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REVIEW ARTICLE

Sitagliptin in the treatment of type 2 diabetes: a meta-analysis

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Key words
Meta-analysis; Sitagliptin; Type 2 diabetes.

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Abstract

Objective: To evaluate the benefits and harms of sitagliptin in people with type 2 diabetes mellitus.

Methods: Randomized controlled trials (RCTs) were retrieved from PubMed, Embase, and the Cochrane central register of controlled trials (Cochrane Library). We used the method recommend by the Cochrane Collaboration to perform a meta-analysis of RCTs of sitagliptin therapy for type 2 diabetes.

Results: Of 817 studies retrieved in the literature search, 18 were eligible for inclusion. When sitagliptin was compared with placebo there was a statistically significant reduction in haemoglobin A1C (HbA_{1c}) (MD = 0.74, 95% CI 0.63 to 0.85) and fasting plasma glucose (FPG) (MD = 1.20, 95% CI 1.03 to 1.38). Sitagliptin significantly improved the homeostasis model assessment of β-cell (HOMA-β index) (MD = –10.84, 95% CI –14.07 to –7.80) versus placebo. In participants treated with placebo, hypoglycemia adverse experiences (RR = 2.11, 95% CI 1.50 to 2.36) and serious adverse experiences (RR = 1.20, 95% CI 0.89 to 1.63) were less common. Meta-analysis did not show a significant difference in change in FPG (MD = –0.32, 95% CI –0.76 to 0.13) or HOMA-β index (MD = 4.42, 95% CI –1.22 to 10.07) between the sitagliptin and active control groups, but active treatments provided modestly greater reduction in HbA_{1c} (MD = –0.20, 95% CI –0.37 to –0.03) compared with sitagliptin. No significant difference was observed between the sitagliptin and active treatments in incidence of hypoglycemia adverse experiences (RR = 0.38, 95% CI 0.14 to 1.08) or serious adverse experiences (RR = 1.15, 95% CI 0.83 to 1.65).

Conclusions: Sitagliptin treatment for type 2 diabetes was effective and well tolerated. Sitagliptin offers a novel therapeutic approach for the treatment of type 2 diabetes. Continued assessment in longer term studies is required to determine the role of sitagliptin in type 2 diabetes.

Introduction

Type 2 diabetes is a worldwide health problem that is increasing in prevalence. Despite the availability of abundant management tools for patients, type 2 diabetes continues to lead to serious complications, including heart disease, stroke, amputation, blindness, nephropathy, neuropathy, and premature death (1). As type 2 diabetes develops, glycemic control deteriorates in most patients due to a progressive loss of β-cell function; as a result, intensification of therapy is necessary. However, therapies such as metformin and insulin are limited by the risk of weight gain, hypoglycemia, and gastrointestinal intolerance (2). Dipeptidyl peptidase-4 (DPP-4) inhibitors have changed the management of type 2 diabetes. DDP-4 inhibitors increase levels of the incretin hormones glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP); both GLP-1 and GIP increase insulin secretion after meals, and GLP-1 lowers glucagon secretion (3–4). Sitagliptin is the first of a new class of antidiabetic agents, DPP-4 inhibitors, for improving glycemic

control in type 2 diabetes mellitus. There is insufficient evidence to support the use of sitagliptin as monotherapy or triple oral therapy with metformin and a sulfonylurea. Therefore, we conducted a meta-analysis to determine the benefits and harms of sitagliptin in the treatment of type 2 diabetes.

Materials and Methods

Search strategy and selection criteria

We searched different electronic databases for studies of people with type 2 diabetes who received sitagliptin with a cut-off date of 24 March 2010, including PubMed, the Cochrane central register of controlled trials (Cochrane Library 2010, issue 1), and EMbase. Searches were limited to studies involving humans and reports of clinical trials. The search strategy is presented in full in Appendix A. In addition, reference lists of relevant primary or review articles were checked for additional citations.

All potentially relevant articles were reviewed independently by two investigators according to the inclusion criteria, and any disagreements were resolved by consensus or by a third author. The following inclusion criteria were used: (1) types of participants: adult patients with type 2 diabetes according to the standard criteria, including ADA (American Diabetes Association) 1997 and WHO (World Health Organization) 1998; (2) types of interventions: patients treated with sitagliptin alone or in combination with other hypoglycemic agents for at least 12 weeks, compared with placebo or an active control; (3) types of outcome measures: the primary outcome was the HbA1c change from baseline, and secondary outcomes included beta-cell function, fasting plasma glucose (FPG), and adverse events; and (4) language: we only included articles published in English.

The following exclusion criteria were applied: (1) examining a non-adult population, (2) participants with type 1 diabetes, unstable cardiac disease, or significant renal impairment, and (3) results published in reviews, letters, and abstracts. In cases in which there were two or more published reports on the same population or group of participants, we only included the most recent study. We included separate studies on participants from the same source if the earlier article focused on a given mutation and the subsequent article(s) examined additional mutations.

Assessment of risk of bias in included studies

Risk of bias in the included studies was assessed by several domains: allocation generation; allocation concealment; blinding of participants, outcome assessors and investigators; incomplete outcome data addressed; free of selective reporting; and free of other bias (5).

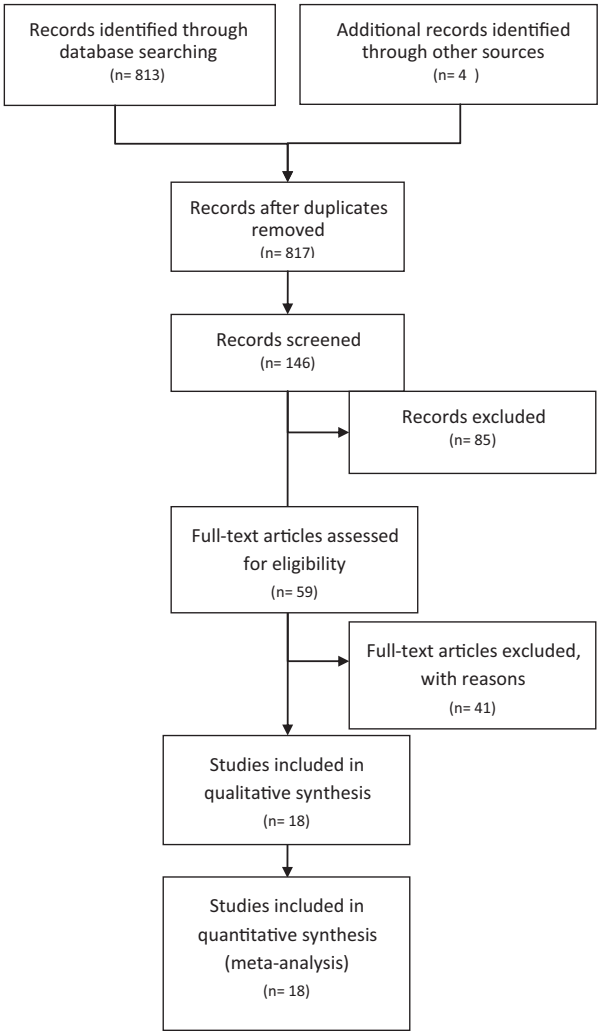

Figure 1 Result of literature search.

Data extraction and analysis

The primary measure for glycemic efficacy was change from baseline in HbA_{1c}. The secondary glycemic efficacy outcome was change from baseline in FPG. The end point for β-cell function is change from baseline in HOMA-β (6). For safety, we analyzed the number of participants reporting serious adverse experiences and hypoglycemia adverse experiences. For continuous variables (HbA1c, FPG, HOMA-β), we calculated mean differences (MD) and 95% CIs for change from baseline in experimental (sitagliptin) versus control (placebo or active control) groups. For dichotomous variables (serious adverse experiences and hypoglycemia adverse experiences), we calculated the risk ratios (RR) and 95% CIs for experimental versus control groups. We used the Chi^2 test, P values, and the I^2 statistic to evaluate heterogeneity. In the absence of statistically significant heterogeneity ($P \geq 0.1$),

Table 1 Characteristics of included studies

Study	Sample size (E/C)	Gender (M/F)	Duration of DM (years) (E/C)	Age (years) (E/C)	BMI (kg/m^2) (E/C)	HbA1c (%) (E/C)	Intervention	Follow-u time
Aschner 2010[20]	528/522	E: 217/311 C: 194/328	2.6/2.1	56.3/55.7	30.7/30.9	7.2/7.1	E: sitagliptin, 100 mg q.d C: metformin, 1000 mg b.i.d	24 w
Marfella 2010[24]	20/18	E: 11/9 C: 9/9	7.7/7.8	61/60	29.7/29.6	8.3/8.4	E: sitagliptin, 100 mg q.d + metformin, 3000 mg/day C: vildagliptin, 1000 mg b.i.d + metformin, 3000 mg/day	3 m
Nauck 2007[23]	588/584	E: 336/252 C: 358/226	5.8	56.8/56.6	31.2/31.3	7.7/7.6	E: sitagliptin, 100 mg q.d + metformin C: glipizide + metformin	52 w
Charbonnel 2006[18]	464/237	E: 259/205 C: 141/96	6.6/6.0	54.7/54.4	31.5/30.9	8.03/7.96	E: sitagliptin, 100 mg q.d + metformin C: placebo + metformin	24 w
Hermansen 2007[15]	222/219	E: 117/105 C: 117/102	8.3/9.3	55.6/56.5	31.2/31.0	8.34/8.34	E: sitagliptin, 100 mg q.d + glimepiride ± metformin C: placebo + glimepiride ± metformin	24 w
Raz 2008[14]	96/94	E: 47/49 C: 55/39	7.3/8.4	56.1/53.6	30.4/30.1	9.1/9.3	E: sitagliptin, 100 mg q.d + metformin C: placebo + metformin	18 w
Raz 2006[12]	464/237	E: 259/205 C: 141/96	6.0/6.6	54.5/54.7	30.9/31.5	8.0/8.0	E: sitagliptin, 100 mg q.d C: placebo	
Scott 2008[16]	94/92/87	E: 52/42 C1: 54/38 C2: 55/32	4.9/5.4/4.6	55.2/55.3/54.8	30.3/30.3/30.4	7.8/7.7/7.7	E: sitagliptin, 100 mg q.d + metformin C1: placebo + metformin C2: Rosiglitazone, 8 mg q.d + metformin	18 w

Continued.

Table 1 Continued

Study	Sample size (E/C)	Gender (M/F)	Duration of DM (years) (E/C)	Age (years) (E/C)	BMI (kg/m^2) (E/C)	HbA1c (%) (E/C)	Intervention	Follow-u time
Rosenstock 2006[17]	175/178	E: 82/93 C: 75/103	6.1/6.1	55.6/56.9	32.0/31.0	8.1/8.0	E: sitagliptin, 100 mg q.d + pioglitazone C: placebo + pioglitazone	24 w
Vilsboll 2010[19]	322/319	E: 157/165 C: 169/150	13/12	58.3/57.2	31/31	8.7/8.6	E: sitagliptin, 100 mg q.d + insulin ± metformin C: placebo + insulin ± metformin	24 w
Aschner 2006[8]	238/253	E: 136/102 C: 130/123	4.3/4.6	53.4/54.3	30.3/30.8	8.0/8.0	E: sitagliptin, 100 mg q.d C: placebo	24 w
Goldstein 2007[9]	179/176	E: 93/86 C: 93/83	4.5	53.3/53.6	31.2/32.5	8.9/8.7	E: sitagliptin, 100 mg q.d C: placebo	24 w
Williams-Herman 2009[22]	141/153	/	3.9/4.1	53.6/53.7	32/32	8.8/8.7	E: sitagliptin, 100 mg q.d C: metformin, 1000 mg b.i.d	54 w
Hanefeld 2007[11]	110/111	E: 61/49 C: 70/41	31.6/31.4	56.0/55.3	31.6/31.4	7.8/7.6	E: sitagliptin, 100 mg q.d C: placebo	12 w
Mohan 2009[13]	352/178	E: 200 /152 C: 106/72	2.1/1.9	50.9/50.9	25.1/24.9	8.7/8.8	E: sitagliptin, 100 mg q.d C: placebo	18 w
Nonaka 2008[7]	75/76	E: 45 /30 C: 50/26	4.0/4.1	55.6/55.0	25.1/25.3	7.7/7.5	E: sitagliptin, 100 mg q.d C: placebo	12 w
Scott 2007[10]	124/125/123	E: 65/59 C1: 78/47 C2: 70/53	4.2/4.8/4.7	55.1/55.1/54.7	30.4/31.6/30.6	7.8/7.9/7.9	E: sitagliptin, 50 mg b.i.d C1: placebo C2: glipizide	12 w
Derosa 2010[21]	175/178	E: 37/38 C: 39/37	5/6	57/58	27.9/27.7	8.5/8.4	E: sitagliptin, 100 mg q.d + pioglitazone, 30 mg q.d C: metformin, 850 mg b.i.d + pioglitazone, 15 mg b.i.d	12 m

E/C = experimental/control; M/F = female/male.

Table 2 Risk of bias in included studies

Study	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Aschner 2010[20]	Yes (computer-generated allocation schedule)	Multinational	Double-blind (unclear)	No	No	Unclear
Marfella 2010[24]	Unclear	Unclear	Double-blind (investigators and patients)	Unclear	Unclear	Unclear
Nauck 2007[23]	Unclear	Multinational	Double-blind (unclear)	No	No	Unclear
Charbonnel 2006[18]	Yes	Multinational	Double-blind (unclear)	No	No	Unclear
Hermansen 2007[15]	Yes (interactive voice response system)	Multinational	Double-blind (unclear)	No	Unclear	Unclear
Raz 2008[14]	Yes (computer-generated allocation schedule)	Multinational	Double-blind (unclear)	No	No	Unclear
Raz 2006[12]	Unclear	Multinational	Double-blind (unclear)	No	Unclear	Unclear
Scott 2008[16]	Unclear	Multinational	Double-blind (unclear)	No	No	Unclear
Rosenstock 2006[17]	Unclear	Multinational	Double-blind (unclear)	No	No	Unclear
Vilsboll 2010[19]	Yes (computer-generated allocation schedule)	Multinational	Double-blind (unclear)	No	No	Unclear
Aschner 2006[8]	Unclear	Multinational	Double-blind (unclear)	No	No	Unclear
Goldstein 2007[9]	Yes (computer-generated allocation schedule)	Multinational	Double-blind (investigators and patients)	No	No	Unclear
Williams-Herman 2009[22]	Yes (computer-generated allocation schedule)	Multinational	Double-blind (investigators and patients)	No	No	Unclear
Hanefeld 2007[11]	Unclear	Multinational	Double-blind (patients)	No	No	Unclear
Mohan 2009[13]	Yes (computer-generated allocation schedule)	Multinational	Double-blind (investigators and patients)	No	No	Unclear
Nonaka 2008[7]	Unclear	Unclear	Double-blind (investigators and patients)	No	Unclear	No
Scott 2007[10]	Yes (computer-generated allocation schedule)	Multinational	Double-blind (unclear)	No	No	Unclear
Derosa 2010[21]	Yes (randomization codes)	Multinational	Double-blind (investigators and patients)	No	No	Unclear

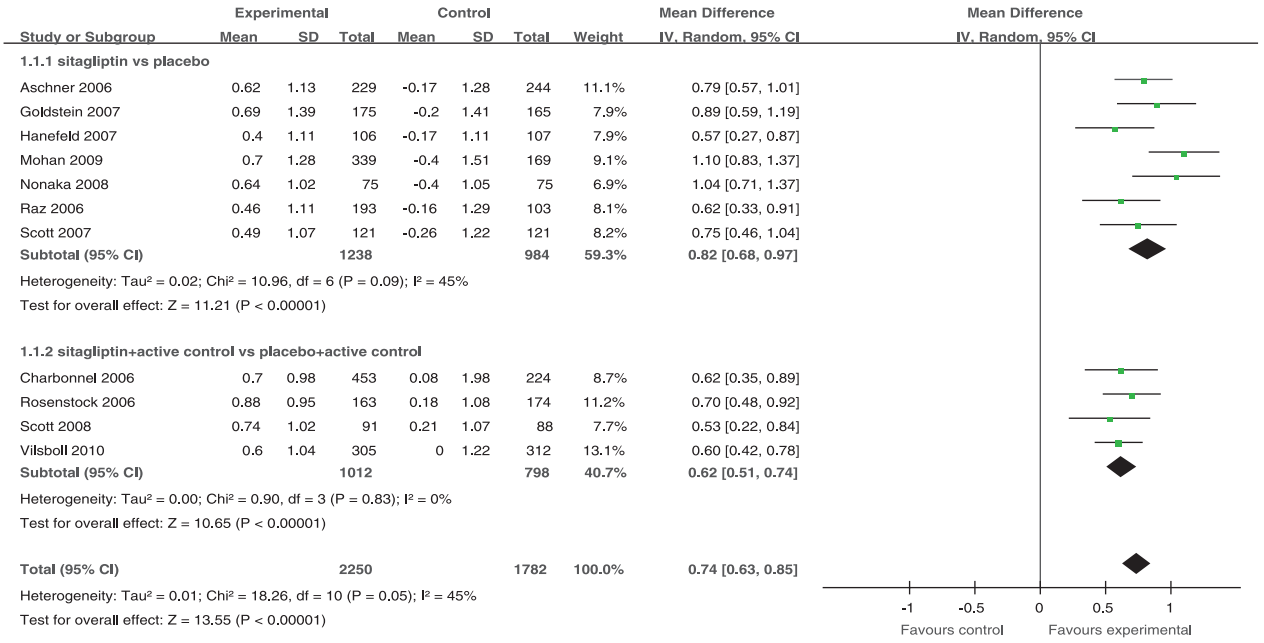

Figure 2 Mean difference in change in haemoglobin A1C (HbA1c) percentage value for sitagliptin vs. placebo in adults with type 2 diabetes.

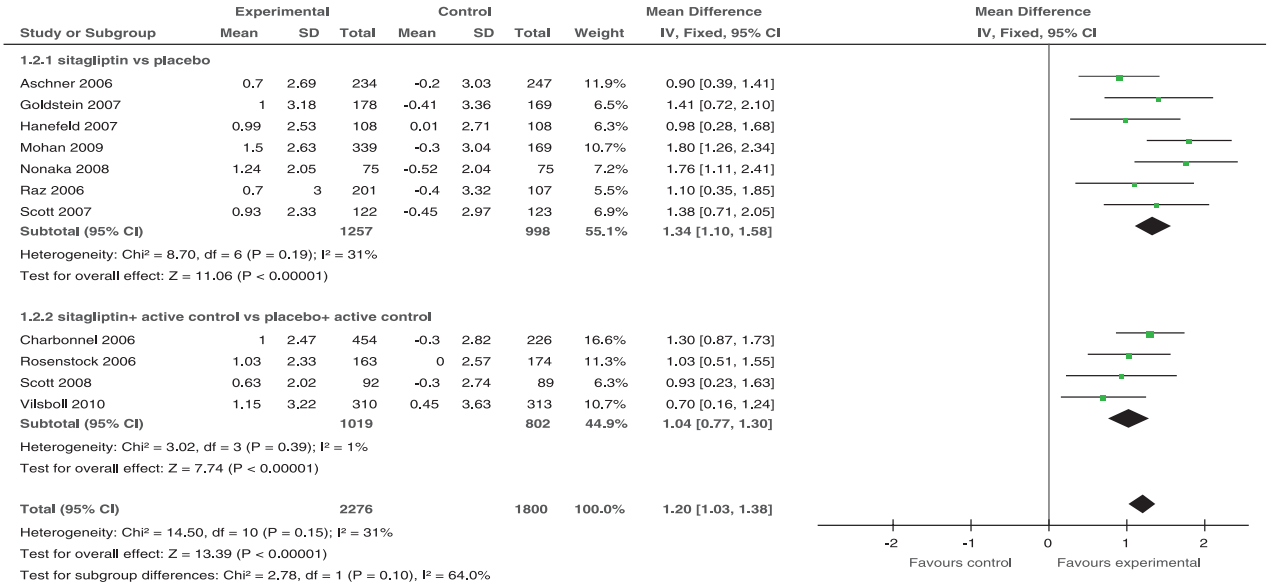

Figure 3 Mean difference in change in fasting plasma glucose (mmol/L) for sitagliptin vs. placebo in adults with type 2 diabetes.

the fixed-effect model was used to combine the results. When heterogeneity was confirmed ($P < 0.1$; or $P > 0.1$, but $I^2 >$ 50%–70%), a random-effects model was used. We performed a meta-analysis of outcomes by combining different groups of studies, and used the Review Manager statistical software package (version 5.0).

Results

Search results and study characteristics

The study selection process is summarized in Figure 1. A total of 59 clinical trials and reports were identified, and 18 RCTs were judged according to our inclusion criteria to

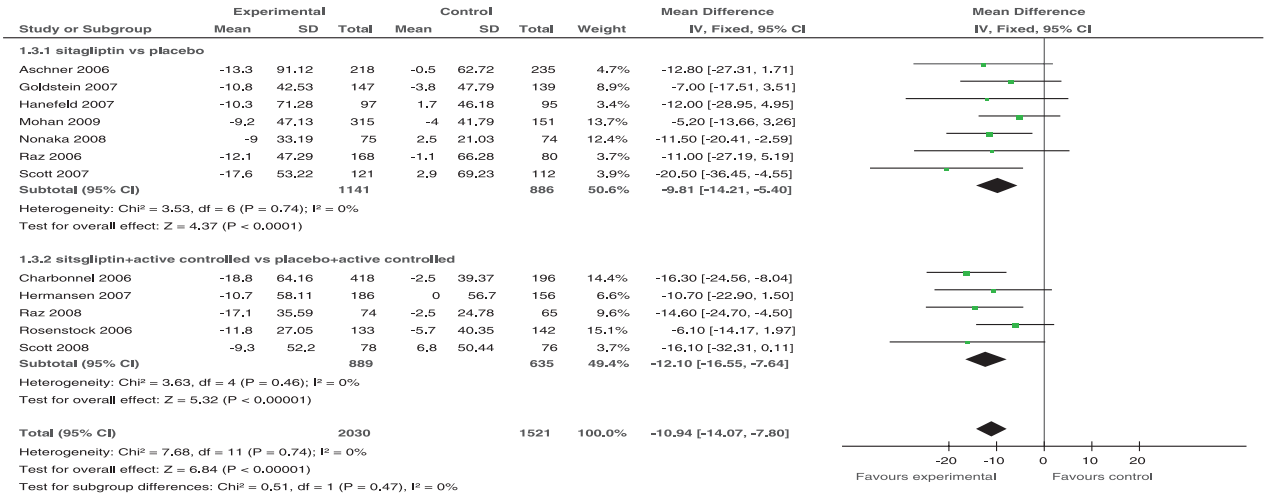

Figure 4 Mean difference in change in HOMA-β for sitagliptin vs. placebo in adults with type 2 diabetes.

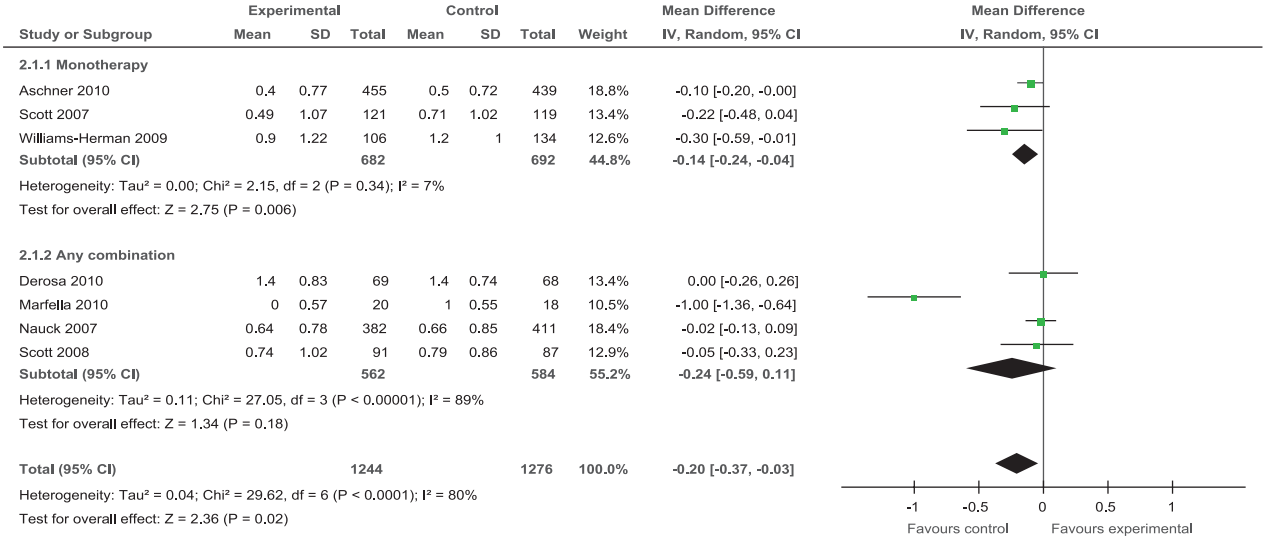

Figure 5 Mean difference in change in haemoglobin A1C percentage value for sitagliptin vs. active control in adults with type 2 diabetes.

be appropriate for the meta-analysis. There were 13 studies in which a placebo was compared with sitagliptin given as monotherapy (7–13), or as an add-on therapy to oral hypoglycemic agents (14–18) or insulin (19). Seven studies compared sitagliptin with an oral anti-hyperglycemic agent, including metformin (20–22), rosiglitazone (16), glipizide (10,23), and vildagliptin (24). The main characteristics of the included RCTs in the meta-analysis are summarized in Table 1. Risk for bias was judged to be high for only three studies, including Marfella 2010 (24), Mohan 2009 (13), and Nonaka 2008 (7) (Table 2).

Efficacy outcomes

Sitagliptin versus placebo: All included studies reported data on HbA1c, FPG, and HOMA-β, but the data describing the change in HbA1c and FPG from Hermansen (15) and Raz (14) were not adequate for meta-analysis. Both of those studies found that sitagliptin led to a significantly greater reduction in levels of HbA1c and FPG than did placebo. On meta-analysis, sitagliptin significantly reduced HbA1c compared with placebo (MD = 0.74, 95% CI 0.63 to 0.85, $P <$ 0.00001) (Figure 2). The reduction from baseline in FPG was significantly larger with sitagliptin compared with placebo

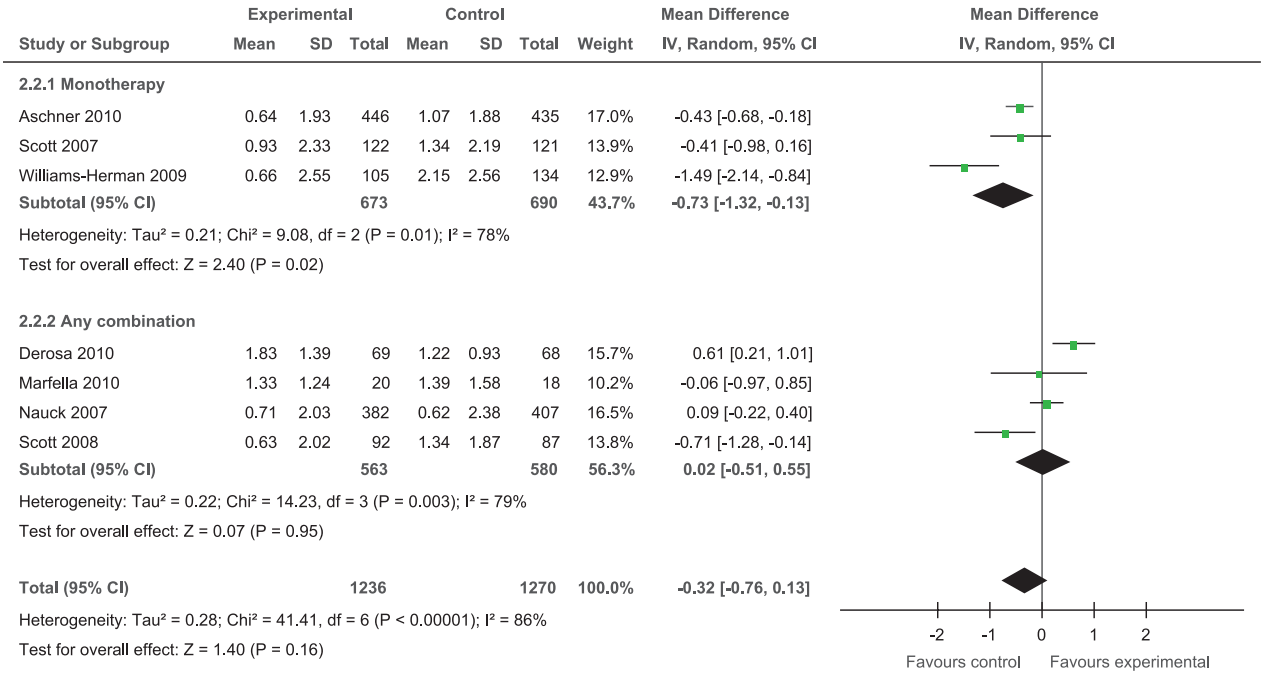

Figure 6 Mean difference in change in fasting plasma glucose (mmol/L) for sitagliptin vs. active control in adults with type 2 diabetes.

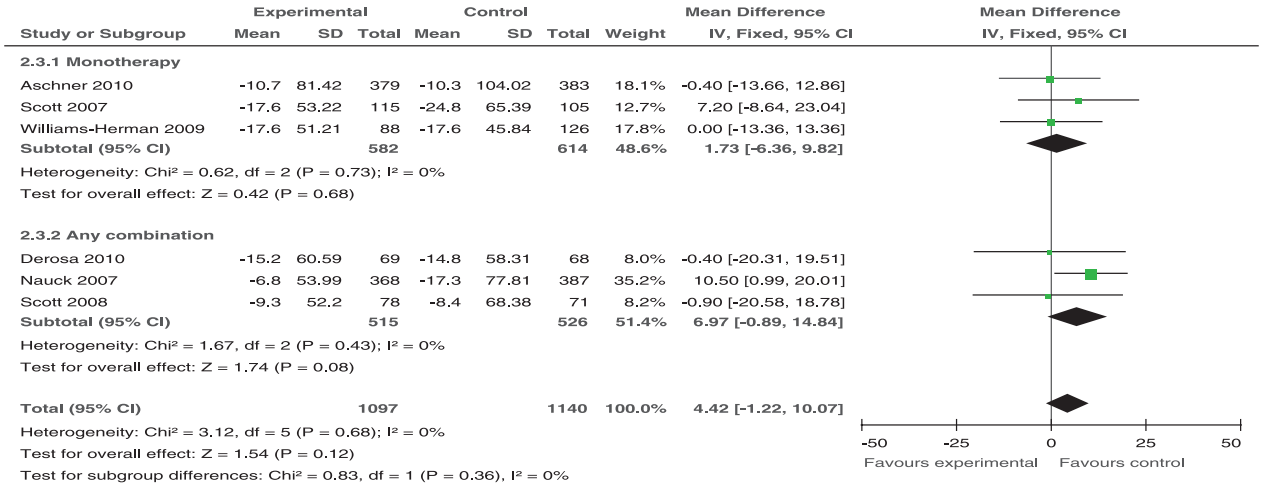

Figure 7 Mean difference in change in HOMA-β for sitagliptin vs. active control in adults with type 2 diabetes.

(MD = 1.20, 95% CI 1.03 to 1.38, $P < 0.00001$) (Figure 3). HOMA-β was significantly improved in participants who received sitagliptin therapy compared with placebo (MD = –10.94, 95% CI –14.07 to –7.8, $P < 0.00001$) (Figure 4).

Sitagliptin versus active control: All included articles reported data on HbA1c, FPG, and HOMA-β, with the exception of Marfella 2010 (24), which did not describe the change in HOMA-β. In subgroup analysis, evaluations of sitagliptin's monotherapy efficacy and combination therapy with sitagliptin and other anti-hyperglycemic agents in participants with type 2 diabetes were conducted. Oral anti-hyperglycemic agents as monotherapy produced a greater reduction in levels of HbA1c (MD = –0.14, 95% CI –0.24 to –0.04, $P = 0.006$) (Figure 5) and PFG (MD = –0.73, 95% CI –0.24 to –0.04, $P = 0.02$) (Figure 6) compared

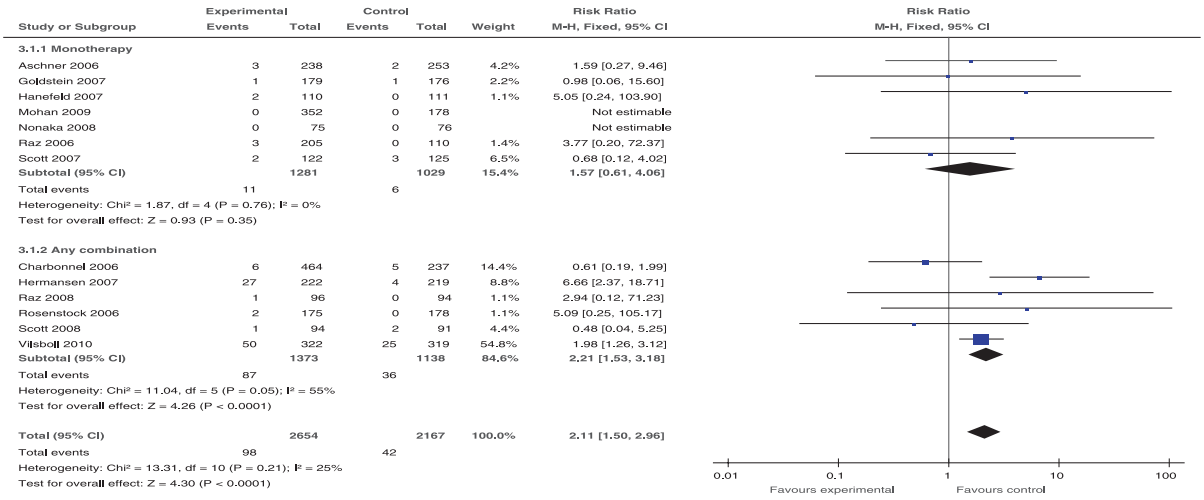

Figure 8 Rates of hypoglycemia for sitagliptin vs. placebo in adults with type 2 diabetes.

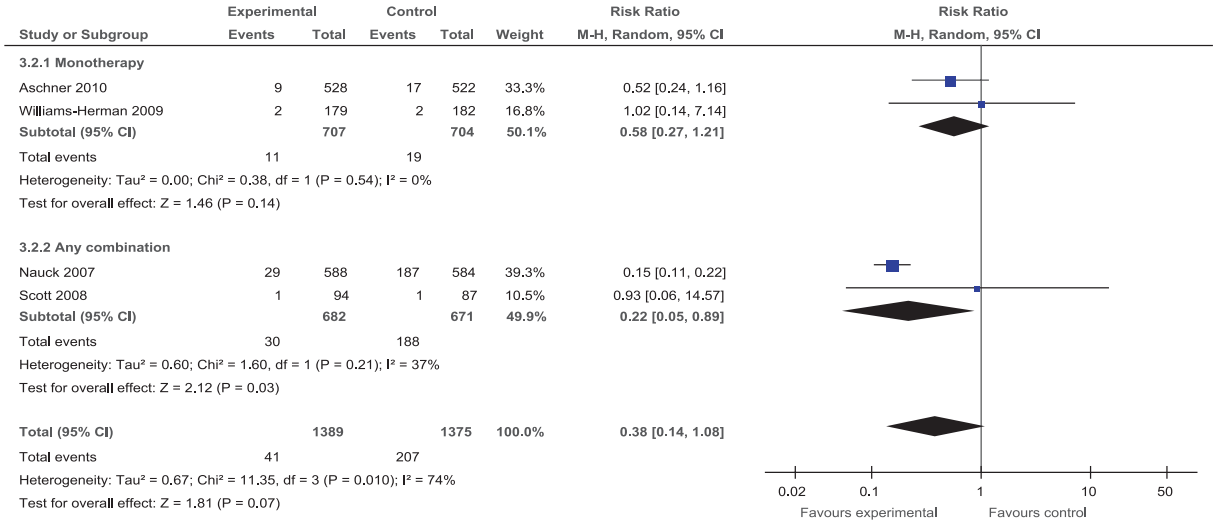

Figure 9 Rates of hypoglycemia for sitagliptin vs. active control in adults with type 2 diabetes.

with sitagliptin monotherapy. Sitagliptin lowered HbA1c (MD = –0.24, 95% CI –0.59 to 0.11, $P = 0.18$) (Figure 5) and PFG (MD = 0.02, 95% CI –0.51 to 0.55, $P = 0.95$) (Figure 6) compared with oral anti-hyperglycemic agents with similar efficacy as add-on therapy. Sitagliptin and oral anti-hyperglycemic agents as monotherapy or add-on therapy produced similar increases in HOMA-β (MD = 1.73, 95% CI –6.36 to 9.82, $P = 0.68$) (Figure 7).

Safety and tolerability

There were no significant differences in the incidence of hypoglycemia (RR = 0.38, 95% CI 0.14 to 1.08, $P = 0.07$) (Figure 9) or serious adverse experiences (RR = 1.15, 95% CI 0.83 to 1.61, $P = 0.40$) (Figure 11) between the sitagliptin and active control groups. The incidence of serious adverse experiences was similar between the placebo and sitagliptin groups (RR = 1.15, 95% CI 0.83 to 1.61, $P = 0.40$) (Figure 10). The incidence of hypoglycemia was similar between the sitagliptin and placebo as monotherapy groups (RR = 1.57, 95% CI 0.61 to 4.06, $P < 0.0001$), but sitagliptin as an add-on therapy produced higher incidence of hypoglycemia compared with placebo as add-on therapy (RR = 2.21, 95% CI 1.53 to 3.18, $P < 0.0001$) (Figure 8).

Discussion

This meta-analysis assessed the efficacy and safety of sitagliptin in people with type 2 diabetes, and demonstrated

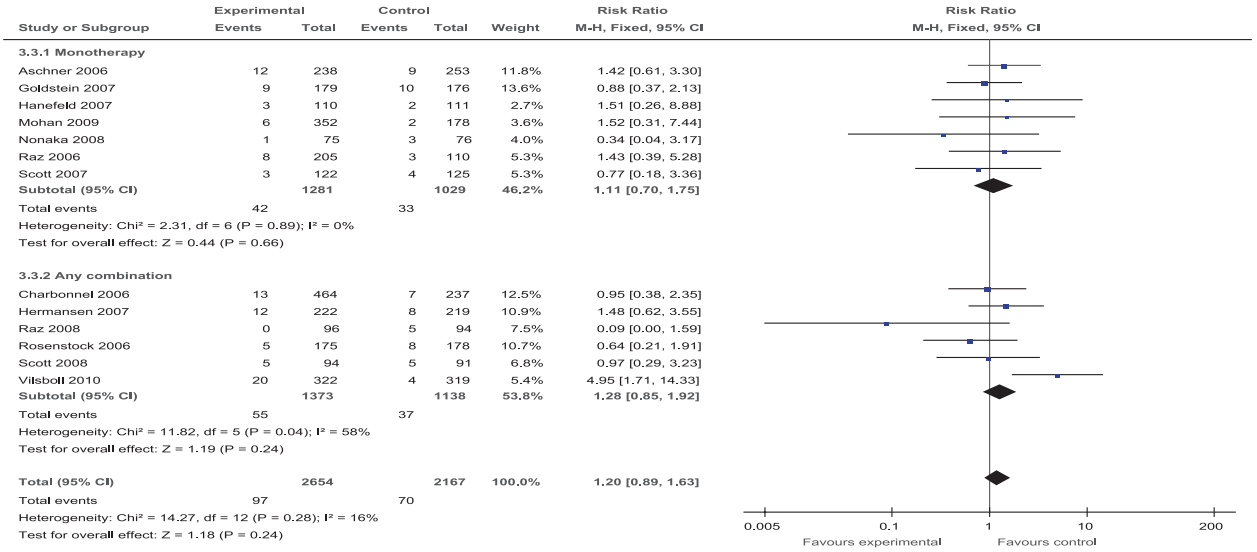

Figure 10 Rates of serious adverse events for sitagliptin vs. placebo in adults with type 2 diabetes.

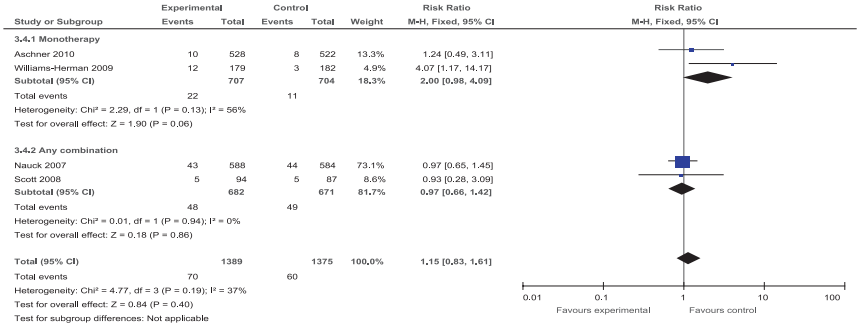

Figure 11 Rates of serious adverse events for sitagliptin vs. active control in adults with type 2 diabetes.

that treatment with sitagliptin provided clinically meaningful reduction in HbA1c and FPG compared with placebo. The increase in HOMA-β supports the conclusion that sitagliptin improved β-cell function. Sitagliptin was generally well tolerated, with no clinically meaningful differences in the incidence of serious adverse experiences compared with the placebo group. The incidence of hypoglycemic adverse experiences was similar between sitagliptin and placebo as monotherapy, but a higher proportion of people experienced hypoglycemia with sitagliptin in combination with other anti-hyperglycemic agents. Sitagliptin has been shown to be noninferior to oral anti-hyperglycemic agents. When sitagliptin was used as an add-on therapy, the incidence of hypoglycemia was lower compared with other oral anti-hyperglycemic agents. Based on this meta-analysis we concluded that sitagliptin is efficacious and well tolerated.

To our knowledge, this paper is the most current meta-analysis on this topic. The main limitation of this paper is that data was insufficient to draw any conclusions on possible long-term effects of sitagliptin for type 2 diabetes. A second limitation is the possibility that important published articles and unpublished data were missed. Searches were limited to published English- and Chinese-language articles, and it is likely we missed some RCTs published in other languages. Furthermore, different definitions of hypoglycemia were used in the included RCTs.

Taken together, this study shows that sitagliptin improved glycemic control and β-cell function, and was well tolerated in people with type 2 diabetes. Further studies on larger populations of participants are necessary to provide more conclusive evidence on the long-term therapeutic efficacy and safety of sitagliptin.

Authors' Contributions

MZ, FW, TX, and YT designed the article; conduct/data collection was done by MZ and FW; analysis was done by MZ, FW, TX, and YT; and manuscript was written by MZ, FW, TX, and YT.

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Appendix A (The search strategy)

PubMed

#1 randomized controlled trial [pt]
#2 controlled clinical trial [pt]
#3 randomized [tiab]
#4 placebo [tiab]
#5 drug therapy [sh]
#6 randomly [tiab]
#7 trial [tiab]
#8 groups [tiab]
#9 or/#1∼#8
#10 sitagliptin/
#11 sitagliptin [ab/ti/kw]
#12 januvia [ab/ti/kw]
#13 MK 0431 [ab/ti/kw]
#14 MK0431 [ab/ti/kw]
#15 MK-0431 [ab/ti/kw]
#16 or/#10∼#15 [ab/ti/kw]
#17 #9 and #16 [ab/ti/kw]

Embase

#1 'controlled clinical trial'/exp
#2 'double blind procedure'/exp
#3 'single blind procedure'/exp
#4 'crossover procedure'/exp
#5 'prospective study'/exp
#6 'comparative study'/exp
#8 'randomization'/exp
#9 'placebo'/exp
#10 blind∗:ab,ti
#11 random∗:ab,ti
#12 control∗:ab,ti
#13 placebo∗:ab,ti
#14 or/#1∼#13
#15 'sitagliptin'/syn and [embase]/lim
#16 and #14,#15

Cochrane central register of controlled trials

#1 sitagliptin [ab/ti/kw]
#2 januvia [ab/ti/kw]
#3 MK 0431[ab/ti/kw]
#4 MK0431 [ab/ti/kw]
#5 MK-0431 [ab/ti/kw]
#6 or/#10∼#15 [ab/ti/kw]
#7 clinical trial [pt]
#8 #6 and #7