# Efficacy and safety of dipeptidyl peptidase-4 inhibitors: systematic review and meta-analysis.

# Background

- Clinical practice guidelines recommend metformin as first-line pharmacological therapy in type 2 diabetes mellitus (T2DM) patients and the addition of another antidiabetic agent [sulfonylurea (SU), thiazolidinedione (TZD), dipeptidyl peptidase-4 (DPP-4), inhibitor glucagon-like peptide-1 (GLP-1) agonist or basal insulin] if glycemic control is not achieved. The agents choice depends on different aspects including the reduction of HbA1c, risk of hypoglycemia, weight changes, adverse effects or cost in a patient-centered aproach<sup>1</sup>.
  - Vildagliptin, sitagliptin, saxagliptin and linagliptin are DPP-4 inhibitors approved for use in T2DM patients in recent years. It is important to assess their effects

#### DPP-4 inhibitors + metformin vs. metformin

• DPP-4 inhibitors added to metformin lowered HbA1c and FPG levels significantly more than metformin monotherapy (Figure 2 and 3).

#### Figure 2. Forest plot for meta-analysis of HbA1c change of DPP-4+metformin vs. metformin

Study	HbA1c change	SMD	95% CI	Weight (%)
Vilsbol(2010)		-0.67	[-0.83; -0.51]	10.2%
Charbonnel(2006)		-0.53	[-0.69; -0.36]	10.2%
Olansky(2011)		-0.46	[-0.60; -0.33]	11.2%
Williams-Herman(2010)		-0.53	[-0.82; -0.24]	6.6%
Williams-Herman(2009)		-0.41	[-0.64; -0.17]	8.1%
Goldstein(2007)		-0.71	[-0.92; -0.49]	8.6%
Hermans(2012)		-0.13	[-0.36; 0.11]	8.1%

Paz S.<sup>4</sup>, Prades M.<sup>4</sup>, Granell M.<sup>3</sup> Servicio de Endocrinología y Nutrición, Hospital de la Santa

Pérez A.<sup>1</sup>, Franch J.<sup>2</sup>, Fuster E.<sup>3</sup>,

- Creu i Sant Pau, Barcelona, Spain
- <sup>2</sup> Centro de Atención Primaria Drassanes, Área Básica de Salud de Raval Sur, Barcelona, Spain
- <sup>3</sup> Novartis, Barcelona, Spain

<sup>4</sup> Outcomes'10, Castellón, Spain

for lowering HbA1c and fasting plasma glucose (FPG) levels, hypoglycemia risk or weight changes compared with other available antidiabetic agents.

# **Objective**

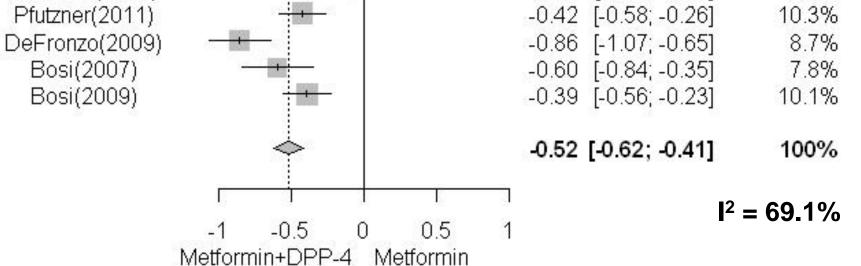
• To determine the efficacy and safety of DPP-4 inhibitors in T2DM patients according to published data.

# **Materials and methods**

- A systematic review of randomized clinical trials (RCT) in MEDLINE, Cochrane, ISI WOK, SCOPUS and clinicaltrials.gov databases was performed.
- Eligible studies were RCT with a treatment duration of at least 24 weeks evaluating efficacy (HbA1c, FPG and weight changes from baseline) and/or safety (hypoglycemia rate) of DPP4 inhibitors (vildagliptin, linagliptin, saxagliptin, sitagliptin) compared to placebo or non-insulin monotherapy or combination. These studies were published in English or Spanish until June 2013.
- Several meta-analysis were conducted using random effects models. Standardized mean difference (SMD) for efficacy variables and relative risk (RR) for safety variable with 95% confidence intervals (CI) were calculated<sup>2</sup>. Heterogeneity between studies was assessed by I<sup>2</sup> statistic. I<sup>2</sup> values of 25%, 50% and 75% were interpreted as low, moderate and high heterogeneity, respectively<sup>3</sup>.

