR	NR
Saxagliptin									
Rosenstock [51]	271/67	Placebo	12	53	1.0	7.9	7.1/7.7	31.0	30.7/30.7

ID/C: investigational drug/comparator; DM: diabetes mellitus; and glip.: glipizide.
[a] Mean values.

unpublished trials, the results of which have been disclosed on different websites, and are therefore available. The decision to publish a trial is, in most instances, performed by the sponsor which has a specific interest in pursuing the greater safety and tolerability of the new drug. This bias is unfortunate and limits the reliability of this and other meta-analysis, often based only on data provided from manufacturers; however, the retrieval of all available

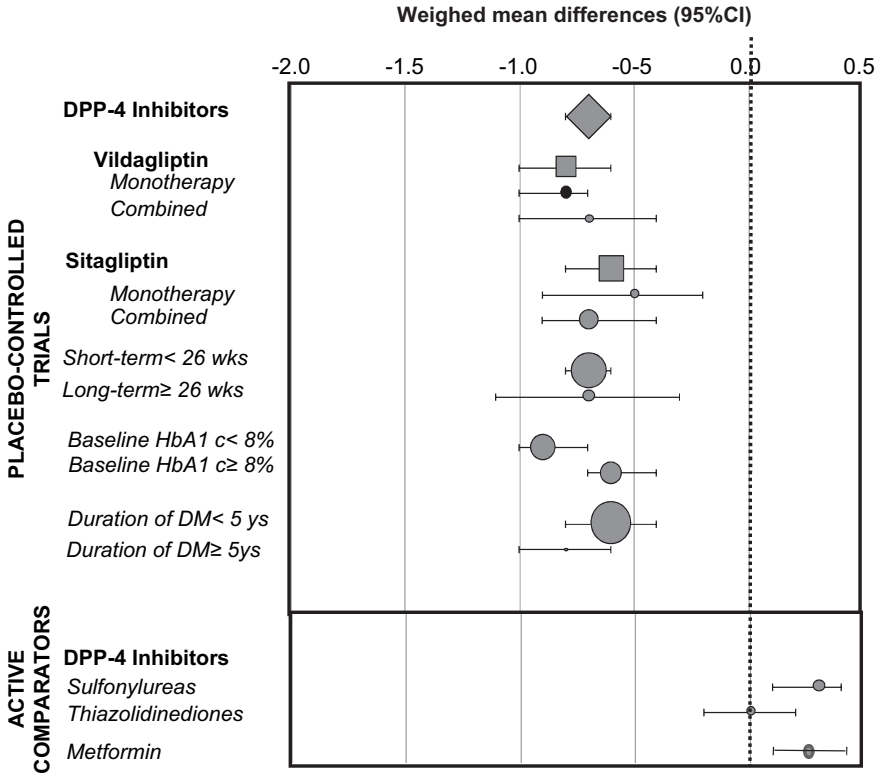

Figure 2 Standardized differences (with 95% CI) of mean HbA1c at endpoint.

information should always be attempted, although the possibility of including some information of poorer methodological quality should be taken into account. The overall amount of evidence from randomized clinical trials which can be retrieved using this comprehensive approach is relevant, and probably sufficient for a reliable assessment of the clinical profile of this new class.

The overall efficacy on HbA1c of DPP-4 inhibitors in placebo-controlled trials is similar to that reported in previous meta-analyses [1,6—8]. However, the greater number of available studies allowed separate analyses of trials in which DPP-4 inhibitors were used either as monotherapy or as an add-on to other agents. In fact, most currently available hypoglycemic treatments show a smaller additional effect on HbA1c when used as an add-on to metformin, in comparison with monotherapy trials [26]. Conversely, DPP-4 inhibitors produce a similar placebo-subtracted reduction of HbA1c either in monotherapy or as an add-on to other agents. This pattern resembles that of other drugs specifically active on post-prandial glucose, such as acarbose or glinides [26]. In fact, DPP-4 inhibitors, as well as GLP-1 receptor agonists, show a relevant effect on post-prandial hyperglycemia. Although data on post-prandial glucose measured through self-monitoring were not

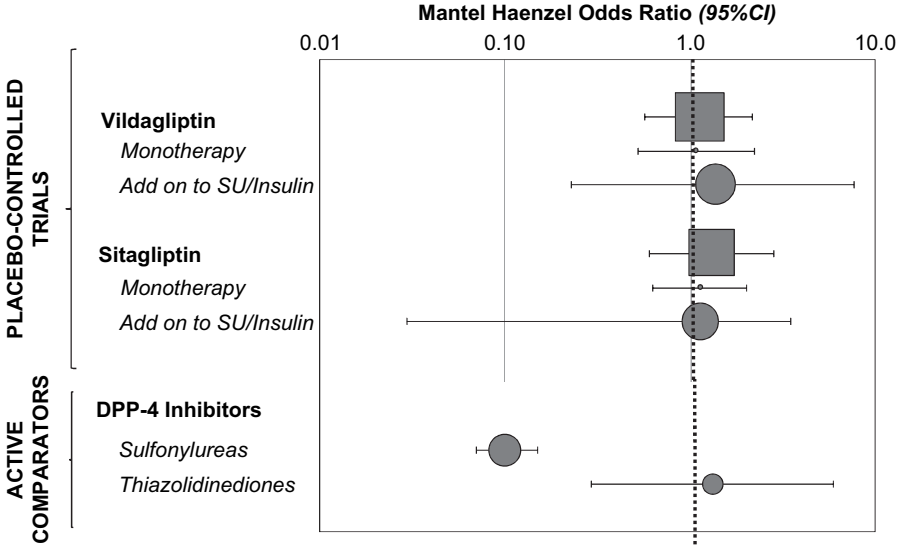

Figure 3 Mantel—Haenszel odds ratio (with 95% CI) for any hypoglycemia (logarithmic scale).

available, the results obtained in many trials with meal tests [7,27] support the hypothesis of a specific action of DPP-4 inhibitors on post-prandial hyperglycemia.

Based on the considerations reported above, DPP-4 inhibitors, when used in combination with other drugs, should not be expected to be less effective on HbA1c than other agents (such as sulphonylureas, thiazolidinediones or insulin). Unfortunately, only a small number of head-to-head comparisons with other drugs are currently available. The efficacy of DPP-4 inhibitors on HbA1c, either in monotherapy or in combination with metformin, appears to be somewhat smaller than that of sulphonylureas, and similar to thiazolidinediones; the only two available comparisons with metformin, both in monotherapy, one with vildagliptin [28] and one with sitagliptin (PN-036 on www.merck.com/mrl/clinical_trials/results.html) suggest a smaller effect on HbA1c. It should be considered that most trials are of a relatively short duration and it is possible that sulphonylureas, which are known to produce a less durable effect on glucose than other available agents, [29] could provide less favorable results in the long-term.

Taken together, the present results on efficacy do not support the use of DPP-4 inhibitors in monotherapy as an alternative to metformin. On the other hand, these drugs appear to be effective as add-on treatments in patients failing with metformin monotherapy, with a specific effect on post-prandial glucose, although the short-term efficacy of sulphonylureas on HbA1c could be greater than that of DPP-4 inhibitors.

With respect to body mass index, this meta-analysis confirms the neutrality of DPP-4 inhibitors [1,6—8]. In direct comparison, DPP-4 inhibitors appear to have an advantage in this respect over thiazolidinediones.

GLP-1 stimulates insulin secretion and inhibits glucagon production in a glucose-dependent manner, i.e. its effects are blunted when blood glucose reaches the lower limits of the normal range [30]. Therefore, DPP-4 inhibitors are expected to reduce glycemia with a low hypoglycemic risk. In fact, DPP-4 inhibitors do not induce any additional risk, in comparison with a placebo, either in monotherapy or in combination with sulphonylureas or insulin. This confirms the results of a recent meta-analysis performed on patient-level data from randomized clinical trials with sitagliptin [31]. Interestingly, in the only trial performed in insulin-treated patients, vildagliptin reduced the incidence of hypoglycemia in comparison with a placebo [20]. The mechanisms underlying this phenomenon need to be further elucidated. As expected, DPP-4 inhibitors do not increase the incidence of hypoglycemic episodes when compared with insulin-sensitizing drugs; on the other hand, they show a markedly reduced risk of hypoglycemia in head-to-head comparisons with sulphonylureas. This difference, which could be partly determined by a marginally greater efficacy of sulphonylureas on HbA1c, is consistent with the different mechanisms of action of the classes of drugs.

No patient experienced severe hypoglycemia during vildagliptin therapy. Unexpectedly, episodes of severe hypoglycemia occurred in five patients treated with sitagliptin, either in monotherapy or in combination with metformin, in three different trials [16—18]. Notably, two of those trials [16,18], although published, did not report those events but since those trials were included in the registration data for drug approval in the US, the information on severe hypoglycemia can be retrieved from the FDA website. Furthermore, episodes of severe hypoglycemia were not considered in a recent meta-analysis of trials with sitagliptin, although a greater number of such events had occurred in comparator groups, which included sulphonylureas [31]. It should also be considered that some of the trials did not report any information on severe hypoglycemia, raising the possibility of a selective reporting bias. The occurrence of cases of severe hypoglycemia with DPP-4 inhibitor monotherapy is difficult to explain on the basis of the current knowledge of the mechanism of action of those drugs, and deserved further investigation.

Among other expected adverse events, the previously reported increased incidence of some infections during DPP-4 inhibitor therapy [6,8] is confirmed, with sitagliptin, but not vildagliptin, associated with nasopharyngitis, and with a nonsignificant trend toward an increased risk of urinary tract infections. These results are consistent with those of a recent meta-analysis on patient-level data from trials with sitagliptin, which included only a fraction of the studies summarized in the present meta-analysis, and which showed a similar trend toward the increase of risk of nasopharyngitis with the DPP-4 inhibitor, although it failed to reach statistical significance [31]. It should be considered that DPP-4 is involved in the interaction between immune cells and that it could therefore modulate immune responses [32]; however, there is no evidence from mechanistic studies that inhibition of DPP-4 with currently available agents has an immunodepressant effect. Consistently, treatment with DPP-4 inhibitors does not appear to increase the risk of infections other than nasopharyngitis and urinary tract infections.

The introduction of a new class of drugs which are designed for long-term use always raises some concerns about safety during prolonged treatment. The possibility of rare, unexpected serious adverse events, which could not be detected in registration trials, should be considered. The number of reported deaths in available trials is still very small; however, there is no evidence suggesting an increase in mortality during treatment with DPP-4 inhibitors. The number of cardiovascular events registered in clinical trials is remarkably greater, although still inadequate to detect minor differences between groups. The two drugs which have been more thoroughly studied (sitagliptin and vildagliptin) do not seem to be associated with increased cardiovascular risk; in fact, the actual risk is lower than with comparators, although differences do not reach statistical significance. In fact, available data do not rule out the possibility of an increase of cardiovascular risk up to 28%, or of a reduction up to 54%. It should be considered that the duration of the available trials (up to one year) is insufficient to detect any effect of treatment (either detrimental or beneficial) on atherogenesis.

The addition of unpublished trials does not substantially modify the estimates of efficacy of DPP-4 inhibitors. However, the retrieval of unpublished, but publicly disclosed, information allowed the identification of some potentially interesting phenomena, such as cases of severe hypoglycemia with DPP-4 inhibitor monotherapy, which could not be detected in published papers.

Table 4 Adverse events in individual studies included in the meta-analysis.

Study (Ref.)	Any Hypos (*n*, ID/C)	Severe Hypos (*n*, D/C)	Nausea (*n*, D/C)	>Vomiting (*n*, D/C)	Diarrhea (*n*, D/C)	Nasopharyng. (*n*, D/C)	Urinary infect. (*n*, D/C)	CVD (*n*, D/C)	Death (*n*, D/C)	Any AEs (*n*, D/C)
DPP-4 inhibitors										
Vildagliptin										
Pan [33]	0/0	0/0	NR	NR	11/6	18/14	NR	3/1	0/0	154/113
Schweizer [28]	2/1	0/0	17/26	11/11	31/66	50/24	NR	0/2	2/2	364/190
Rosenstock [34]	1/0	0/0	NR	NR	NR	31,718	NR	NR	1/0	282/152
2329 [14]	NR	NR	NR	NR	NR	NR	NR	NR	1/0	89/25
Bolli [21]	1/0	0/0	NR	NR	1078	12/13	NR	2/2	0/0	177/158
Rosenstock [35]	1/0	0/0	NR	NR	NR	4/6	NR	NR	NR	78/83
	1/0	0/0	NR	NR	NR	8/6	NR	NR	NR	141/83
Dejager [36]	3/0	0/0	7/6	NR	11/5	40/13	NR	5/0	0/0	313/97
Scherbaum [37]	0/1	0/0	NR	NR	NR	4/3	NR	NR	0/1	28/28
Mari [38]	0/0	0/0	NR	NR	NR	16/13	NR	5/2	0/1	114/109
Scherbaum [39]	0/0	0/0	NR	NR	NR	16/13	NR	NR	0/1	114/109
Pratley [27]	1/0	0/0	1/1	NR	NR	NR	NR	0/0	0/0	39/20
Pi-Sunyer [40]	0/0	0/0	NR	NR	NR	1973	NR	NR	0/0	150/53
Ristic [41]	14/3	NR	5/3	NR	5/3	15/5	NR	0/1	0/0	126/33
1202 [14]	NR	NR	NR	NR	NR	41/18	NR	0/1	0/0	136/53
Ahren [42]	2/0	0/0	0/0	NR	NR	2/6	1/3	0/0	0/0	29/28
Bosi [22]	1/1	0/0	13/9	NR	11/10	31/13	1/0	4/4	0/0	231/115
Garber [43]	2/3	0/0	10/4	NR	NR	NR	11/2	1/1	0/0	160/77
Garber [19]	8/1	0/1	9/6	3/6	9/8	18/4	NR	NR	0/0	226/113
1302 [14]	NR	NR	NR	NR	NR	14/14	NR	0/0	0/0	61/57
Fonseca [20]	33/45	0/4	8/4	NR	8/3	NR	NR	0/1	1/1	117/133
1303 [14]	NR	NR	NR	NR	7/0	42/20	NR	0/0	0/0	108/41
D'Alessio [44]	0/0	0/0	NR	NR	NR	NR	NR	NR	NR	NR
Sitagliptin										
PN-036 [15]	NR	NR	0/2	1/0	2/4	NR	NR	NR	0/0	96/214
Scott [45]	1/1	0/0	1/1	1/1	3/3	4/3	NR	1/0	0/0	37/38
	1/2	0/0	1/2	1/1	3/1	4/3	NR	1/0	0/0	37/28
PN-035 [15]	NR	NR	NR	NR	NR	NR	NR	NR	2/2	NR
Nauck [17]	29/187	1/7	15/16	5/9	34/32	60/42	31/15	0/3	1/2	419/444
PN-028 [15]	NR	NR	NR	NR	6/5	NR	3/2	5/0	3/0	NR
Scott [18]	12/21	3/1	NR	NR	NR	NR	NR	4/2	3/1	284/77
	12/3	3/0	NR	NR	NR	NR	NR	4/0	3/0	284/67
Nonaka [46]	0/0	0/0	NR	NR	NR	NR	NR	0/1	0/0	44/49
Hanefeld [16]	5/0	1/0	NR	NR	NR	33/2	NR	3/0	0/0	201/38
Raz [47]	5/0	0/0	5/0	1/1	11/6	13/0	10/3	3/0	0/0	194/57
Goldstein [23]	1/1	NR	2/2	0/1	5/7	NR	NR	NR	0/1	96/89
Rosenstock [35]	2/0	0/0	2/0	1/1	3/2	NR	NR	0/0	0/0	84/93
Hermansen [24]	27/4	0/0	1/1	3/1	3/6	NR	NR	NR	1/0	132/103
Goldstein [23]	6/3	NR	22/24	11/6	40/35	NR	NR	NR	1/0	225/214
Charbonnel [48]	6/5	0/0	6/2	5/2	12/6	19/8	11/3	2/0	1/0	262/128
Aschner [49]	5/2	0/0	15/3	5/3	21/6	32/12	13/7	3/3	0/0	317/167
Raz [50]	1/0	0/0	2/2	0/1	6/5	7/7	4/3	0/1	0/1	55/56
PN-040 [15]	NR	NR	NR	NR	NR	NR	NR	NR	1/0	82/27
PN-044 [15]	NR	NR	NR	NR	NR	NR	NR	NR	0/0	NR
Saxagliptin										
Rosenstock [51]	0/0	0/0	12/5	NR	NR	16/5	19/5	NR	0/0	215/53

Hypos: hypoglycemia; *n*: number; ID/C: investigational drug/comparator; nasopharyng.: nasopharyngitis; infect.: infections; CVD: cardiovascular disease; and NR: not reported.

The limitations of the present meta-analysis should be recognized and considered when interpreting the results. The analysis was performed on summary data, therefore lacking the accuracy of assessment which can be obtained when using patient-level data. For the very same reason, a time-to-event analysis for categorial outcomes (including cardiovascular events) could not be performed; the proportion of patients experiencing at least one event during the trial, which was used for meta-analysis, approximates the actual incidence of events only if this

Table 5 Selected adverse events during treatment with DPP-4 inhibitors.

Adverse event	# Cases/# Patients		# Trials[a]	MH-OR [95% CI]	*p*
	ID	C			
Nausea					
DPP-4 Inhibitors	153/5795	119/3906	21	0.77 [0.57; 1.04]	0.09
Vildagliptin	70/2102	59/1014	8	0.63 [0.38; 1.07]	0.08
Sitagliptin	71/3689	55/2892	12	1.03 [0.71; 1.51]	0.86
Saxagliptin	12/271	5/67	1	–	–
Vomiting					
DPP-4 Inhibitors	47/4575	44/3119	14	0.73 [0.48; 1.12]	0.15
Vildagliptin	14/810	17/417	2	0.40 [0.19; 0.83]	0.014
Sitagliptin	33/3765	27/2702	12	1.02 [0.61; 1.69]	0.93
Saxagliptin	–	–	–	–	–
Diarrhea					
DPP-4 Inhibitors	249/6318	227	22	0.80 [0.56; 1.15]	0.23
Vildagliptin	103/2909	109/478	13	0.72 [0.74; 1.20]	0.34
Sitagliptin	146/3409	118/2641	9	0.98 [0.76; 1.26]	0.87
Saxagliptin	–	–	–	–	–
Nasopharyngitis					
DPP-4 Inhibitors	566/7589	282/4132	27	1.04 [0.60; 1.68]	0.59
Vildagliptin	373/4688	200/2442	18	0.93 [0.77; 1.12]	0.42
Sitagliptin	168/2901	77/1690	8	1.43 [1.07; 1.91]	0.017
Saxagliptin	16/271	5/67	1	–	–
Urinary infections					
DPP-4 Inhibitors	104/2938	43/1904	10	1.36 [0.94; 1.97]	0.10
Vildagliptin	13/685	5/379	3	1.30 [0.30; 5.71]	0.73
Sitagliptin	72/2253	33/1525	6	1.44 [0.94; 2.19]	0.09
Saxagliptin	19/271	5/67	1	–	–
Upper respiratory infections					
DPP-4 Inhibitors	302/4902	173/3229	18	0.91 [0.74; 1.12]	0.40
Vildagliptin	150/2885	96/1475	11	0.82 [0.62; 1.10]	0.18
Sitagliptin	131/2017	73/1754	6	0.99 [0.74; 2.32]	0.96
Saxagliptin	21/271	4/67	1	–	–
Other infections					
DPP-4 Inhibitors	178/3059	118/1538	13	0.70 [0.55; 0.90]	0.005
Vildagliptin	110/1618	63/944	8	0.68 [0.47; 0.99]	0.042
Sitagliptin	62/1441	55/594	5	0.72 [0.52; 1.01]	0.056
Saxagliptin	–	–	–	–	–

ID: interventional drug; and C: comparator.
[a] Trials with 0 events or without any information are not included.

incidence is assumed to be constant throughout the duration of the trial. Furthermore, the number of subject studies and the duration of trials performed is insufficient to draw any definitive conclusion on the long-term cardiovascular safety of DPP-4 inhibitors.

In conclusion, DPP-4 inhibitors are effective in reducing HbA1c and post-prandial glucose; when used as an add-on to metformin, they show a medium-term efficacy on HbA1c similar to thiazolidinediones and marginally inferior to sulphonylureas, with a reassuring short- and medium-term safety profile. In fact, the hypoglycemic risk is low, and there is no evidence of detrimental effects on cardiovascular disease. In comparison with sulphonylureas or insulin, which have been proposed as first-choice agents in patients failing with metformin [4], DPP-4 inhibitors exhibit, at least in the short- and medium-term, a lower hypoglycemic risk and a more favorable action on body weight, at the price of a somewhat smaller efficacy and higher cost. The choice of the drugs to be used as add-ons to metformin in monotherapy failure largely depends on the relative weight attributed to each of these three components (safety, efficacy on HbA1c and cost).

Conflict of interest

Authors did not receive any compensation for their contribution. All authors have seen and approved the final version.

Dr. Edoardo Mannucci1 (MD) has the following conflicts of interest:

1) Speaking fees from Abiogen Pharma, Glaxo-Smith—Kline, Guidotti, Eli Lilly, Menarini, Merck Sharp & Dome

(manufacturer of sitagliptin), Merck KgA, Novo Nordisk, Novartis (manufacturer of vildagliptin), Sanofi Aventis, and Takeda.
2) Consultancy fees from Novartis (manufacturer of vildagliptin), Novo Nordisk, and Sanofi Aventis.
3) Research grants from Novartis (manufacturer of vildagliptin), Novo Nordisk, Sanofi Aventis, and Takeda.

Dr. Mannucci had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dr. Matteo Monami1 (MD, PhD) has the following conflicts of interest:

1) Speaking fees from Guidotti, Eli Lilly, Merck Sharpe & Dome (manufacturer of sitagliptin), Menarini, and Takeda.
2) Consultancy fees from Sanofi Aventis and Menarini.

Prof. Niccolò Marchionni1 (MD) has the following conflicts of interest:

1) Speaking fees from Glaxo-Smith and Kline, Guidotti, and Menarini.
2) Research grants from Novartis (manufacturer of vildagliptin), Novo Nordisk, Sanofi Aventis, and Takeda.

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