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RESEARCH ARTICLE

Efficacy and safety of saxagliptin in patients with type 2 diabetes: A systematic review and meta-analysis

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Abstract

Objective

To evaluate the comparative efficacy and safety of saxagliptin for type 2 diabetes (T2D).

Methods

A systematic search of PubMed, Embase, the Cochrane Library, Web of Science, Clinical-Trials.gov and two Chinese databases for randomized controlled trials (RCTs) comparing saxagliptin with placebo or active comparators was performed up to July 2017. A complementary search was done to cover literature until March 2018. For continuous data, estimates were pooled using inverse variance methodology to calculate weighted mean differences (WMDs). Dichotomous data were presented as Mantel-Haenzel risk ratios (RRs).

Results

Thirty-nine references of 30 RCTs involving 29,938 patients were analyzed. Compared with placebo, saxagliptin significantly reduced glycated hemoglobin (HbA1c, WMD -0.52%, 95% CI -0.60 to -0.44) and fasting plasma glucose (WMD -13.78 mg/dL, 95% CI -15.31 to -12.25), and increased the proportion of patients achieving HbA1c <7% (RR 1.64, 95% CI 1.53 to 1.75). When combined with submaximal-dose metformin, saxagliptin significantly increased the proportion of patients achieving HbA1c <7% compared with acarbose (RR 2.38, 95% CI 1.17 to 4.83) and uptitrated metformin (RR 1.30, 95% CI 1.04 to 1.63). Saxagliptin was similar to other DPP-4 inhibitors but inferior to liraglutide and dapagliflozin on glycemic control. Saxagliptin significantly decreased the incidences of overall adverse events compared with acarbose (RR 0.71, 95% CI 0.57 to 0.89) and liraglutide (RR 0.41, 95% CI 0.24 to 0.71) when added to metformin. Weight gain and hypoglycemia with saxagliptin was slightly but significantly higher than placebo and lower than sulfonylureas. Saxagliptin did not increase the risk of arthralgia, heart failure, pancreatitis and other adverse events.

Conclusions

Generally, saxagliptin has similar efficacy compared with most oral antidiabetic drugs and may be more effective than acarbose, while having a better safety profile than both acarbose and sulfonylureas.

Introduction

Type 2 diabetes (T2D) is a chronic disease rapidly increasing in prevalence that imposing enormous medical and economic burdens on on individuals, families, and national health systems worldwide. It is estimated that approximately 415 million people in the world had diabetes in 2015, and this figure is projected to increase to 642 million by 2040 [1]. Health spending on diabetes accounted for 11.6% of total health expenditure worldwide in 2015 [2]. A diversity of antidiabetic drugs to treat the condition is now available, including metformin, sulfonylureas, thiazolidinediones, α -glucosidase inhibitors, prandial glucose regulators, sodiumglucose cotransporter 2 (SGLT2) inhibitors, and insulin in various forms. Because of the progressive nature of diabetes, clinicians and patients often experience difficulty in achieving and sustaining glycemic control. Utilization of antidiabetic drugs should be based on the individual patient's characteristics and preferences and balance the need to optimize the benifits of glycaemic control with the need to limit the risk of adverse effects.

Dipeptidyl peptidase 4 (DPP-4) inhibitors (gliptins) are a relatively new class of oral antidiabetic drugs for the treatment of type 2 diabetes. They act by increasing postprandial concentrations of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) [3–4]. GLP-1 and GIP stimulate insulin secretion in a glucose-dependent manner, suppressing glucagon secretion and slowing gastric emptying. The American Diabetes Association and the European Association for the Study of Diabetes have advocated the use of DPP-4 inhibitors as first-line agent in circumstances where metformin is contraindicated or not tolerated, or within a dual or triple agent regimen [5]. Saxagliptin is an orally active, once-daily, selective and reversible inhibitor of DPP-4 enzyme indicated/approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes [6,7].

With the growing number of pharmacological options for treating type 2 diabetes, there is a need for state-of-the-art evidence to inform clinical decisions about differences among the various medications. Recent systematic reviews and meta analyses of DPP-4 inhibitors have mainly focused on the clinical profiles of these drugs as a whole class [8–11]. For saxagliptin, only one meta-analysis [12] examined its efficacy based on 14 phase 2 and 3 trials, without systematically database searches. This systematic review synthesized currently available evidence to provide a better understanding of the comparative efficacy and safety of saxagliptin in treating type 2 diabetes.

Methods

Data sources and search strategy

This meta-analysis of the available data on saxagliptin was undertaken using a predetermined protocol, and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (see <u>S1 Text</u>) [13]. Relevant studies for the analysis were selected by searching PubMed, Embase, the Cochrane Library, Web of Science, and 2 Chinese databases [China National Knowledge Infrastructure (CNKI) and Chinese Biomedical Literature Database (CBM)] up to the end of July 2017. A complementary search was

performed in order to include the most recent articles (published before March 2018). The generic drug name "saxagliptin" was used as the only search term. If necessary, specific filters for retrieving randomized controlled trials (RCTs) conducted in humans were incorporated into the search string. We considered all potentially eligible studies for review, irrespective of the primary outcomes or language. We also performed a manual search using the reference lists of published reviews of saxagliptin.

The research questions and eligibility criteria for the systematic review conformed with the PICOS (participants, interventions, comparators, outcomes and study design) approach. Studies meeting the following criteria were considered for inclusion:

- Participants: patients over 18 years of age with type 2 diabetes.
- *Interventions*: saxagliptin used in the treatment of type 2 diabetes (as monotherapy or in dual or triple therapy).
- *Comparators*: placebo or other active antidiabetic interventions (as monotherapy or in dual or triple therapy).
- *Outcomes*: glycated hemoglobin (HbA1c), proportion of patients achieving HbA1c targets of <7%, fasting plasma glucose (FPG) concentration, overall and serious adverse events, body weight, confirmed hypoglycemia, heart failure, pancreatitis, arthralgia, and other adverse events [hypertension, urinary tract infection, upper respiratory tract infection, nasopharyngitis]. For continuous data, the mean change from baseline was examined.
- Study type: RCTs involving >150 patients.

Study selection and data extraction

The titles and abstracts of all retrieved citations were independently screened by 2 reviewers to identify potentially relevant studies. The full texts of relevant citations were then retrieved to determine their suitability for inclusion. If there were any discrepancies between the 2 reviewers, a third reviewer became involved.

Data were independently abstracted by the 2 principal reviewers and any discrepancies were resolved by consensus. The data extracted included study characteristics (design, total number of participants, trial duration, antidiabetic treatments, patient inclusion and exclusion criteria), patient demographics (age, sex, baseline HbA1c levels), and pre-specified efficacy and safety outcomes. For extension studies, if the treatment assignment was switched from placebo to saxagliptin, only the outcome data up to that point were documented. Only information that related to dosages currently approved by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) were abstracted. Corresponding authors were contacted for data not provided within studies, or when outcomes were presented in an unsuitable format for data synthesis.

Quality assessment

Two reviewers independently applied the Cochrane Risk of Bias tool to assessed the risk of bias in the RCTs. The following methodological features relevant to the minimization of bias were assessed: randomization, random allocation concealment, masking of treatment allocation, blinding, incomplete outcomes data, selective reporting, and other items. The following judgements were used: low risk, high risk, or unclear risk (either lack of information or uncertainty regarding the potential for bias). Disagreements were resolved by consensus with a third reviewer.

Data synthesis and analysis

Outcomes were pooled using Review Manager 5.2 software (RevMan, Cochrane, London, UK). For continuous data, estimates were pooled using inverse variance methodology to calculate weighted mean differences (WMDs). Dichotomous data were presented as Mantel-Haenzel risk ratios (RRs). All results were estimated from each study with 95% confidence intervals (CIs). Heterogeneity was assessed using the chi-square test and the I² statistic. If I² was 50%, a fixed-effect model with the Mantel-Haenszel method was used; otherwise, the random-effect model was adopted.

Where studies did not report standard deviations (SDs) explicitly, these were derived from the available published information. If possible, standard errors (SEs) were calculated from CIs. If these data were unavailable, they were derived from *p*-values for changes from baseline. All trials were included in at least one of the analyses, and each trial could be used in multiple sets of analyses. Data were reported first from studies involving placebo comparisons, and then from studies involving active comparators.

Results

The selection process for articles included in the systematic review is shown in Fig 1. From the 5773 citations identified by the initial and complementary literature searching, 38 references [14–51], including 30 trials involving 29,938 participants, ultimately met the inclusion criteria for the meta-analysis. The study characteristics and the demographics of the patient populations in the retrieved studies were comparable (Table 1). Enrolled patients in these RCTs had a mean age of 42.0 to 72.6 years. The mean duration of type 2 diabetes ranged from 0.4 to 16.7 years, with mean baseline HbA1c levels between 7.6% and 10.7%.

Quality of the included studies

A risk of bias summary is shown in S1a Fig, and an assessment of the risk of bias for each of the studies selected is shown in S1b Fig. Random sequence generation was adequate in 25 trials, and allocation concealment was adequately described in 16 trials. Two trials were considered to be at high risk of performance and detection bias. All studies were judged to be at low risk of attrition, reporting and other bias.

Glycemic control

Glycated hemoglobin (HbA1c). In comparison with placebo, saxagliptin produced significantly greater reductions in HbA1c (WMD -0.52%, 95% CI -0.60 to -0.44; p < 0.00001; Fig 2a), whether used as monotherapy (WMD -0.50%, 95% CI -0.62 to -0.37; p < 0.00001) or add-on therapy (WMD -0.52%, 95% CI -0.62 to -0.43; p < 0.00001). Both the 2.5 mg/day and 5 mg/day dosages of saxagliptin produced significant improvements in HbA1c, with similar absolute effect sizes.

Overall, saxagliptin produced similar reduction in HbA1c compared with active comparators when added to metformin (WMD 0.01%, 95% CI –0.11 to 0.13; p = 0.89; Fig 2b). Saxagliptin significantly reduced HbA1c in comparison with acarbose (WMD –0.12%, 95% CI –0.22 to –0.02; p = 0.02), but not compared with liraglutide (WMD 0.27%, 95% CI 0.09 to 0.45; p = 0.003) or dapagliflozin (WMD 0.32%, 95% CI 0.11 to 0.53; p = 0.003). Saxagliptin produced similar reduction compared with metformin (WMD -0.30%, 95% CI -0.74 to 0.13; p = 0.17), sulfonylureas (WMD 0.14%, 95% CI -0.02 to 0.30; p = 0.08), sitagliptin (WMD 0.10%, 95% CI -0.01 to 0.20; p = 0.07), vildagliptin (WMD 0.02%, 95% CI -0.15 to 0.19; p = 0.79) and repaglinide (WMD 0.30%, 95% CI -0.18 to 0.78; p = 0.22).





Fig 1. Selection process for articles in the systematic review.

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A significantly greater proportion of patients treated with saxagliptin also achieved a target HbA1c of <7% compared with placebo (RR 1.64, 95% CI 1.53 to 1.75; p < 0.00001; S2a Fig), whether used as monotherapy (RR 1.53, 95% CI 1.32 to 1.77; p < 0.00001) or add-on therapy (RR 1.67, 95% CI 1.55 to 1.81; p < 0.00001). Similar results was shown when compared with metformin (RR 1.30, 95% CI 1.04 to 1.63; p = 0.02) and acarbose (RR 2.38, 95% CI 1.17 to 4.83; p = 0.02). However, no significant differences were observed in comparisons of saxagliptin with other active comparators (S2b Fig).

Fasting plasma glucose (FPG). In comparison with placebo, saxagliptin produced significantly greater reductions in FPG (WMD –13.78 mg/dL, 95% CI –15.31 to –12.25; p < 0.00001; Fig 3a), whether used as monotherapy (WMD –14.89 mg/dL, 95% CI –20.14 to –9.64; p < 0.00001) or add-on therapy to other antidiabetic agents (WMD –13.68 mg/dL, 95%

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Trial No.	Reference, year	Clinicaltrial. gov No.	Trial duration (weeks)	n	Mean age (years)	Sex (male/ female)	Baseline HbA1c (%)	Baseline FPG (mg/ dL)	Baseline body weight (kg)	T2D duration (years)	Interventions	Added-on to
1	Barnett et al., 2012 [<u>14]</u>	NCT00757588	24	455	57.3	188/267	8.7	173.4	87.2	11.9	SAXA 5 mg/d PLB	INS
	Barnett et al., 2013 [<u>15</u>]		52									
2	Chacra et al., 2009 [<u>16</u>]	NCT00313313	24	768	55.0	346/422	8.4	173.4	75.7	6.9	SAXA 2.5 mg/d SAXA 5 mg/d PLB	GLY
	Chacra et al., 2011 [<u>17</u>]		76									
3	Chen et al., 2017 [<u>18</u>]	NCT02104804	24	462	59.1	209/253	8.5	167.6	NA	13.4	SAXA 5 mg/d PLB	INS±MET
4	DeFronzo et al., 2009 [<u>19</u>]	NCT00121667	24	743	54.6	NA	8.0	176.0	NA	6.5	SAXA 2.5 mg/d SAXA 5 mg/d	MET
	Rosenstock et al., 2013 [20]		206								SAXA 10 mg/d PLB	
5	Dou et al., 2017 [<u>21</u>]	NCT02273050	24	630	50.1	419/211	9.4	182.7	73.8	0.81	SAXA 5 mg/d PLB	MET
6	Du et al., 2017 [22]	NCT02243176	24	481	55.6	285/196	8.2	160.3	72.9	5.2	SAXA 5 mg/ dACBO 300 mg/d	MET
7	Fonseca et al., 2012 [23]	NCT00960076	18	282	55.3	130/152	8.4	162.9	NA	6.2	SAXA 5 mg/d MET (uptitrated to 2000 mg/d)	MET
8	Frederich et al., 2012 [24]	NCT00316082	76	365	54.8	168/197	7.9	162.1	84.9	1.7	SAXA 2.5 mg/d SAXA 5 mg/d PLB	-
9	Goke et al., 2010 [25]	NCT00575588	52	858	57.6	444/414	7.7	162.0	88.7	5.5	SAXA 5 mg/d GLPZ 5–20 mg/d	MET
	Goke et al., 2013 [<u>26</u>]		104									
10	Hermans et al., 2012 [27]	NCT01006590	24	286	58.7	164/122	7.8	169.8	NA	6.5	SAXA 5 mg/d MET (uptitrated to 2000 mg/d)	MET
11	Hollander et al., 2009 [28]	NCT00295633	24	565	54.0	280/285	8.3	162.9	81.1	5.2	SAXA 2.5 mg/d SAXA 5 mg/d PLB	TZD
	Hollander et al. 2011 [29]		76									
12	Jadzinsky et al., 2009 [<u>30</u>]	NCT00327015	24	1306	52.0	643/663	9.5	201.3	82.5	1.7	SAXA 5 mg/d SAXA 10 mg/d PLB	MET
	Pfutzner et al., 2011 [31]		76									
13	Kadowaki et al., 2017 [<u>32</u>]	1	16	240	63.4	139/89	8.3	163.1	65.5	15.8	SAXA 5 mg/d PLB	INS
14	Kumar et al., 2014 [<u>33]</u>	NCT00918879	24	213	49.1	120/93	8.3	151.2	69.6	0.9	SAXA 5 mg/d PLB	-
15	Li et al., 2014A [34]	1	24	207	46.6	109/81	8.7	153.1	74.4	NA	SAXA 5 mg/d SITA 100mg/d VIDA 100mg/d	MET + another OAD
16	Li et al., 2014B [35]	/	24	178	47.1	109/69	8.5	160.9	75.9	5.6	SAXA 5 mg/d VIDA 100mg/d LRAG 1.2mg/d	OAD
17	Lv et al., 2013 [36]	1	12	180	44.0	NA	7.8	150.2	82.0	0.5	SAXA 5 mg/d ACBO 150 mg/d	MET

Table 1. Patient demographics and study characteristics of the included studies.

(Continued)

Table 1. (Continued)

Trial No.	Reference, year	Clinicaltrial. gov No.	Trial duration (weeks)	n	Mean age (years)	Sex (male/ female)	Baseline HbA1c (%)	Baseline FPG (mg/ dL)	Baseline body weight (kg)	T2D duration (years)	Interventions	Added-on to
18	Matthaei et al., 2015 [37]	NCT01619059	24	315	54.6	149/166	7.9	161.0	NA	7.7	SAXA 5mg/d PLB	DAPA +MET
	Matthaei et al., 2016 [<u>38</u>]		52									
19	Moses et al., 2014 [39]	NCT01128153	24	257	57.0	154/103	8.3	159.3	81.4	-	SAXA 5 mg/d PLB	MET+SU
20	Nowicki et al., 2011 [<u>40,41</u>]	NCT00614939	12, 52	170	66.5	73/97	8.3	178.3	82.9	16.7	SAXA 2.5 mg/d PLB	-
21	Pan et al., 2012 [42]	NCT00698932	24	568	51.4	315/253	8.2	164.7	69.2	1.0	SAXA 5 mg/d PLB	-
22	Rosenstock et al., 2008 [43]	NCT00950599	12	338	54.0	197/141	7.9	164.7	89.9	1.1	SAXA 2.5 mg/d SAXA 5 mg/d SAXA 10 mg/d SAXA 20 mg/d SAXA 40 mg/d PLB	_
			6	85	52.1	50/35	7.7	148.7	91.2	0.4	SAXA 100 mg/d PLB	-
23	Rosenstock et al., 2009 [44]	NCT00121641	24	401	53.5	204/197	7.9	175.0	89.8	2.6	SAXA 2.5 mg/d SAXA 5 mg/d SAXA 10 mg/d PLB	-
	Rosenstock et al., 2013 [20]			68	49.1	79/82	10.7	241.0	91.4	3.1	SAXA 10 mg/d	-
24	Rosenstock et al., 2015 [45]	NCT01606007	24	534	54.0	268/266	8.9	186	NA	7.6	SAXA 5 mg/d DAPA 10 mg/d SAXA 5 mg/d + DAPA 10 mg/d	MET
25	Scheen et al., 2010 [46]	NCT00666458	18	801	58.4	392/409	7.7	161.1	NA	6.3	SAXA 5 mg/d SITA 100mg/d	MET
26	Schernthaner et al., 2015 [47]	NCT01006603	52	720	72.6	445/275	7.6	NA	NA	7.6	SAXA 5 mg/d ≤ 6 mg/d	MET
27	Scirica et al., 2013 [48]	NCT01107886	109	16492	65.1	11037/ 5455	8.0	156.5	87.9	10.3	SAXA 5 mg/d PLB	-
28	White et al., 2014 [49]	NCT00885378	12	160	55.7	85/75	8.0	163.1	NA	6.0	SAXA 5 mg/d PLB	MET
29	Xia et al., 2014 [50]	/	12	240	42.0	126/114	8.3	157.5	NA	1.0	SAXA 5 mg/d REGL 3 mg/d	MET
30	Yang et al., 2011 [51]	NCT00661362	24	570	54.1	275/295	7.9	159.3	69.0	5.1	SAXA 5 mg/d PLB	MET

ACBO, acarbose; DAPA, dapagliflozin; GLMR, glimepiride; GLPZ, glipizide; GLY, glyburide; INS, insulin; LINA, linagliptin; MET, metformin; NA, not available; PLB, placebo; REGL, repaglinide; SAXA, saxagliptin; SITA, sitagliptin; SU, sulfonylurea; TZD, thiazolidinedione; VIDA, vildagliptin.

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CI –15.28 to –12.08; p < 0.00001). Both the 2.5 mg/day and 5 mg/day dosages of saxagliptin produced significant improvements in FPG.

When added to metformin, saxagliptin produced a significantly smaller reduction in FPG compared with sulfonylureas (WMD 9.05 mg/dL, 95% CI 6.18 to 11.93; p < 0.00001), liraglutide (WMD 7.60 mg/dL, 95% CI 1.76 to 13.44; p = 0.01) and dapagliflozin (WMD 18.00 mg/dL, 95% CI 10.10 to 25.90; p < 0.00001). However, no significant differences were observed when saxagliptin was compared with other active comparators (Fig 3b), including sitagliptin

Study or Subgroup		eriment SD			ontrol SD	Total	Weight	Mean Difference IV, Random, 95%	CI	Mean Di IV, Rando	fference m. 95% Cl
1.1.1 SAXA 2.5 mg m	nonother	ару									
Frederich 2012 Nowicki 2011	-0.71 -1.35	0.84 1.54	67 78	-0.26 -0.53		68 82	3.9% 2.2%	-0.45 [-0.74, -0.1 -0.82 [-1.28, -0.3			
Rosenstock 2008	-0.72		51		0.87	62	3.5%	-0.45 [-0.77, -0.1			
Subtotal (95% CI)			196			212	9.6%	-0.52 [-0.72, -0.3	2]	•	
Heterogeneity: Tau ² = Fest for overall effect:					0.35); I	² = 4%					
				,							
.1.2 SAXA 2.5 mg ao Chacra 2009	dd-on th -0.54		246	0.08	0.93	264	6.1%	-0.62 [-0.78, -0.4	61 -		
DeFronzo 2009	-0.59		186	0.13		175	5.5%	-0.72 [-0.91, -0.5		-	
Iollander 2009	-0.66	1.03	192	-0.3	1.02	180	5.2%	-0.36 [-0.57, -0.1	5]		
Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect:					0.04); I	619 ² = 69%	16.9% %	-0.57 [-0.77, -0.3	8] •	•	
			00001	,							
.1.3 SAXA 5 mg mo rederich 2012	notherap -0.66		69	-0.26	0.85	68	4.0%	-0.40 [-0.68, -0.1	21		
Kumar 2014	-0.51		104	-0.05		105	4.1%	-0.46 [-0.74, -0.1			
Rosenstock 2008		0.91	42	-0.27		62	3.1%	-0.63 [-0.98, -0.2	8]	-	
Subtotal (95% CI)			215			235	11.1%	-0.48 [-0.65, -0.3	1]	•	
leterogeneity: Tau ² = est for overall effect:					0.60); I	² = 0%					
1.1.4 SAXA 5 mg add											
Barnett 2012	-0.73		300	-0.32	0.9	149	5.8%	-0.41 [-0.59, -0.2			
Chacra 2009	-0.64	0.93	250	0.08	0.93	264	6.1%	-0.72 [-0.88, -0.5	6]	-	
Chen 2017	-0.64	0.73	229	-0.06		227	7.1%	-0.58 [-0.69, -0.4		_	
DeFronzo 2009 Dou 2017	-0.69 -3	0.95 1.01	186 209	0.13 -2.8	0.93 1	175 204	5.5% 5.5%	-0.82 [-1.01, -0.6	3] 1]		
Jou 2017 Hollander 2009	-0.94	1.01	209 183	-2.8 -0.3	1 1.02	204 180	5.5% 5.2%	-0.20 [-0.39, -0.0 -0.64 [-0.85, -0.4		-	
Matthaei 2015	-0.54	0.74	139	-0.16	0.74	149	5.9%	-0.35 [-0.52, -0.1			
Moses 2014	-0.74	0.83	127	-0.08	0.46	127	6.1%	-0.66 [-0.83, -0.4	9] -	-	
futzner 2011	-2.31	1.22	303	-1.79	1.23	308	5.5%	-0.52 [-0.71, -0.3			
Rosenstock 2015	-1.47 -0.56	1.01	158	-1.2	1	151	4.9%	-0.27 [-0.49, -0.0			
White 2014 Subtotal (95% CI)	-0.56	0.77	74 2158	-0.22	0.73	84 2018	4.7% 62.4%	-0.34 [-0.57, -0.1 -0.51 [-0.62, -0.4		•	
Heterogeneity: Tau ² =	0.03; CH	ni² = 42.	94, df	= 10 (P	< 0.00	001); l ^a		,	.,		
Fest for overall effect:	Z = 8.89	P < 0.	00001)							
Γotal (95% Cl) Heterogeneity: Tau² =	0.02. CF		3193 84 df	- 10 /P			100.0%	-0.52 [-0.60, -0.4	4]	•	
Test for overall effect:					- 0.00	01), 1	0070		-1 Favours (s	-0.5 0	0.5 1 Favours [placebo]
										0. 1	
(b)											
	Expe	eriment	al	<u> </u>	ontrol			Mean Difference		Mean Di	fference
	Maan	e D				Total	Mainht				
	Mean ormin	SD				Total	Weight	IV, Random, 95% (m, 95% Cl
1.2.1 SAXA vs metfo		<u>SD</u> 0.9	Total 137		SD	Total 142	48.8%	IV. Random, 95% 0]		m, 95% Cl
1.2.1 SAXA vs metfo Fonseca 2012 Hermans 2012	ormin -0.88		<u>Total</u> 137 146	Mean	SD	142 137	48.8% 51.2%	IV. Random. 95% (-0.53 [-0.74, -0.32 -0.09 [-0.26, 0.08]]		<u>m, 95% Cl</u>
1.2.1 SAXA vs metfo Fonseca 2012 Hermans 2012 Subtotal (95% CI)	ormin -0.88 -0.47	0.9 0.72	Total 137 146 283	Mean -0.35 -0.38	SD 0.91 0.7	142 137 279	48.8% 51.2% 100.0%	IV. Random, 95% 0]		m, 95% Cl - -
1.2.1 SAXA vs metfo Fonseca 2012 Hermans 2012 Subtotal (95% CI) Heterogeneity: Tau ² =	ormin -0.88 -0.47 = 0.09; Cł	0.9 0.72 hi² = 10.	137 146 283 26, df :	Mean -0.35 -0.38	SD 0.91 0.7	142 137 279	48.8% 51.2% 100.0%	IV. Random. 95% (-0.53 [-0.74, -0.32 -0.09 [-0.26, 0.08]]		m, 95% Cl - -
1.2.1 SAXA vs metfo Fonseca 2012 Hermans 2012 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect:	-0.88 -0.47 = 0.09; Cf : Z = 1.39	0.9 0.72 hi² = 10.	137 146 283 26, df :	Mean -0.35 -0.38	SD 0.91 0.7	142 137 279	48.8% 51.2% 100.0%	IV. Random. 95% (-0.53 [-0.74, -0.32 -0.09 [-0.26, 0.08]]		m. 95% Cl - -
1.2.1 SAXA vs metfo Fonseca 2012 Hermans 2012 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.2.2 SAXA vs sitagl	-0.88 -0.47 = 0.09; Cf : Z = 1.39	0.9 0.72 hi² = 10.	Total 137 146 283 26, df = 17)	Mean -0.35 -0.38	SD 0.91 0.7 0.001)	142 137 279	48.8% 51.2% 100.0%	<u>IV. Random. 95% (</u> -0.53 [-0.74, -0.32 -0.09 [-0.26, 0.08 -0.30 [-0.74, 0.13]]		m, 95% Cl
1.2.1 SAXA vs metfo Fonseca 2012 Hermans 2012 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.2.2 SAXA vs sitagl Li 2014 A Scheen 2010	-0.88 -0.47 = 0.09; Cf : Z = 1.39 liptin -1.21	0.9 0.72 hi ² = 10. 9 (P = 0.	Total 137 146 283 26, df = 17) 66 334	<u>-0.35</u> -0.38 = 1 (P =	SD 0.91 0.7 0.001)	142 137 279 ; I ² = 9 61 343	48.8% 51.2% 100.0% 0% 1.4% 98.6%	IV. Random, 95% C -0.53 [-0.74, -0.32 -0.09 [-0.26, 0.08 -0.30 [-0.74, 0.13] -0.14 [-1.04, 0.76 0.10 [-0.01, 0.21]]]] —		m, 95% Cl
1.2.1 SAXA vs metfo Fonseca 2012 Hermans 2012 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.2.2 SAXA vs sitagl Li 2014 A Scheen 2010 Subtotal (95% CI)	-0.88 -0.47 = 0.09; CP : Z = 1.39 liptin -1.21 -0.52	0.9 0.72 hi ² = 10. 9 (P = 0. 2.9 0.71	Total 137 146 283 26, df = 17) 66 334 400	-0.35 -0.38 = 1 (P = -1.07 -0.62	SD 0.91 0.7 : 0.001) 2.27 0.7	142 137 279 1; 1 ² = 9 61 343 404	48.8% 51.2% 100.0% 0%	IV. Random, 95% (-0.53 [-0.74, -0.32 -0.09 [-0.26, 0.08 -0.30 [-0.74, 0.13] -0.14 [-1.04, 0.76]]]] —		m. 95% Cl - -
1.2.1 SAXA vs metfo Fonseca 2012 Hermans 2012 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.2.2 SAXA vs sitagi Li 2014 A Scheen 2010 Subtotal (95% CI) Heterogeneity: Tau ² =	-0.88 -0.47 = 0.09; Cf : Z = 1.39 liptin -1.21 -0.52 = 0.00; Cf	$0.9 \\ 0.72 \\ hi^2 = 10 \\ 0 (P = 0. \\ 2.9 \\ 0.71 \\ hi^2 = 0.2 \\ 0.2$	Total 137 146 283 26, df = 17) 66 334 400 7, df =	-0.35 -0.38 = 1 (P = -1.07 -0.62	SD 0.91 0.7 : 0.001) 2.27 0.7	142 137 279 1; 1 ² = 9 61 343 404	48.8% 51.2% 100.0% 0% 1.4% 98.6%	IV. Random, 95% C -0.53 [-0.74, -0.32 -0.09 [-0.26, 0.08 -0.30 [-0.74, 0.13] -0.14 [-1.04, 0.76 0.10 [-0.01, 0.21]]]] —		m. 95% Cl
1.2.1 SAXA vs metfo Fonseca 2012 Subtotal (85% CI) Heterogeneity: Tav ² = Test for overall effect: 1.2.2 SAXA vs sitagl Li 2014 A Scheen 2010 Subtotal (85% CI) Heterogeneity: Tav ² = Test for overall effect:	ormin -0.88 -0.47 : Z = 1.39 iptin -1.21 -0.52 = 0.00; CP : Z = 1.80	$0.9 \\ 0.72 \\ hi^2 = 10 \\ 0 (P = 0. \\ 2.9 \\ 0.71 \\ hi^2 = 0.2 \\ 0.2$	Total 137 146 283 26, df = 17) 66 334 400 7, df =	-0.35 -0.38 = 1 (P = -1.07 -0.62	SD 0.91 0.7 : 0.001) 2.27 0.7	142 137 279 1; 1 ² = 9 61 343 404	48.8% 51.2% 100.0% 0% 1.4% 98.6%	IV. Random, 95% C -0.53 [-0.74, -0.32 -0.09 [-0.26, 0.08 -0.30 [-0.74, 0.13] -0.14 [-1.04, 0.76 0.10 [-0.01, 0.21]]]] —		m. 95% Cl
1.2.1 SAXA vs metfo Fonseca 2012 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.2.2 SAXA vs sitagl Li 2014 A Scheen 2010 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.2.3 SAXA vs vildag	ormin -0.88 -0.47 : Z = 1.39 iptin -1.21 -0.52 = 0.00; CP : Z = 1.80	$0.9 \\ 0.72 \\ hi^2 = 10 \\ 0 (P = 0. \\ 2.9 \\ 0.71 \\ hi^2 = 0.2 \\ 0.2$	Total 137 146 283 26, df = 17) 66 334 400 7, df = 07)	-0.35 -0.38 = 1 (P = -1.07 -0.62	SD 0.91 0.7 = 0.001) 2.27 0.7 0.60); I [*]	142 137 279 1; 1 ² = 9 61 343 404	48.8% 51.2% 100.0% 0% 1.4% 98.6%	IV. Random, 95% C -0.53 [-0.74, -0.32 -0.09 [-0.26, 0.08 -0.30 [-0.74, 0.13] -0.14 [-1.04, 0.76 0.10 [-0.01, 0.21]] 		m. 95% Cl - -
1.2.1 SAXA vs metfo Fonseca 2012 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.2.2 SAXA vs sitagl Li 2014 A Scheen 2010 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.2.3 SAXA vs vildag Li 2014 A Li 2014 B	ormin -0.88 -0.47 = 0.09; CH : Z = 1.39 liptin -1.21 -0.52 = 0.00; CH : Z = 1.80 gliptin	0.9 0.72 hi ² = 10. 9 (P = 0. 2.9 0.71 hi ² = 0.2 9 (P = 0.	Total 137 146 283 26, df = 17) 66 334 400 7, df = 07) 66 60	-0.35 -0.38 = 1 (P = -1.07 -0.62 1 (P = 0	SD 0.91 0.7 : 0.001) 2.27 0.7 0.60); I ² 2.82	142 137 279 5, 1 ² = 91 61 343 404 ² = 0% 63 57	48.8% 51.2% 100.0% 0% 1.4% 98.6% 100.0% 3.0% 97.0%	IV. Random. 95% O -0.53 [-0.74, -0.32 -0.09 [-0.26, 0.08 -0.30 [-0.74, 0.13] -0.14 [-1.04, 0.76 0.10 [-0.01, 0.21] 0.10 [-0.01, 0.20] 0.13 [-0.86, 1.12 0.02 [-0.15, 0.19			m. 95% Cl
1.2.1 SAXA vs metfo Fonseca 2012 Bubtotal (85% CI) Heterogeneity: Tau ² = Test for overall effect: 1.2.2 SAXA vs sitagl Li 2014 A Scheen 2010 Subtotal (85% CI) Heterogeneity: Tau ² = Test for overall effect: 1.2.3 SAXA vs vildag Li 2014 A Li 2014 B Subtotal (85% CI)	ormin -0.88 -0.47 = 0.09; CF : Z = 1.39 liptin -1.21 -0.52 = 0.00; CF : Z = 1.80 gliptin -1.21 -1.23	0.9 0.72 hi ² = 10. P = 0. 0.71 hi ² = 0.2 P = 0. (P = 0. 2.9 0.5	Total 137 146 283 26, df = 17) 66 334 400 7, df = 07) 66 60 126	Mean -0.35 -0.38 = 1 (P = -1.07 -0.62 1 (P = 0 -1.34 -1.25	SD 0.91 0.7 0.001) 2.27 0.7 0.60); I ² 2.82 0.46	$ \begin{array}{c} 142\\ 137\\ 279\\ 61\\ 343\\ 404\\ 5=0\%\\ 63\\ 57\\ 120\\ \end{array} $	48.8% 51.2% 100.0%)% 1.4% 98.6% 100.0% 3.0%	IV. Random. 95% C -0.53 [-0.74, -0.32 -0.09 [-0.26, 0.08 -0.30 [-0.74, 0.13] -0.14 [-1.04, 0.76 0.10 [-0.01, 0.21 0.10 [-0.01, 0.20] 0.13 [-0.86, 1.12			m. 95% Cl
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1.2.1 SAXA vs metfo Fonseca 2012 Hermans 2012 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.2.2 SAXA vs situag Li 2014 A Scheen 2010 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.2.3 SAXA vs vildag Li 2014 B Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.2.4 SAXA vs sulfor	ormin -0.88 -0.47 = 0.09; Cł Z = 1.39 liptin -1.21 -0.52 = 0.00; Cł Z = 1.80 gliptin -1.21 -1.23 = 0.00; Cł Z = 0.00; Cł Z = 0.00; Cł Z = 0.00; Cł	$\begin{array}{c} 0.9\\ 0.72\\ \text{hi}^2 = 10.\\ 0 \ (\text{P} = 0.\\ 2.9\\ 0.71\\ \text{hi}^2 = 0.2\\ 0 \ (\text{P} = 0.\\ 2.9\\ 0.5\\ \text{hi}^2 = 0.0\\ 7\ (\text{P} = 0.\\ 7\ (\text{P} = 0.\\ 10.\\ 10.\\ 10.\\ 10.\\ 10.\\ 10.\\ 10.\\ $	Total 137 146 283 26, df = 17) 66 334 400 7, df = 07) 66 60 126 5, df =	Mean -0.35 -0.38 = 1 (P = -1.07 -0.62 1 (P = 0 -1.34 -1.25	SD 0.91 0.7 0.001) 2.27 0.7 0.60); I ² 2.82 0.46 0.83); I ²	$ \begin{array}{c} 142\\ 137\\ 279\\ 61\\ 343\\ 404\\ 5=0\%\\ 63\\ 57\\ 120\\ \end{array} $	48.8% 51.2% 100.0% 0% 1.4% 98.6% 100.0% 3.0% 97.0%	IV. Random. 95% 0 -0.53 [-0.74, -0.32 -0.09 [-0.26, 0.08 -0.30 [-0.74, 0.13] -0.14 [-1.04, 0.76 0.10 [-0.01, 0.21 0.10 [-0.01, 0.21] 0.13 [-0.86, 1.12 0.02 [-0.15, 0.19] 0.02 [-0.15, 0.19]	1 1 1 1		m. 95% Cl
1.2.1 SAXA vs metfo Fonseca 2012 Hermans 2012 Subtotal (95% Cl) Heterogeneity: Tau ² = Test for overall effect: 1.2.2 SAXA vs sittag Li 2014 A Subtotal (95% Cl) Heterogeneity: Tau ² = Test for overall effect: 1.2.3 SAXA vs vildag Li 2014 A Subtotal (95% Cl) Heterogeneity: Tau ² = Test for overall effect: 1.2.4 SAXA vs sulfor Goke 2013 Schernthaner 2015	ormin -0.88 -0.47 = 0.09; Cł Z = 1.39 liptin -1.21 -0.52 = 0.00; Cł Z = 1.80 gliptin -1.21 -1.23 = 0.00; Cł Z = 0.00; Cł Z = 0.00; Cł Z = 0.00; Cł	$\begin{array}{c} 0.9\\ 0.72\\ \text{hi}^2=10.\\ 0\ (P=0.\\ 2.9\\ 0.71\\ \text{hi}^2=0.2\\ 0\ (P=0.\\ 2.9\\ 0.5\\ \text{hi}^2=0.0\\ 7\ (P=0.\\ 3\\ 0.65\\ \end{array}$	Total 137 146 283 26, df = 334 400 7, df = 07) 66 60 126 5, df = 79) 293 353	Mean -0.35 -0.38 = 1 (P = -1.07 -0.62 1 (P = 0 -1.34 -1.25 1 (P = 0	SD 0.91 0.7 0.001) 2.27 0.7 0.60); I ² 2.82 0.46 0.83); I ² 0.65	$\begin{array}{c} 142\\ 137\\ 279\\ \vdots \ ^2=9\\ 61\\ 343\\ 404\\ 2^2=0\%\\ 63\\ 57\\ 120\\ 2=0\%\\ 293\\ 345\end{array}$	48.8% 51.2% 100.0% 0% 1.4% 98.6% 100.0% 3.0% 97.0% 100.0% 49.3% 50.7%	IV. Random. 95% 0 -0.53 [-0.74, -0.32 -0.09 [-0.26, 0.08 -0.30 [-0.74, 0.13] -0.14 [-1.04, 0.76 0.10 [-0.01, 0.21 0.10 [-0.01, 0.20] 0.13 [-0.86, 1.12 0.02 [-0.15, 0.19] 0.02 [-0.15, 0.19] 0.06 [-0.05, 0.17 0.22 [0.12, 0.32			m. 95% Cl
1.2.1 SAXA vs metfo Fonseca 2012 Subtotal (85% CI) Heterogeneity: Tau ² = Test for overall effect: 1.2.2 SAXA vs sitagl Li 2014 A Scheen 2010 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.2.3 SAXA vs villag Li 2014 A Li 2014 B Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.2.4 SAXA vs sulfor Goke 2013 Schernthaner 2015 Schernthaner 2015	ormin -0.88 -0.47 = 0.09; Cf: z Z = 1.39 liptin -1.21 -0.52 = 0.00; Cf: z Z = 1.80 gliptin -1.21 -1.23 = 0.00; Cf: z Z = 0.27 nylureas -0.74 -0.44	$\begin{array}{c} 0.9\\ 0.72\\ \text{hi}^2 = 10.\\ 9 \ (\text{P}=0.\\ 2.9\\ 0.71\\ \text{hi}^2 = 0.2\\ 0 \ (\text{P}=0.\\ 2.9\\ 0.5\\ \text{hi}^2 = 0.0\\ 7 \ (\text{P}=0.\\ 3\\ 0.65\\ 0.67\\ \end{array}$	Total 137 134 283 26, df = 177 66 334 400 7, df = 077 66 60 126 5, df = 79) 293 353 646 648	Mean0.35 -0.38 = 1 (P = -1.07 -0.62 1 (P = (-1.34 -1.25 1 (P = (-0.8 -0.66	SD 0.91 0.7 0.001) 2.27 0.7 0.001) 2.27 0.7 0.001) 2.27 0.7 0.01) 2.82 0.46 0.83); F 0.65 0.66	$\begin{array}{c} 142\\ 37\\ 279\\ 0\\ 1343\\ 404\\ 2^{2}=0\%\\ 63\\ 57\\ 120\\ 2^{2}=0\%\\ 293\\ 345\\ 638\\ \end{array}$	48.8% 51.2% 100.0% 98.6% 100.0% 3.0% 97.0% 100.0% 49.3% 50.7% 100.0%	IV. Random. 95% 0 -0.53 [-0.74, -0.32 -0.09 [-0.26, 0.08 -0.30 [-0.74, 0.13] -0.14 [-1.04, 0.76 0.10 [-0.01, 0.21 0.10 [-0.01, 0.21] 0.13 [-0.86, 1.12 0.02 [-0.15, 0.19] 0.02 [-0.15, 0.19]			m. 95% Cl
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1.2.1 SAXA vs metfo Fonseca 2012 Hermans 2012 Subtotal (05% CI) Heterogeneity: Tau ² = Test for overall effect: 1.2.2 SAXA vs sittagi Li 2014 A Scheen 2010 Subtotal (05% CI) Heterogeneity: Tau ² = Test for overall effect: 1.2.3 SAXA vs vildag Li 2014 A Li 2014 A Li 2014 A Li 2014 A Schemthaner 2015 Subtotal (05% CI) Heterogeneity: Tau ² = Test for overall effect: 1.2.5 SAXA vs acarb Du 2017 Lv 2013 Subtotal (05% CI) Heterogeneity: Tau ² = Test for overall effect: 1.2.5 SAXA vs acarb Du 2017 Lv 2013 Subtotal (05% CI) Heterogeneity: Tau ² = Test for overall effect: 1.2.6 SAXA vs acarb Du 2017 Lv 2013 Subtotal (05% CI) Heterogeneity: Not ag Test for overall effect: 1.2.7 SAXA vs dapag Rosenstock 2015 Subtotal (05% CI) Heterogeneity: Not ag Test for overall effect: 1.2.8 SAXA vs liragli Li 2014 B Subtotal (05% CI)	$\begin{tabular}{lllllllllllllllllllllllllllllllllll$	$\begin{array}{c} 0.9\\ 0.72\\ 0.72\\ 0.72\\ 0.72\\ 0.72\\ 0.72\\ 0.71\\ 0.71\\ 0.71\\ 0.71\\ 0.71\\ 0.71\\ 0.71\\ 0.71\\ 0.72\\ 0.71\\ 0.72\\ 0.71\\ 0.72\\ $	Total 137 146 283 26, df : 177 66 60 334 400 7, df = 077 26, df : 734 400 726 66 60 126 79) 293 353 646 90 228 120 1220 175 175 003)	Mean -0.35 -0.38 = 1 (P = -1.07 -0.62 1 (P = (-1.34 -1.25 1 (P = (-0.8 -0.66 1 (P = (-0.78 1 (P = (-0.78 -0.82 -1.6 -1.6 -1.2	SD 0.91 0.7 0.001) 2.27 0.7 0.7 0.60); F 2.82 0.46 0.46 0.65 0.66 0.03); F 0.94 0.3 0.27); F 1.93 1.01	$\begin{array}{c} 142\\ 137\\ 279\\ 61\\ 343\\ 404\\ =0\%\\ 63\\ 57\\ 120\\ =0\%\\ 293\\ 345\\ 638\\ =79\%\\ 243\\ 90\\ 333\\ =18\%\\ 120\\ 120\\ 120\\ 120\\ 172\\ 172\\ 172\\ 61\end{array}$	48.8% 51.2% 51.2% 91.6% 100.0% 98.6% 100.0% 100.0% 49.3% 69.3% 100.0% 69.3% 100.0% 100.0% 100.0%	IV. Random. 95% 0 -0.53 [-0.74, -0.32 -0.09 [-0.26, 0.08 -0.30 [-0.74, 0.13] -0.14 [-1.04, 0.76 0.10 [-0.01, 0.21 0.10 [-0.01, 0.21 0.10 [-0.01, 0.21 0.10 [-0.01, 0.20] 0.13 [-0.86, 1.12 0.02 [-0.15, 0.19] 0.02 [-0.15, 0.19] 0.02 [-0.15, 0.19] 0.06 [-0.05, 0.17 0.22 [0.12, 0.32 0.14 [-0.2, 0.30] -0.04 [-0.21, 0.13 -0.15 [-0.25, -0.05 -0.12 [-0.22, -0.02] 0.30 [-0.18, 0.78] 0.30 [-0.18, 0.78] 0.32 [0.11, 0.53]			
1.2.1 SAXA vs metfo Fonseca 2012 Hermans 2012 Subtotal (95% Cl) Heterogeneily: Tau ² = Test for overall effect: 1.2.2 SAXA vs sittagt Li 2014 A Scheen 2010 Subtotal (95% Cl) Heterogeneily: Tau ² = Test for overall effect: 1.2.3 SAXA vs vildaç Li 2014 A Li 2014 A Li 2014 A Subtotal (95% Cl) Heterogeneily: Tau ² = Test for overall effect: 1.2.4 SAXA vs sulfor Coke 2013 Schemthaner 2015 Subtotal (95% Cl) Heterogeneily: Tau ² = Test for overall effect: 1.2.5 SAXA vs acarb Du 2017 Li 2014 (95% Cl) Heterogeneily: Tau ² = Test for overall effect: 1.2.6 SAXA vs acarb Li 2014 Subtotal (95% Cl) Heterogeneily: Not ag Test for overall effect: 1.2.7 SAXA vs dapaq Rosenstock 2015 Subtotal (95% Cl) Heterogeneily: Not ag Test for overall effect: 1.2.8 SAXA vs liragli Li 2014 B Subtotal (95% Cl) Heterogeneily: Not ag Test for overall effect: 1.2.8 SAXA vs liragli Li 2014 B Subtotal (95% Cl) Heterogeneily: Not ag	$\begin{tabular}{lllllllllllllllllllllllllllllllllll$	$\begin{array}{c} 0.9\\ 0.72\\ 0.72\\ 0 \ (P=0, \\ 2.9\\ 0.71\\ 0 \ (P=0, \\ 0.71\\ 0 \ (P=0, \\ 0.71\\ 0 \ (P=0, \\ 0.5\\ 0.67\\ 0.65\\ 0.67\\ 0.7\\ 0.93\\ 0.73\\ 0.93\\ 0.73\\ 0 \ (P=0, \\ 0.93\\ 0.73\\ 0 \ (P=0, \\ 0.73\\ 0 \$	Total 137 146 283 26, dr1 177 66 334 400 07 66 07 70 66 00 126 5, dr = 79) 293 353 646 90 328 3.0 dr = 002) 120 120 1220 175 0003) 60 60	Mean -0.35 -0.38 = 1 (P = -1.07 -0.62 1 (P = (-1.34 -1.25 1 (P = (-0.8 -0.66 1 (P = (-0.78 1 (P = (-0.78 -0.82 -1.6 -1.6 -1.2	SD 0.91 0.7 0.001) 2.27 0.7 0.7 0.60); F 2.82 0.46 0.46 0.65 0.66 0.03); F 0.94 0.3 0.27); F 1.93 1.01	$\begin{array}{c} 142\\ 137\\ 279\\ 61\\ 343\\ 404\\ =0\%\\ 63\\ 57\\ 120\\ =0\%\\ 293\\ 345\\ 638\\ =79\%\\ 243\\ 90\\ 333\\ =18\%\\ 120\\ 120\\ 120\\ 120\\ 172\\ 172\\ 172\\ 61\end{array}$	48.8% 51.2% 51.2% 1.4% 98.6% 98.6% 97.0% 100.0% 49.3% 50.7% 100.0% 49.3% 100.0% 100.0% 100.0% 100.0%	IV. Random. 95% C -0.53 [-0.74, -0.32 -0.09 [-0.26, 0.08 -0.30 [-0.74, 0.13] -0.14 [-1.04, 0.76 0.10 [-0.01, 0.21 0.10 [-0.01, 0.21 0.13 [-0.86, 1.12 0.02 [-0.15, 0.19] 0.02 [-0.15, 0.19] 0.06 [-0.05, 0.17 0.22 [0.12, 0.32 0.14 [-0.22, -0.02] -0.04 [-0.21, 0.13 -0.15 [-0.25, -0.05 -0.12 [-0.22, -0.02] 0.30 [-0.18, 0.78 0.32 [0.11, 0.53] 0.32 [0.11, 0.53] 0.27 [0.09, 0.45			m. 95% Cl
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Fig 2. Mean change of HbA1c from baseline (a. saxagliptin vs placebo; b. saxagliptin vs active comparators).

	Mean		r Total		ontrol SD	Total	Weight	Mean Difference IV, Fixed, 95% C	Mean Difference I IV. Fixed, 95% CI
1.3.1 SAXA 2.5mg m Frederich 2012	onotherap -11.4	ру 37.6	70	3.3	37.6	72	1.5%	-14.70 [-27.07, -2.33]	
Rosenstock 2008	-10.85	32.6	50	2.81	32.5	63	1.6%	-13.66 [-25.75, -1.57]	
Subtotal (95% CI)			120			135	3.1%	-14.17 [-22.81, -5.52]	
Heterogeneity: Chi ² = Test for overall effect:				= 0%					
			,						
1.3.2 SAXA 2.5 mg a Chacra 2009	dd-on the -7.1	rapy 38	247	0.7	37.9	265	5.4%	-7.80 [-14.38, -1.22]	
DeFronzo 2009	-14.3	34	188	1.2	34	176	4.8%	-15.50 [-22.49, -8.51]	
Hollander 2009	-14.3	39.9	193	-2.8	40	181	3.6%	-11.50 [-19.60, -3.40]	
Subtotal (95% CI) Heterogeneity: Chi ² =	2 47 df -	2 (P = 0	628	- 10%		622	13.8%	-11.44 [-15.56, -7.31]	▼
Test for overall effect:				- 1376					
1.3.4 SAXA 5mg mor	notherapy								
Frederich 2012	-10.7	37.6	71	3.3	37.6	72	1.5%	-14.00 [-26.33, -1.67]	
Kumar 2014	-10.45	38.4	106	-0.36	36.2	104	2.3%	-10.09 [-20.18, 0.00]	
Rosenstock 2008 Subtotal (95% CI)	-21.68	32.6	46 223	2.81	32.5	63 239	1.5% 5.4%	-24.49 [-36.87, -12.11] -15.31 [-21.92, -8.71]	
Heterogeneity: Chi ² =	3.18, df =	2 (P = 0		= 37%		200	0.470	10.01[21.02, 0.11]	-
Test for overall effect:	Z = 4.54 (P < 0.00	001)						
1.3.5 SAXA 5 mg add	d-on thera	ру							
Barnett 2012	-10.08	49.7	300	-6.06	48.6	149	2.5%	-4.02 [-13.64, 5.60]	
Chacra 2009 Chen 2017	-9.7 -11.16	37.9 32.9	252 232	0.7 4.68	37.9 32.69	265 229	5.5% 6.6%	-10.40 [-16.94, -3.86]	
DeFronzo 2009	-11.16 -22	32.9 34.1	232 187	4.68	32.69 34	229 176	4.8%	-15.84 [-21.83, -9.85] -23.20 [-30.21, -16.19]	
Dou 2017	-58.5	28.7	210	-52.9	28.5	207	7.8%	-5.60 [-11.09, -0.11]	
Hollander 2009 Kadowski, 2017	-17.3	40	185	-2.8	40	181	3.5%	-14.50 [-22.70, -6.30]	
Kadowaki 2017 Matthaei 2015	11.2 -9.1	10.79 31.2	113 139	30.3 -5.3	10.54 31.3	115 146	30.6% 4.5%	-19.10 [-21.87, -16.33] -3.80 [-11.06, 3.46]	
Moses 2014	-5.25	41.5	121	2.72	40.1	123	2.2%	-7.97 [-18.21, 2.27]	
Pfutzner 2011	-54	46.1	315	-40	50.1	320	4.2%	-14.00 [-21.49, -6.51]	
Rosenstock 2015 White 2014	-38 -13.7	37.2 38.5	176 73	-32 -4.22	36.7 38.5	172 84	3.9% 1.6%	-6.00 [-13.76, 1.76] -9.48 [-21.55, 2.59]	.
Subtotal (95% CI)	-13.7		2303	4.22	50.5	2167		-14.08 [-15.82, -12.34]	♦
Heterogeneity: Chi ² =				001); l²	= 77%				
Test for overall effect:	∠ = 15.87	ر۳ < 0.0	10001)						.
Total (95% CI)			3274			3163	100.0%	-13.78 [-15.31, -12.25]	· · · · · · · · · · · · · · · · · · ·
Heterogeneity: Chi ² = Test for overall effect:)1); I* =	66%				-20 -10 0 10 20
	2 11.00	(1 . 0.0							Favours [saxagliptin] Favours [placebo
(b)	_								
Study or Subgroup		erimenta SD			ontrol SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV. Random, 95% Cl
1.4.1 SAXA vs metfe									
Fonseca 2012 Hermans 2012	-20	36.8	137	-6.85	36.8	142	49.6%	-13.15 [-21.79, -4.51]	
Subtotal (95% CI)	-19.4	34.9	146 283	-20.6		137	50.4%	1.20 [-7.07, 9.47]	
Subtotal (95% CI) Heterogeneity: Tau ²	-19.4 = 84.35; C	34.9 hi² = 5.5	146 283 3, df =	-20.6	36	137 279			
Subtotal (95% CI)	-19.4 = 84.35; C	34.9 hi² = 5.5	146 283 3, df =	-20.6	36	137 279	50.4%	1.20 [-7.07, 9.47]	-
Subtotal (95% CI) Heterogeneity: Tau ² Test for overall effect 1.4.2 SAXA vs sitag	-19.4 = 84.35; C I: Z = 0.82	34.9 hi² = 5.5 (P = 0.4	146 283 3, df = 1)	-20.6 1 (P = 0	36).02); I²	137 279 = 82%	50.4% 100.0%	1.20 [-7.07, 9.47] -5.92 [-19.98, 8.14]	
Subtotal (95% CI) Heterogeneity: Tau ² Test for overall effect 1.4.2 SAXA vs sitag Li 2014 A	-19.4 = 84.35; C t: Z = 0.82 liptin -33	34.9 hi ² = 5.53 (P = 0.4 22.4	146 283 3, df = 1) 66	-20.6 1 (P = 0 -26.8	36).02); I² 14.3	137 279 = 82%	50.4% 100.0% 47.5%	1.20 [-7.07, 9.47] -5.92 [-19.98, 8.14] -6.20 [-12.69, 0.29]	-
Subtotal (95% CI) Heterogeneity: Tau ² Test for overall effect 1.4.2 SAXA vs sitag	-19.4 = 84.35; C I: Z = 0.82	34.9 hi² = 5.5 (P = 0.4	146 283 3, df = 1)	-20.6 1 (P = 0	36).02); I²	137 279 = 82% 61 392	50.4% 100.0%	1.20 [-7.07, 9.47] -5.92 [-19.98, 8.14]	
Subtotal (95% CI) Heterogeneity: Tau ² : Test for overall effect 1.4.2 SAXA vs sitag Li 2014 A Scheen 2010 Subtotal (95% CI) Heterogeneity: Tau ² :	-19.4 = 84.35; Cl t: Z = 0.82 liptin -33 -10.8 = 59.21; Cl	34.9 hi ² = 5.5 (P = 0.4 22.4 29 hi ² = 8.7	146 283 3, df = 1) 66 397 463 8, df =	-20.6 1 (P = 0 -26.8 -16.16	36).02); I ² 14.3 29	137 279 = 82% 61 392 453	50.4% 100.0% 47.5% 52.5% 100.0%	1.20 [-7.07, 9.47] -5.92 [-19.98, 8.14] -6.20 [-12.69, 0.29] 5.36 [1.31, 9.41]	
Subtotal (95% CI) Heterogeneity: Tau ² Test for overall effect 1.4.2 SAXA vs sitag Li 2014 A Scheen 2010 Subtotal (95% CI)	-19.4 = 84.35; Cl t: Z = 0.82 liptin -33 -10.8 = 59.21; Cl	34.9 hi ² = 5.5 (P = 0.4 22.4 29 hi ² = 8.7	146 283 3, df = 1) 66 397 463 8, df =	-20.6 1 (P = 0 -26.8 -16.16	36).02); I ² 14.3 29	137 279 = 82% 61 392 453	50.4% 100.0% 47.5% 52.5% 100.0%	1.20 [-7.07, 9.47] -5.92 [-19.98, 8.14] -6.20 [-12.69, 0.29] 5.36 [1.31, 9.41]	+
Subtotal (95% CI) Heterogeneity: Tau ² Test for overall effect 1.4.2 SAXA vs sitag Li 2014 A Scheen 2010 Subtotal (95% CI) Heterogeneity: Tau ² Test for overall effect 1.4.3 SAXA vs vilda	-19.4 = 84.35; Cl :: Z = 0.82 liptin -33 -10.8 = 59.21; Cl :: Z = 0.02 gliptin	34.9 hi ² = 5.5: (P = 0.4 22.4 29 hi ² = 8.7: (P = 0.9)	146 283 3, df = 1) 66 397 463 8, df = 3)	-20.6 1 (P = (-26.8 -16.16 1 (P = (36 0.02); I ² 14.3 29 0.003);	137 279 = 82% 61 392 453 ² = 89 ⁶	50.4% 100.0% 47.5% 52.5% 100.0%	1.20 [-7.07, 9.47] -5.92 [-19.98, 8.14] -6.20 [-12.69, 0.29] 5.36 [1.31, 9.41] -0.13 [-11.44, 11.18]	*
Subtotal (95% cl) Heterogeneity: Tau ² Test for overall effect 1.4.2 SAXA vs sitag Li 2014 A Scheen 2010 Subtotal (95% cl) Heterogeneity: Tau ² Test for overall effect 1.4.3 SAXA vs vilda Li 2014 A	-19.4 = 84.35; C :: Z = 0.82 liptin -33 -10.8 = 59.21; C :: Z = 0.02 gliptin -33	34.9 hi ² = 5.53 (P = 0.4 22.4 29 hi ² = 8.7 (P = 0.9 22.4	146 283 3, df = 1) 66 397 463 8, df = 3) 66	-20.6 1 (P = 0 -26.8 -16.16 1 (P = 0 -43.9	36 0.02); l ² 14.3 29 0.003); 41.9	137 279 = 82% 61 392 453 ² = 89 ⁶ 63	50.4% 100.0% 47.5% 52.5% 100.0% %	1.20 [-7.07, 9.47] -5.92 [-19.98, 8.14] -6.20 [-12.69, 0.29] 5.36 [1.31, 9.41] -0.13 [-11.44, 11.18]	
Subtotal (95% CI) Heterogeneity: Tau ² Test for overall effect 1.4.2 SAXA vs sitag Li 2014 A Scheen 2010 Subtotal (95% CI) Heterogeneity: Tau ² Test for overall effect 1.4.3 SAXA vs vilda Li 2014 A Li 2014 B Subtotal (95% CI)	-19.4 = 84.35; C :: Z = 0.82 liptin -33 -10.8 = 59.21; C :: Z = 0.02 gliptin -33 -33	34.9 hi ² = 5.5: (P = 0.4 22.4 29 hi ² = 8.7? (P = 0.9i 22.4 18.8	146 283 3, df = 1) 66 397 463 3, df = 3) 66 60 126	-20.6 1 (P = 0 -26.8 -16.16 1 (P = 0 -43.9 -36.6	36 0.02); l ² 14.3 29 0.003); 41.9 15.6	137 279 61 392 453 1 ² = 89 ⁶ 63 57 120	50.4% 100.0% 47.5% 52.5% 100.0%	1.20 [-7.07, 9.47] -5.92 [-19.98, 8.14] -6.20 [-12.69, 0.29] 5.36 [1.31, 9.41] -0.13 [-11.44, 11.18]	
Subtotal (95% cl) Heterogeneity: Tau ² Test for overall effect 1.4.2 SAXA vs sitag Li 2014 A Scheen 2010 Subtotal (95% cl) Heterogeneity: Tau ² Test for overall effect 1.4.3 SAXA vs vilda Li 2014 A Li 2014 A Subtotal (95% cl)	-19.4 = 84.35; C :: Z = 0.82 liptin -33 -10.8 = 59.21; C :: Z = 0.02 gliptin -33 -33 = 3.83; Ch	34.9 hi ² = 5.5: (P = 0.4 22.4 29 hi ² = 8.7: (P = 0.9: 22.4 18.8 i ² = 1.17;	146 283 3, df = 1) 66 397 463 3, df = 3) 66 60 126 , df = 1	-20.6 1 (P = 0 -26.8 -16.16 1 (P = 0 -43.9 -36.6	36 0.02); l ² 14.3 29 0.003); 41.9 15.6	137 279 61 392 453 1 ² = 89 ⁶ 63 57 120	50.4% 100.0% 47.5% 52.5% 100.0% %	1.20 [-7.07, 9.47] -5.92 [-19.96, 8.14] -6.20 [-12.69, 0.29] 5.36 [1.31, 9.41] -0.13 [-11.44, 11.18] 10.90 [-0.77, 22.57] 3.60 [-2.65, 9.85]	
Subtotal (95% cl) Heterogeneity: Tau ² Test for overall effect 1.4.2 SAXA vs sitag Li 2014 A Scheen 2010 Subtotal (95% cl) Heterogeneity: Tau ² Test for overall effect 1.4.3 SAXA vs vilda Li 2014 A Li 2014 A Subtotal (95% cl) Heterogeneity: Tau ² Test for overall effect	-19.4 = 84.35; Cl :: Z = 0.82 liptin -33 -10.8 = 59.21; Cl :: Z = 0.02 gliptin -33 = 3.83; Ch :: Z = 1.72	34.9 hi ² = 5.5: (P = 0.4 22.4 29 hi ² = 8.7: (P = 0.9: 22.4 18.8 i ² = 1.17;	146 283 3, df = 1) 66 397 463 3, df = 3) 66 60 126 , df = 1	-20.6 1 (P = 0 -26.8 -16.16 1 (P = 0 -43.9 -36.6	36 0.02); l ² 14.3 29 0.003); 41.9 15.6	137 279 61 392 453 1 ² = 89 ⁶ 63 57 120	50.4% 100.0% 47.5% 52.5% 100.0% %	1.20 [-7.07, 9.47] -5.92 [-19.96, 8.14] -6.20 [-12.69, 0.29] 5.36 [1.31, 9.41] -0.13 [-11.44, 11.18] 10.90 [-0.77, 22.57] 3.60 [-2.65, 9.85]	
Subtotal (95% cT) Heterogeneity: Tau ² : Test for overall effect 1.4.2 SAXA vs sitag Li 2014 A Scheen 2010 Subtotal (95% cT) Heterogeneity: Tau ² : Test for overall effect 1.4.3 SAXA vs vilda Li 2014 A Li 2014 A Subtotal (95% cT) Heterogeneity: Tau ² : Test for overall effect 1.4.4 SAXA vs sulfo	-19.4 = 84.35; C I: Z = 0.82 liptin -33 -10.8 = 59.21; C I: Z = 0.02 gliptin -33 -33 = 3.83; Ch I: Z = 1.72 mylureas	34.9 $hi^{2} = 5.5;$ $(P = 0.4;$ $22.4;$ $29;$ $hi^{2} = 8.7i;$ $(P = 0.9i;$ $22.4;$ $18.8;$ $i^{2} = 1.17;$ $(P = 0.09;$ $(P = 0.09$	146 283 3, df = 1) 66 397 463 8, df = 3) 66 60 126 . df = 1 9)	-20.6 1 (P = 0 -26.8 -16.16 1 (P = 0 -43.9 -36.6 (P = 0.	36).02); I ² 14.3 29).003); 41.9 15.6 28); I ² =	137 279 61 392 453 1 ² = 89 ⁰ 63 57 120 = 14%	50.4% 100.0% 47.5% 52.5% 100.0% %	1.20 [-7.07, 9.47] -5.92 [-19.98, 8.14] -6.20 [-12.69, 0.29] 5.36 [1.31, 9.41] -0.13 [-11.44, 11.18] 10.90 [-0.77, 22.57] 3.69 [-26.5, 9.85] 5.52 [-0.78, 11.81]	
Subtotal (95% cl) Heterogeneity: Tau ² Test for overall effect 1.4.2 SAXA vs sitag Li 2014 A Scheen 2010 Subtotal (95% cl) Heterogeneity: Tau ² Test for overall effect 1.4.3 SAXA vs vilda Li 2014 A Li 2014 A Li 2014 (95% cl) Heterogeneity: Tau ² Test for overall effect	-19.4 = 84.35; Cl :: Z = 0.82 liptin -33 -10.8 = 59.21; Cl :: Z = 0.02 gliptin -33 = 3.83; Ch :: Z = 1.72	34.9 hi ² = 5.5: (P = 0.4 22.4 29 hi ² = 8.7: (P = 0.9: 22.4 18.8 i ² = 1.17;	146 283 3, df = 1) 66 397 463 3, df = 3) 66 60 126 , df = 1	-20.6 1 (P = 0 -26.8 -16.16 1 (P = 0 -43.9 -36.6 (P = 0.	36 0.02); l ² 14.3 29 0.003); 41.9 15.6	137 279 61 392 453 1 ² = 89 ⁶ 63 57 120	50.4% 100.0% 47.5% 52.5% 100.0% %	1.20 [-7.07, 9.47] -5.92 [-19.96, 8.14] -6.20 [-12.69, 0.29] 5.36 [1.31, 9.41] -0.13 [-11.44, 11.18] 10.90 [-0.77, 22.57] 3.60 [-2.65, 9.85]	
Subtotal (95% cl) Heterogeneity: Tau ² , Test for overall effect 1.4.2 SAXA vs sitag Li 2014 A Scheen 2010 Subtotal (95% cl) Heterogeneity: Tau ² , Test for overall effect Li 2014 A Li 2014 B Subtotal (95% cl) Heterogeneity: Tau ² T Test for overall effect 1.4.4 SAXA vs sulfo Goke 2013 Schernthaner 2015 Subtotal (95% cl)	-19.4 = 84.35; C :: Z = 0.82 liptin -33 -10.8 = 59.21; C :: Z = 0.02 gliptin -33 -33 = 3.83; Ch :: Z = 1.72 mylureas -9 -13.2	34.9 $hi^{2} = 5.5;$ $(P = 0.4;$ $22.4,$ 29 $hi^{2} = 8.7;$ $(P = 0.9;$ $22.4,$ $18.8,$ $i^{2} = 1.17;$ $(P = 0.0;$ $32.8,$ $18.5,$	146 283 3, df = 1) 66 397 463 8, df = 8) 66 60 126 60 126 46 127 463 3, df = 1 9)	-20.6 1 (P = (-26.8 -16.16 1 (P = (-43.9 -36.6 (P = 0. -23.3	36 0.02); ² 14.3 29 0.003); 41.9 15.6 28); ² = 32.8 18.4	137 279 = 82% 61 392 453 1 ² = 89 ⁴ 63 57 120 = 14% 420 339 759	50.4% 100.0% 47.5% 52.5% 100.0% 26.3% 73.7% 100.0% 33.7%	1.20 [-7.07, 9.47] -5.92 [-19.98, 8.14] -6.20 [-12.69, 0.29] 5.36 [1.31, 9.41] -0.13 [-11.44, 11.18] 10.90 [-0.77, 22.57] 3.60 [-2.65, 9.85] 5.52 [-0.78, 11.81] 7.00 [2.56, 11.44]	
Subtotal (95% cl) Heterogeneity: Tau ² Test for overall effect 1.4.2 SAXA vs sitag Li 2014 A Scheen 2010 Subtotal (95% cl) Heterogeneity: Tau ² Test for overall effect 1.4.3 SAXA vs vilda Li 2014 A Li 2014 A Subtotal (95% cl) Heterogeneity: Tau ² Test for overall effect 1.4.4 SAXA vs suff Goke 2013 Schernthaner 2015 Subtotal (95% cl) Heterogeneity: Tau ²	-19.4 = 84.35; Ci :: Z = 0.82 liptin -0.8 = 59.21; Ci :: Z = 0.02 gliptin -33 = 3.83; Ch :: Z = 1.72 mylureas -9 -13.2 = 1.25; Ch	34.9 hi ² = 5.5 (P = 0.4' 22.4 29 hi ² = 8.7' (P = 0.9' 22.4 18.8 i ² = 1.17, (P = 0.0' 32.8 18.5 i ² = 1.35,	146 283 3, df = 1) 66 397 463 3, df = 8) 66 60 126 60 126 60 126 420 344 764 df = 1	-20.6 1 (P = (-26.8 -16.16 1 (P = (-43.9 -36.6 (P = 0. -23.3	36 0.02); ² 14.3 29 0.003); 41.9 15.6 28); ² = 32.8 18.4	137 279 = 82% 61 392 453 1 ² = 89 ⁴ 63 57 120 = 14% 420 339 759	50.4% 100.0% 47.5% 52.5% 100.0% 26.3% 73.7% 100.0% 33.7% 66.3%	1.20 [-7.07, 9.47] -5.92 [-19.98, 8.14] -6.20 [-12.69, 0.29] 5.36 [1.31, 9.41] -0.13 [-11.44, 11.18] 10.90 [-0.77, 22.57] 3.60 [-2.65, 9.85] 5.52 [-0.78, 11.81] 7.00 [2.56, 11.44] 10.10 [7.33, 12.87]	
Subtotal (95% cl) Heterogeneity: Tau ² Test for overall effect 1.4.2 SAXA vs sitag Li 2014 A Scheen 2010 Subtotal (95% cl) Heterogeneity: Tau ² Test for overall effect 1.4.3 SAXA vs vilda Li 2014 A Li 2014 A Li 2014 A Heterogeneity: Tau ² Test for overall effect 1.4.4 SAXA vs sulfa Schernthaner 2015 Subtotal (95% cl) Heterogeneity: Tau ² Test for overall effect	-19.4 = 84.35; Ci :: Z = 0.82 liptin -10.8 = 59.21; Ci :: Z = 0.02 gliptin -33 = 3.83; Ch :: Z = 1.72 onylureas -9 -13.2 = 1.25; Ch :: Z = 6.18	34.9 hi ² = 5.5 (P = 0.4' 22.4 29 hi ² = 8.7' (P = 0.9' 22.4 18.8 i ² = 1.17, (P = 0.0' 32.8 18.5 i ² = 1.35,	146 283 3, df = 1) 66 397 463 3, df = 8) 66 60 126 60 126 60 126 420 344 764 df = 1	-20.6 1 (P = (-26.8 -16.16 1 (P = (-43.9 -36.6 (P = 0. -23.3	36 0.02); ² 14.3 29 0.003); 41.9 15.6 28); ² = 32.8 18.4	137 279 = 82% 61 392 453 1 ² = 89 ⁴ 63 57 120 = 14% 420 339 759	50.4% 100.0% 47.5% 52.5% 100.0% 26.3% 73.7% 100.0% 33.7% 66.3%	1.20 [-7.07, 9.47] -5.92 [-19.98, 8.14] -6.20 [-12.69, 0.29] 5.36 [1.31, 9.41] -0.13 [-11.44, 11.18] 10.90 [-0.77, 22.57] 3.60 [-2.65, 9.85] 5.52 [-0.78, 11.81] 7.00 [2.56, 11.44] 10.10 [7.33, 12.87]	
Subtotal (95% CI) Heterogeneity: Tau ² Test for overall effect 1.4.2 SAXA vs sitag Li 2014 A Scheen 2010 Subtotal (95% CI) Heterogeneity: Tau ² