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RESEARCH ARTICLE

Predictors of response to dipeptidyl peptidase-4 inhibitors: evidence from randomized clinical trials

Matteo Monami[1]
Francesco Cremasco[2]
Caterina Lamanna[2]
Niccolò Marchionni[2]
Edoardo Mannucci[2]*

[1]*Diabetes Agency, University of Florence and Careggi Teaching Hospital, Florence, Italy*

[2]*Section of Geriatric Cardiology and Medicine, Department of Cardiovascular Medicine, University of Florence and Careggi Teaching Hospital, Florence, Italy*

*Correspondence to:
Edoardo Mannucci,
Section of Geriatric Cardiology and Medicine,
Department of Cardiovascular Medicine,
University of Florence and Careggi Teaching Hospital,
Viale Pieraccini 18,
50139 Florence, Italy
E-mail:
edoardo.mannucci@unifi.it;
mmonami@libero.it

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Abstract

Aim Dipeptidyl peptidase-4 (DPP-4) inhibitors are used in the treatment of type 2 diabetes. Available sub-group analysis of clinical trials does not allow a clear identification of predictors of therapeutic response to these drugs. The aim of this study is the assessment of predictors of response to DPP-4 inhibitors.

Materials and methods A meta-analysis was performed, exploring correlation between 24-week effects on HbA_{1c} of maximal doses of DPP-4 inhibitors, compared either with placebo or with other active drugs, matches to baseline characteristics of patients enrolled in 63 randomized clinical trials, either published or unpublished but disclosed on different websites were studied.

Results DPP-4 inhibitors significantly reduce HbA_{1c} at 24 weeks [by 0.6 (0.5–0.7)%] when compared with placebo; no difference in HbA_{1c} was observed in comparisons with thiazolidinediones and α-glucosidase inhibitors, whereas sulfonylureas and metformin produced a greater reduction of HbA_{1c}, at least in the short term. DPP-4 inhibitors produced a smaller weight gain than thiazolidinediones, and showed a lower hypoglycaemia risk than sulfonylureas. The placebo-subtracted effect of DPP-4 inhibitors on HbA_{1c} was greater in older patients and in those with lower fasting plasma glucose at baseline. Similar results were obtained in comparisons with thiazolidinediones and metformin.

Conclusions Although drugs for type 2 diabetes are studied in heterogeneous samples of patients, their efficacy can be predicted by some clinical parameters. DPP-4 inhibitors appear to be more effective in older patients with mild/moderate fasting hyperglycaemia. These data could be useful for a better definition of the profile of patients who are likely to benefit most from these drugs. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords DPP-4 inhibitor; meta-analysis; type 2 diabetes

Introduction

The number of available drugs for the treatment of type 2 diabetes has substantially increased over the last decade; at present, it includes metformin, sulfonylureas, glinides, insulin, thiazolidinediones, α-glucosidase inhibitors, glucagon-like peptide-1 receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors. Further classes of drugs (e.g. SLGT-2 inhibitors) are bound to be available in the near future. Treatment guidelines issued by Scientific Societies and other authorities all agree on the need for an accurate control of blood glucose for the prevention of long-term complications of diabetes; however, algorithms and recommendations for pharmacological treatment of

hyperglycaemia in type 2 diabetic patients differ from one guideline to another [1–5]. Most experts agree that metformin should be considered the first-line drug, unless contraindicated, whereas the choice of the agent to be combined with metformin in case of monotherapy failure is controversial. In fact, in randomized clinical trials (RCTs), different classes of drugs show a similar efficacy on medium-term HbA_{1c} when combined with metformin [6].

If two drugs have the same mean effect on HbA_{1c} in a comparative trial, this does not exclude the possibility that specific sub-populations of patients are more responsive to either one or the other agent. In clinical practice, most physicians use a variety of hypoglycaemic drugs, empirically selecting for each patient the pharmacological approach which, in their opinion, is likely to yield the greatest benefits. In other words, clinicians identify different patient profiles to predict responses to different treatments. This process is based on pathophysiological considerations, mechanistic reasoning, and personal experience, but it is not supported by evidence. In fact, a large majority of RCTs includes a rather wide population of patients; furthermore, pre-specified or *post hoc* analyses on sub-groups of patients, identified by specific clinical characteristics, are seldom available.

A possible alternative approach to the identification of predictors of treatment response is represented by meta-regression. This analysis, which includes results of RCTs, can be used to explore the correlation between efficacy and baseline clinical features of patients enrolled, thus providing information on characteristics associated with a greater therapeutic response. The aim of this study is the assessment of predictors of response to DPP-4 inhibitors.

Methods

A meta-analysis was performed including all RCTs with a duration of at least 21 weeks, either with a cross-over or with a parallel series design, enrolling patients with type 2 diabetes, comparing DPP-4 inhibitors with placebo or active drugs (oral hypoglycaemic agents and/or insulin) different from other DPP-4 inhibitors. Trials with a shorter duration were excluded, due to the fact that they could not yield relevant information on glycated haemoglobin, which had been chosen as the principal outcome variable. Trials enrolling non-diabetic, or type 1 diabetic, subjects were also excluded. Only trials with maximal doses of DPP-4 inhibitors were included (sitagliptin and vildagliptin $\geq$100 mg/day, saxagliptin $\geq$0.5 mg/day, alogliptin $\geq$25 mg/day, and linagliptin $\geq$5 mg/day); when multiple doses were tested, only groups receiving a daily dose exceeding the thresholds specified above were considered.

An extensive Medline and Embase search for 'vildagliptin', 'sitagliptin', 'saxagliptin', 'alogliptin', and 'linagliptin' was performed, collecting all RCTs on humans

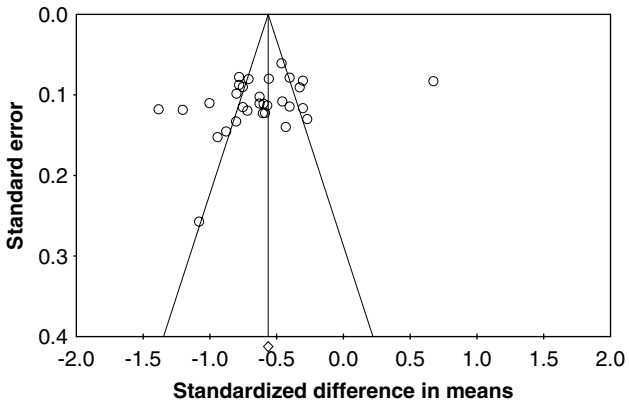

Figure 1. Funnel plot of standard error by standardized difference in means (HbA_{1c} at 24 weeks)

up to 1st November, 2009. 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. and 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*. [7]. 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. The results of those trials were retrieved, if available, on www.clinicaltrials.gov, www.merck.com/mrl/clinical_trials/results.html, www.novartisclinicaltrials.com, or www.clinicalstudyresults.org; Food and Drug Administration (www.fda.gov) and European Medicines Agency (www.ema.europa.eu) reviews of approved drugs were also searched for retrieval of unpublished trials. These sources were also used for complete information on results of published trials, when not reported in publications. For all published trials, results reported in papers were used as the primary source of information, when available.

The principal outcome was the effect of DPP-4 inhibitors, compared with other hypoglycaemic agents or placebo, on HbA_{1c} at 21–30 weeks. For trials with longer duration, HbA_{1c} at 21–30 weeks was considered, in order to avoid the possible interference of duration of treatment. Secondary outcomes included body mass index (BMI) at the end of the trial. Furthermore, data on the incidence of any hypoglycaemia (number of patients with at least one event) and severe adverse events were extracted. Furthermore, cases of cardiovascular events (defined as myocardial infarction, angina pectoris, coronary artery revascularization, chronic heart failure, stroke, and arteriopathy of lower limbs) reported as severe adverse events were considered, together with death by any cause. Microvascular complications of diabetes were not considered, because of the relatively short duration of the trials included in the meta-analysis.

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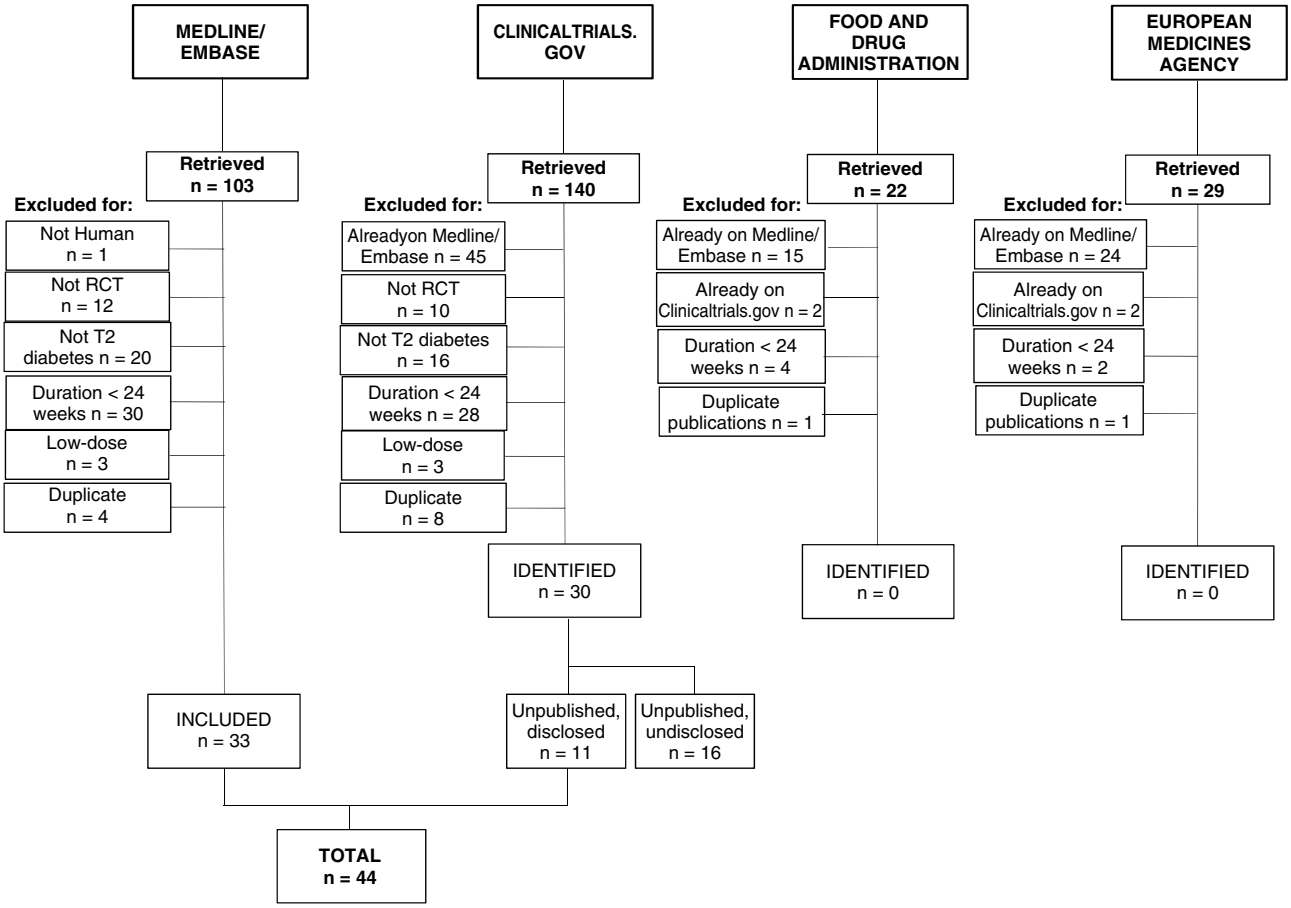

Figure 2. Trial flow diagram. RCT, randomized clinical trial; T2, type 2

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 random-effect and fixed-effect models. We report the results of the random-effect models because the validity of tests of heterogeneity can be limited with a small number of component studies. To estimate possible publication/disclosure bias caused by the tendency of published studies to be positive, we used funnel plots (Figure 1), the Begg adjusted rank correlation test [8,9], including published and unpublished, but disclosed, trials. However, because these tests have low statistical power when the number of trials is small [10], undetected bias may still be present. Standardized mean differences were calculated for HbA_{1c} and BMI, whereas Mantel–Haenszel odds ratio (MH-OR) with 95% confidence interval was calculated for hypoglycaemia, and the adverse events defined above, on an intention-to-treat basis, excluding trials with zero events. A meta-regression was performed to assess the effect of putative moderators on the reduction (*versus* placebo or comparators) of HbA_{1c} at 21–30 weeks. Moderators considered included HbA_{1c}, mean age, duration of diabetes, BMI, and fasting plasma glucose (FPG); the FPG:HbA_{1c} ratio was also considered among moderators, as a proxy measure of post-prandial hyperglycaemia. 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 Figure 2. A total of 33 studies were retrieved through Medline/Embase; further 30 trials were identified through the www.clinicaltrials.gov register. For 11 of 30 unpublished trials, some information could be retrieved from different websites. The European Medicines Agency and Food and Drug Administration reviews did not allow the identification of any further study, although they were useful for the retrieval of some information (particularly on adverse events), which was not reported in publications of some trials. The remaining 15 unpublished trials, planning to enrol 10 889 patients (5863 patient × years), were not disclosed and therefore excluded from the analysis (Table S1, Supporting Information). The meta-analysis included 44 trials; 33 and 15 of those were placebo controlled and active comparator controlled, respectively, whereas two trials included both placebo and active comparator arms. The characteristics of those trials are summarized in Table S2 (see Supporting Information) and Tables 1 and 2.

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Table 1. Moderators in individual studies included in the meta-analysis

Study (Ref.)	Number of patients (ID/C)	Trial duration (weeks)	Age (years)	Age range (years)	Duration of DM (years)
		Vildagliptin *versus* Placebo			
Garber [11]	132/144	24	58	18–80	7
Garber [12]	138/138	24	54	18–80	5
Fonseca [13]	144/152	24	59	18–80	15
Rosenstock [14]	148/161	24	51	18–80	2
Pi-Sunyer [15]	174/92	24	51	18–80	2
Bosi [16]	185/182	24	54	18–78	6
Goodman [17]	248/122	24	55	18–78	NR
CLAF237ADE0214	268/127	24	61	18–85	NR
Dejager [18]	293/149	24	53	18–80	2
Bosi [19]	295/294	24	52	18–78	2
		Vildagliptin *versus* Metformin			
Schweizer [20]	169/166	24	71	18–75	3
Bosi [19][a]	300/294	24	52	18–78	2
CLAF237A23104	456/458	24	57	NR	5
Schweizer [21]	526/254	52	52	18–78	1
		Vildagliptin *versus* Pioglitazone			
Rosenstock [14][a]	154/161	24	51	18–80	2
Bolli [22]	295/281	24	57	18–77	6
		Vildagliptin *versus* Rosiglitazone			
Rosenstock [23]	459/238	24	54	18–80	2
		Vildagliptin *versus* α-Glucosidase inhibitors			
CLAF237A1301	188/192	12	60	>20	5
Pan [24]	441/220	24	52	≥18	1
		Vildagliptin *versus* Glimepiride			
Ferrannini [25]	1396/1393	52	57	18–73	6
		Sitagliptin *versus* Placebo			
PN-047	102/104	24	72	>65	NR
Rosenstock [26]	163/174	24	56	≥18	6
Hermansen [27]	222/219	24	56	18–75	8
Charbonnel [28]	226/454	24	54	18–78	6
PN-064	261/259	24	51	≥18	NR
PN-051	322/319	24	58	≥21	NR
Aschner [29]	468/247	24	54	18–75	4
Goldstein [30]	551/540	24	53	18–78	4
Raz [31]	96/94	30	55	18–78	8
Chan [32]	65/26	12	67	≥18	13
PN-052	170/92	54	54	18–78	NR
		Sitagliptin *versus* Metformin			
Goldstein [30][a]	175/355	24	54	18–78	4
PN-049	528/522	24	56	18–78	NR
		Sitagliptin *versus* Glipizide			
Chan [32][a]	65/26	52	67	≥18	13
Nauck [33]	576/559	52	57	18–78	6
		Saxagliptin *versus* Placebo			
CV181_038	291/74	24	55	18–77	NR
Rosenstock [34]	306/95	24	53	21–70	2
Jadzinsky [35]	323/328	24	52	18–77	2
CV181_013	375/180	24	54	18–77	5
Chacra [36]	501/267	24	55	18–77	7
DeFronzo [37]	565/179	24	54	18–77	6
		Saxagliptin *versus* Metformin			
Jadzinsy [35][a]	325/328	24	52	18–77	2
		Alogliptin *versus* Placebo			
Rosenstock [38]	260/130	26	55	18–80	12
DeFronzo [39]	264/64	26	53	18–80	NR
Pratley [40]	397/97	26	55	18–80	8
Pratley [41]	401/99	26	57	18–80	8
Nauck [42]	420/104	26	55	18–80	6

NR, not reported.
[a]Studies with multiple comparators.

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Table 2. Outcome variables in individual studies included in the meta-analysis

Study (Ref.)	Number of patients (ID/C)	HbA_{1c}/Fasting plasma glucose baseline (%/mmol/L)	HbA_{1c} 12 weeks (%; ID/C)	HbA_{1c} 24 weeks (%; ID/C)	HbA_{1c} range (%)	Body mass index baseline (kg/m^2; ID/C)	Body mass index 24 weeks (kg/m^2; ID/C)	Body mass index range (kg/m^2)
Vildagliptin *versus* Placebo								
Garber [11]	132/144	8.5/10.4	8.0/8.5	8.0/8.6	7.5–11.0	30.9	31.1/30.9	22.0–45.0
Garber [12]	138/138	8.7/10.0	7.7/8.5	7.7/8.4	7.5–11.0	32.2	NR	22.0–45.0
Fonseca [13]	144/152	8.4/9.0	7.8/8.4	7.9/8.2	7.5–11.0	33.1	33.8/33.1	22.0–45.0
Rosenstock [14]	148/161	8.7/10.6	7.1/7.5	6.9/7.3	7.5–11.0	29.2	30.3/29.4	22.0–45.0
Pi-Sunyer [15]	174/92	8.4/10.6	7.6/8.4	7.6/8.4	7.5–10.0	32.2	31.9/32.2	22.0–45.0
Bosi [16]	185/182	8.3/9.9	7.4/8.3	7.4/8.4	7.5–11.0	33.0	33.0/31.7	22.0–45.0
Goodman [17]	248/122	8.6/10.9	7.8/8.8	7.7/8.9	7.5–11.0	31.5	NR	22.0–40.0
CLAF237ADE0214	268/127	7.2/6.8	NR	6.8/7.4	6.5–8.0	NR	NR	NR
Dejager [18]	293/149	8.4/10.0	NR	7.6/8.1	7.5–10.0	32.8	32.0/32.3	22.0–45.0
Bosi [19]	295/294	8.6/10.5	7.0/7.5	6.9/7.2	7.5–11.0	31.3	31.0/30.7	22.0–40.0
Vildagliptin *versus* Metformin								
Schweizer [20]	169/166	7.7/9.2	7.8/7.5	7.1/7.0	NR	29.6	29.6/29.0	22.0–45.0
Bosi [19][a]	300/294	8.6/10.5	7.8/7.5	7.8/7.2	7.5–11.0	31.3	31.1/30.7	22.0–40.0
CLAF237A23104	456/458	7.3/8.6	NR	6.8/6.9	NR	31.1	30.9/30.7	22.0–45.0
Schweizer [21]	526/254	8.7/10.5	7.6/7.4	7.5/7.3	7.5–11.0	32.4	NR	NR
Vildagliptin *versus* Pioglitazone								
Rosenstock [14][a]	154/161	8.7/10.6	7.6/7.5	6.9/7.5	7.5–11.0	29.2	29.4/29.4	22.0–45.0
Bolli [22]	295/281	8.4/10.9	7.5/7.7	7.5/7.4	7.5–11.0	32.1	32.3/32.7	22.0–45.0
Vildagliptin *versus* Rosiglitazone								
Rosenstock [23]	459/238	8.7/10.3	7.7/7.7	7.6/7.4	7.5–11.0	32.5	32.3/33.4	22.0–45.0
Vildagliptin *versus* α-Glucosidase inhibitors								
CLAF237A1301	188/192	7.5/9.0	6.6/7.2	–	NR	NR	–	NR
Pan [24]	441/220	8.6/10.1	7.4/7.5	7.2/7.3	7.5–11.0	26.1	26.3/25.2	20.0–40.0
Vildagliptin *versus* Glimepiride								
Ferrannini [25]	1396/1393	7.3/9.2	6.8/6.6	6.8/6.6	6.5–8.5	31.7	NR	22.0–45.0
Sitagliptin *versus* Placebo								
PN-047	102/104	7.8/NR	NR	7.3/8.0	7.0–10.0	NR	NR	NR
Rosenstock [26]	163/174	8.0/9.2	7.3/7.9	7.2/7.8	7.0–10.0	31.5	32.6/31.6	NR
Hermansen [27]	222/219	8.3/10.0	7.7/8.6	7.9/8.5	7.5–10.5	30.9	31.5/30.5	NR
Charbonnel [28]	226/454	8.0/9.5	7.4/8.0	8.0/7.0	7.0–10.0	31.3	NR	NR
PN-064	261/259	9.5/NR	NR	7.1/8.0	8.0–12.0	NR	NR	NR
PN-051	322/319	8.7/NR	NR	8.1/8.6	7.5–11.0	NR	NR	NR
Aschner [29]	468/247	8.0/9.6	7.4/8.2	7.3/8.2	7.0–10.0	30.5	NR	NR
Goldstein [30]	551/540	8.8/11.0	7.7/8.2	7.5/8.0	7.5–11.0	32.0	NR	NR
Raz [31]	96/94	9.2/11.0	8.3/9.1	8.3/9.0	7.0–10.0	30.2	30.4/30.3	20.0–42.0
Chan [32]	65/26	7.7/8.7	7.0/7.6	–	6.5–10.0	26.7	–	NR
PN-052	170/92	7.8/8.5	NR	NR	7.5–11.0	NR	NR	NR

Table 2. *continued*

Study (Ref.)	Number of patients (ID/C)	HbA_{1c}/Fasting plasma glucose baseline (%/mmol/L)	HbA_{1c} 12 weeks (%; ID/C)	HbA_{1c} 24 weeks (%; ID/C)	HbA_{1c} range (%)	Body mass index baseline (kg/m^2; ID/C)	Body mass index 24 weeks (kg/m^2; ID/C)	Body mass index range (kg/m^2)
Sitagliptin *versus* Metformin								
Goldstein [30][a]	175/355	8.8/11.0	8.3/7.9	8.2/7.8	7.5–11.0	32.0	NR	NR
PN-049	528/522	7.3/NR	NR	6.8/6.7	6.5–9.0	NR	NR	NR
Sitagliptin *versus* Glipizide								
Chan [32][a]	65/26	7.7/8.7	NR	NR	6.5–10.0	26.7	NR	NR
Nauck [33]	576/559	7.6/9.1	6.7/6.6	6.6/6.6	6.5–10	31.2	30.6/31.8	–
Saxagliptin *versus* Placebo								
CV181_038	291/74	8.0/NR	7.3/7.6	7.3/7.6	NR	NR	NR	NR
Rosenstock [34]	306/95	7.9/9.7	NR	7.7/7.7	6.8–9.7	31.7	NR	≤37.0
Jadzinsky [35]	323/328	9.5/11.0	7.3/7.8	7.0/7.5	8.0–12.0	30.2	29.8/29.6	≤40.0
CV181_013	375/180	8.2/9.6	7.6/8.0	7.5/7.9	7.0–10.5	30.0	NR	≤45.0
Chacra [36]	501/267	8.4/9.5	7.7/8.4	7.8/8.5	7.5–10.0	29.0	29.4/29.0	≤40.0
DeFronzo [37]	565/179	8.1/9.9	7.5/8.2	7.5/8.2	7.0–10.0	31.4	NR	≤40.0
Saxagliptin *versus* Metformin								
Jadzinsy [35][a]	325/328	9.5/11.0	7.977.6	7.9/7.5	8.0–12.0	30.2	29.9/29.6	≤40.0
Alogliptin *versus* Placebo								
Rosenstock [38]	260/130	9.3/11.0	8.5/9.0	8.6/9.1	>8.0	32.5	32.6/32.5	23.0–45.0
DeFronzo [39]	264/64	7.9/NR	NR	7.3/7.9	7.0–10.0	NR	NR	23.0–45.0
Pratley [40]	397/97	8.0/NR	NR	7.3/7.9	7.0–10.0	32.8	NR	23.0–45.0
Pratley [41]	401/99	8.1/NR	NR	7.6/8.1	7.0–10.0	30.0	NR	23.0–45.0
Nauck [42]	420/104	7.9/9.6	7.3/7.8	7.4/7.9	7.0–10.0	NR	NR	23.0–45.0

NR, not reported.
[a]Studies with multiple comparators.

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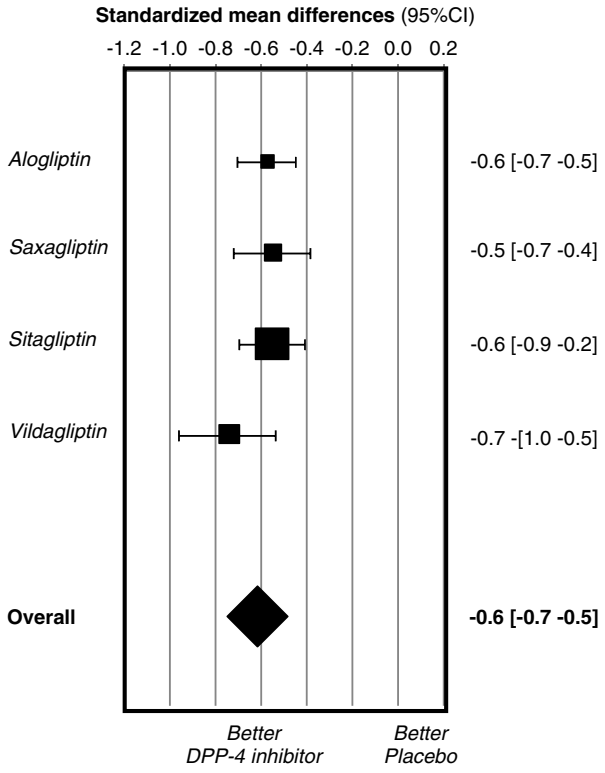

Figure 3. Standardized differences (with 95% confidence interval) of mean HbA_{1c} at 24 weeks in placebo-controlled trials (all $p < 0.001$)

The 33 available placebo-controlled trials enrolled 8774 and 5709 patients in active treatment and control groups, respectively. The Begg adjusted rank correlation test (Kendall tau −0.14; $p = 0.27$), calculated on the basis of 21–30-week HbA_{1c} in placebo-controlled trials, suggested no major publication bias. I^2 test for heterogeneity was 62.5%, suggesting the use of a random-effect model. DPP-4 inhibitors produced a significant reduction of HbA_{1c} in comparison with placebo at 21–30 weeks (Figure 3), when used as monotherapy as well as when added to other glucose-lowering agents [−0.7 (−0.9; −0.6) and −0.7 (−0.8; −0.6), respectively]. In the 14 trials with available data, DPP-4 inhibitors produced a significant increase of BMI at 21–30 weeks [0.10 (0.05; 0.15) kg/m^2; $p < 0.001$]. The overall risk of hypoglycaemia (in the 21 trials with reported events) was greater with DPP-4 inhibitors than with placebo [MH-OR 1.44 (1.09–1.98); $p = 0.024$]; however, this difference was entirely due to the trials in which the drug was used as add-on treatment to insulin and/on sulfonylureas [MH-OR 2.17 (1.05; 4.49); $p = 0.04$]. Conversely, no increased risk of hypoglycaemia was observed when DPP-4 inhibitors were used as monotherapy or added to insulin sensitizers [MH-OR 1.05 (0.74; 1.51); $p = 0.77$]. The risk of serious adverse events was similar to that observed with placebo (data not shown). No significant risk of major cardiovascular events or death was observed in comparison with controls [MH-OR 1.04 (0.70; 1.55), $p = 0.84$ and 0.89 (0.36; 1.99), $p = 0.64$; 17 and 9 trials with at least one major cardiovascular event and death, respectively].

In the 15 available active comparator studies, which enrolled 6053 and 5447 patients in DPP-4 inhibitor and comparator groups, respectively, the effect of DPP-4 inhibitors on HbA_{1c} at 21–30 weeks was inferior to that of metformin, while no statistically significant differences were observed in comparison with sulfonylureas, thiazolidinediones, and α-glucosidase inhibitors. In active comparator studies, 21–30-week treatment with DPP-4 inhibitors was associated with a significantly lower BMI in comparison with thiazolidinediones [−0.10 (−0.21; −0.01) kg/m^2; $p = 0.049$], whereas no significant difference was observed with respect to metformin [0.05 (−0.02; 0.13) kg/m^2; $p = 0.18$]. DPP-4 inhibitors were associated with a lower risk of hypoglycaemia than sulfonylureas [MH-OR 0.10 (0.07–0.13), $p < 0.01$; $n = 3$ trials], whereas no significant difference was observed in comparisons with metformin [MH-OR 0.71 (0.24–2.09), $p = 0.53$; $n = 6$ trials] or thiazolidinediones [MH-OR 1.32 (0.30; 5.83), $p = 0.71$; $n = 4$ trials]. In direct comparisons, the proportion of patients experiencing at least one serious adverse event was significantly lower with DPP-4 inhibitors than with sulfonylureas [MH-OR 0.78 (0.63; 0.98), $p = 0.03$; $n = 4$ trials with events]; no significant difference was observed in comparisons with metformin, α-glucosidase inhibitors, and thiazolidinediones [MH-OR 1.01 (0.64; 1.60), 0.58 (0.04; 8.83), and 0.68 (0.38; 1.22), respectively; all $p > 0.20$]. In the eight active comparator trials in which information on cardiovascular events was available, and at least one event was observed, 29 and 45 events were recorded in DPP-4 inhibitors and comparator groups, respectively [MH-OR 0.66 (0.41; 1.06); $p = 0.09$]; a significant difference was observed in the two trials comparing DPP-4 inhibitors with sulfonylureas [MH-OR 0.50 (0.25; 0.99); $p = 0.05$], but not in the five metformin-controlled studies [MH-OR 0.95 (0.46; 1.96); $p = 0.88$]. Only 24 deaths (14 and 10 in the DPP-4 inhibitor and active comparator groups, respectively) were observed in the 13 trials reporting this information (seven of which with events); the limited number of events prevented any further analysis on this endpoint.

Meta-regression analysis on placebo-controlled trials showed that DPP-4 inhibitors have a greater efficacy on HbA_{1c} in older patients, whereas mean values of baseline HbA_{1c}, FPG, and FPG:HbA_{1c} ratio were all associated with a smaller effect of DPP-4 treatment on HbA_{1c}, in comparison with placebo (Figure 4). In comparisons with metformin, DPP-4 inhibitors showed a greater efficacy in trials enrolling older patients [slope −0.017 (−0.029; −0.005), $p = 0.006$; intercept 1.145 (0.463; 1.827), $p = 0.001$] and with lower HbA_{1c}, FPG, and FPG:HbA_{1c} ratio (data not shown).

Discussion

DPP-4 inhibitors, when compared with placebo, reduce HbA_{1c} in a relevant manner, either in monotherapy or

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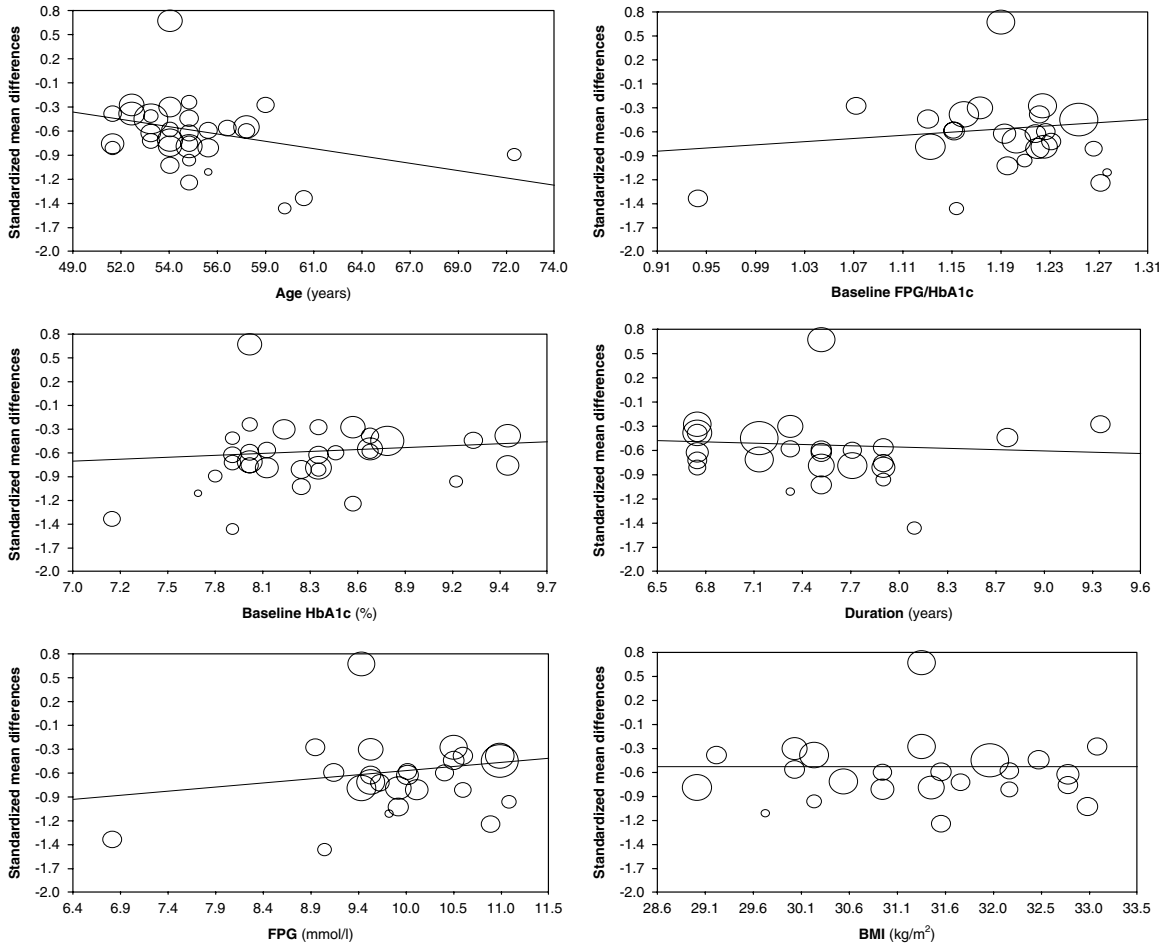

Figure 4. Meta-regression of placebo-subtracted effect on 24-week HbA_{1c}, in relation to average baseline characteristics (age, HbA_{1c}, FPG, FPG:HbA_{1c} ratio, duration of diabetes, and body mass index) of patients enrolled in each trial. Each dot represents the difference in HbA_{1c} between active drug and placebo; the size of the dots is proportional to the number of patients enrolled in each trial

combined with other drugs, without increasing the risk for hypoglycaemia, unless DPP-4 inhibitors are added to sulfonylureas and/or insulin. These findings confirm previous meta-analyses, performed on a smaller number of clinical trials [43–45]. The modest difference in endpoint BMI between DPP-4 inhibitors and placebo, which had been described previously [45], can be easily explained by the improvement of metabolic control and the consequent reduction of glycosuria.

DPP-4 inhibitors show a smaller efficacy on HbA_{1c} in comparison with metformin as previously reported [44]. This difference had already been detected by one 52-week monotherapy trial, which failed to demonstrate the non-inferiority of vildagliptin in comparison with metformin [21]. Conversely, DPP-4 inhibitors are similarly effective as α-glucosidase inhibitors [22]. Direct comparisons with thiazolidinediones fail to show any difference in efficacy on HbA_{1c}; however, most of those studies have a very short follow-up, and they may underestimate the effect of PPAR-γ agonists, which have been shown to perform much better than other classes of drugs in the longer term [46]. Interestingly, in comparison with sulfonylureas, DPP-4 inhibitors produce a similar reduction of HbA_{1c}. The limited number of available data and the small number of trials with longer duration [25,32] suggest caution in the interpretation of results; however, the effect of DPP-4 inhibitors on HbA_{1c} although slower, does not appear to be inferior to that of sulfonylureas in the longer term. The possibility that a divergent effect of DPP-4 inhibitors and sulfonylureas on β-cell mass and function, suggested by some experimental studies [47], produces a longer-term difference in hypoglycaemic efficacy needs to be assessed through clinical trials of appropriate duration, which are currently unavailable.

DPP-4 inhibitors confirm their good tolerability, with an incidence of severe adverse events similar to placebo, a lower hypoglycaemic risk than sulfonylureas, and a lower weight gain than thiazolidinediones. The number and duration of available trials are still insufficient to draw definitive conclusions on the cardiovascular effects of DPP-4 inhibitors; however, these drugs do not seem to induce any increase in cardiovascular morbidity, or in overall mortality, in comparison with placebo, confirming previous observations [44]. Available trials confirm, to date, the satisfactory cardiovascular safety profile of DPP-4 inhibitors, whereas further data are needed to

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verify their potential beneficial effects in this respect. Considering the small number of available trials reporting complete information on this point, the observed risk reduction for major cardiovascular events in direct comparisons with sulfonylureas, although statistically significant, could be a casual finding.

Clinical trials provide an estimate of the average effect of a drug on a pre-defined endpoint. However, in clinical practice, the individual response to each agent varies from one patient to another. The identification of clinical predictors of therapeutic responses to individual agents, or to a class of drugs, could be very useful for clinicians in their everyday practise. Ideally, this information should be obtained through pre-defined subgroup analyses of RCTs; unfortunately, this information was seldom available. Meta-regression analysis can be used as an alternative source of information, although its results should be considered with caution because of the risk of ecological fallacy [48]. Although meta-regression can provide useful information, it can at best be hypothesis generating. For example, a correlation between the mean age of the respective study populations and the mean glycaemic effect would not necessarily be similar to the correlation among all pooled individual data between age and glycaemic response. In addition, summarizing studies does not account for potential differences in study background population which may affect the response to therapy as well. However, based on results of available placebo-controlled trials, DPP-4 inhibitors seem to be more effective in older patients and in those with lower HbA_{1c} and FPG; interestingly, a lower FPG:HbA_{1c} ratio, which can be considered a proxy of post-prandial hyperglycaemia, is associated with a greater placebo-subtracted effect of DPP-4 inhibitors. These results are confirmed by those obtained in trials with active comparators. It should be recognized that the FPG:HbA_{1c} ratio is only a very indirect index of post-prandial glucose; the direct measurment of glycaemia after meals would be preferrable. However, the methods used for measurement of post-prandial glucose vary widely across trials, preventing any reliable meta-analysis/meta-regression. The fact that DPP-4 inhibitors are more effective in patients with prevailing post-prandial hyperglycaemia is not surprising, considering that these drugs increase the levels of endogenous glucagon-like peptide-1 and gastro-intestinal polypeptide, which are mainly produced after meals. Interestingly, these drugs seem to have a greater efficacy in older patients, who show, on average, a greater degree of impairment of meal-induced insulin secretion and post-prandial hyperglycaemia than subjects with an earlier onset of type 2 diabetes. Although data on this point are conflicting, it has been suggested that ageing could be associated with disturbances of the incretin axis [49]. The greater efficacy of DPP-4 inhibitors in older patients was suggested by a previous meta-analysis of patient-level data from alogliptin trials, but differences among age groups did not quite reach statistical significance [50].

In conclusion, these data could be useful for a better definition of the profile of patients who are likely to benefit most from DPP-4 inhibitors.

Supporting information

Supporting information may be found in the online version of this article.

Conflicts of interest

Edoardo Mannucci has received consultancy fees from Eli Lilly and Novo Nordisk; speaking fees from Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Merck, Novartis, Novo Nordisk, and Sanofi-Aventis; and research grants from Merck, Novartis, Eli Lilly, Novo Nordisk, Sanofi-Aventis, and Takeda. Matteo Monami has received speaking fees from Bristol Myers Squibb, Eli Lilly, Merck, Sanofi-Aventis, and Takeda. Francesco Cremasco is currently employed by Eli Lilly. Caterina Lamanna has received speaking fees from Merck. Niccolò Marchionni has received speaking fees from Eli Lilly, Novo Nordisk, and Sanofi-Aventis, and research grants from Eli Lilly, Novo Nordisk, and Sanofi-Aventis.

Authors' contribution

Edoardo Mannucci was involved in each of the following points:

1. Design
2. Data collection
3. Analysis
4. Writing manuscript

Matteo Monamiwas involved in each of the following points:

1. Design
2. Data collection
3. Analysis
4. Writing manuscript

Francesco Cremasco was involved in each of the following points:

1. Data collection
3. Analysis

Caterina Lamanna was involved in each of the following points:

1. Data collection
2. Analysis
3. Writing manuscript

Marchionni was involved in each of the following points:

1. Analysis
2. Writing manuscript

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