## Results

- Of the 4,582 publications identified, 55 RCT were selected (Figure 1).
- **Figure 1.** Results of systematic review

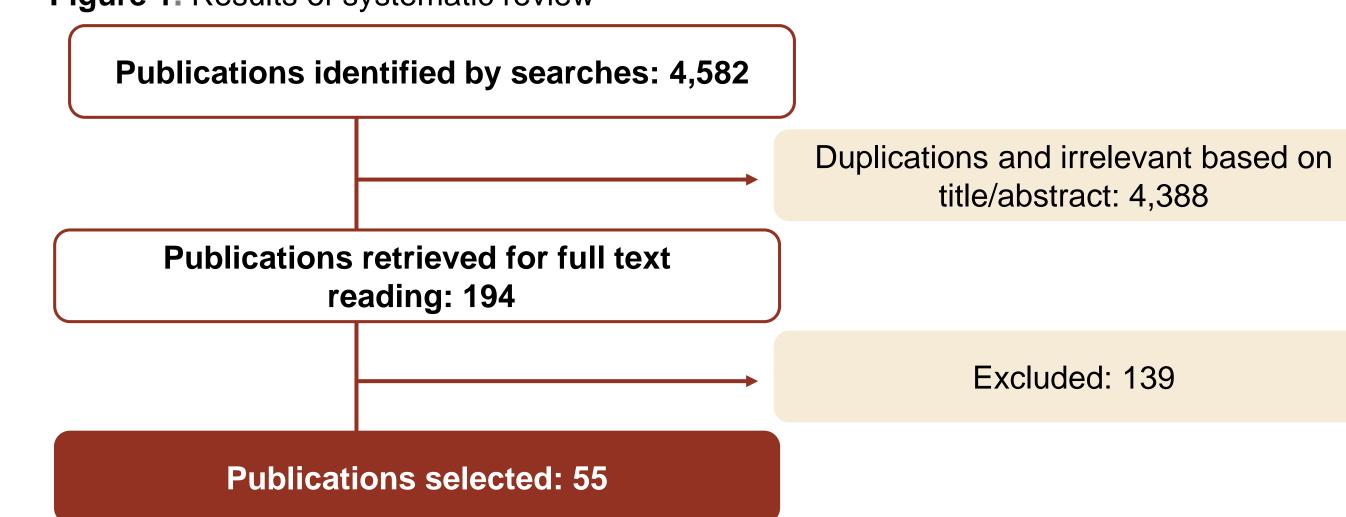


#### Figure 3. Forest plot for meta-analysis of FPG change of DPP-4+metformin vs. metformin

Study	FPG change	SMD	95% CI	Weight (%)
Vilsboll(2010)	· · · ·	-0.25	[-0.41; -0.09]	7.5%
Charbonnel(2006)	<u> </u>	-0.34	[-0.50; -0.18]	7.5%
Olansky(2011)		-0.19	[-0.31; -0.08]	8.2%
Williams-Herman(2010)		-0.42	[-0.71; -0.13]	5.4%
Williams-Herman(2009)		-0.42	[-0.66; -0.19]	6.3%
Raz(2008) -		-0.56	[-0.86; -0.27]	5.3%
Goldstein(2007) -	-	-0.77	[-0.98; -0.55]	6.6%
Bergenstal(2012)		-0.29	[-0.54; -0.03]	5.9%
Hermans(2012)		0.00	[-0.23; 0.23]	6.3%
Pfutzner(2011)	<del></del>	-0.29	[-0.45; -0.13]	7.6%
DeFronzo(2009) -		-0.68	[-0.89; -0.47]	6.6%
Taskinen(2011)		-0.52	[-0.70; -0.34]	7.2%
Haak(2012)	-	-0.39	[-0.63; -0.15]	6.1%
Bosi(2007) —		-0.79	[-1.03; -0.54]	6.1%
Bosi(2009)		-0.32	[-0.49; -0.16]	7.4%
	$\diamond$	-0.41	[-0.51; -0.30]	<mark>100%</mark>
-1 DPP-4	-0.5 0 0.5 I+Metformin Metformin	1	I	<sup>2</sup> = 76.5%

• Results on weight changes and hypoglycemia rate were not significantly different (weight SMD=0.03; 95% CI: 0.46; 1.32; hypoglycemia RR=0.78; 95% CI: 0.46; 1.32).

### DPP-4 inhibitors + metformin vs. sulfonylurea + metformin



• The main characteristics of studies showed that most of them were published between 2006 and 2009; the number of study participants varied mostly between 501 and 1,000, and a total 5 points in the Jadad scale was assigned to most publications (Table 1).

Table 1. Main characteristics of studies selected

Characteristics of studies	% of studies
Year of publication	49% 2010 -2013; 51% 2006 -2009
Number of participants	24% <500 participants; 49% 501-1,000 participants; 27% >1,000 participants
Jadad scale	82% 5 points; 16% 4 points; 2% 1 point

• Comparisons extracted from clinical trials were classified in DPP-4 inhibitors placebo (n=8); DPP-4 inhibitors vs. metformin (n=6); DPP-4 VS. inhibitors+metformin vs. metformin (n=15); DPP-4 inhibitors+sulfonylurea vs. metformin+sulfonylurea (n=9); and DPP-4 inhibitors+sulfonylurea vs. sulfonylurea (n=3).

• DPP-4 added to metformin achieved a greater decrease in weight and hypoglycemia risk compared to sulfonylurea plus metformin (Figure 4 and 5).

for meta-analysis of weight change of DPP-4+metformin vs. Figure 4. Forest plot sulfonylurea+metformin

Study	Weight change	SMD	95% CI	Weight (%)
Arechavaleta(2011) – Goke(2013) – Matthews(2010) Ferrannini(2009)		-0.68 -0.47	[-0.75; -0.48] [-0.82; -0.54] [-0.55; -0.38] [-0.56; -0.39]	21.6% 21.2% 28.4% 28.8%
		-0.55	[-0.64; -0.45]	100%
DPP	-0.5 0 0.5 -4+Metformin SU+Metform	nin		l <sup>2</sup> = 69.5%

**Figure 5.** Forest plot for meta-analysis of hypoglycemia incidence of DPP-4+metformin vs. sulfonylurea+metformin

Study	Hypoglycemia incidence	RR	95% CI	Weight (%)
Nauck(2007) Seck(2010) Arechavaleta(2011) Goke(2010) Goke(2013) Gallwitz(2012) Filozof(2010) Matthews(2010)		0.15	[0.22; 0.45] [0.05; 0.15] [0.05; 0.15] [0.16; 0.27] [0.20; 1.41]	12.1% 12.2% 12.3% 10.0% 10.5% 13.2% 5.9% 12.4%
Ferrannini(2009)	0.1 0.5 1 2 10 P-4+Metformin SU+Metformin			11.5% 100% I <sup>2</sup> = 80.5%

#### **DPP-4** inhibitors vs. placebo

• DPP-4 inhibitor monotherapy was associated to greater reductions in HbA1c and FPG compared with placebo (Table 2).

#### Table 2. Meta-analysis results of DPP-4 vs. placebo

Efficacy and safety measures	SMD (95% CI)	RR (95% CI)	<b> </b> <sup>2</sup>
HbA1c change	-0.60 (-0.75; -0.46)		72.2%
FPG change	-0.51 (-0.62; -0.39)		0.0%
Weight change	0.11 (-0.06; 0.29)		59.6%
Hypoglycemia incidence		0.88 (0.32; 2.45)	0.0%

## **DPP-4** inhibitors vs. metformin

• DPP-4 in monotherapy compared with metformin showed lower reductions in HbA1c, FPG and weight (Table 3).

#### **Table 3.** Meta-analysis results of DPP-4 vs. metformin

Efficacy and safety measures	SMD (95% CI)	RR (95% CI)	<b>1</b> <sup>2</sup>
HbA1c change	0.28 (0.20; 0.36)		8.4%
FPG change	0.36 (0.27; 0.44)		23.3%
Weight change	0.42 (0.33; 0.50)		24.1%
Hypoglycemia incidence		0.68 (0.37; 1.22)	0.0%

• Results on HbA1c and FPG changes were not significantly different (HbA1c: SMD=0.07; 95% CI: -0.01; 0.1; FPG SMD=0.04; 95% CI: -0.03; 0.12).

## DPP-4 + sulfonylurea vs. sulfonylurea

• The addition of DPP-4 inhibitors to sulfonylurea showed a greater reduction in HbA1c compared with sulfonylurea monotherapy (Figure 6).

**Figure 6.** Forest plot for meta-analysis of HbA1c change of DPP-4+metformin vs. sulfonylurea+metformin

Study	HbA1c change	SMD	95% CI	Weight (%)
Hermansen(2007) — Chacra(2011) Garber(2008) —		-0.41 -0.66	[-0.89; -0.33] [-0.58; -0.23] [-0.90; -0.42] <b>[-0.70; -0.37]</b>	25.3% 44.2% 30.6% <b>100%</b>
	-0.5 0 ( DPP-4+SU SU	ר ).5		I <sup>2</sup> = 38.5%

## Conclusions

DPP-4 inhibitors added to metformin achieved a better glycemic control compared with metformin monotherapy, with a lower risk of hypoglycemia and without affecting weight versus sulfonylurea and metformin combination.

#### **References**:

- 1 Inzucchi SE et al. Diabetologia. 2012;55:1577-96.
- 2 DerSimonian L, Laird N. Control Clin Trials. 1986;7:177-88.
- 3 Higgins JP, Thompson SG. Stat Med. 2002;21:1539-58.

**NOVARTIS**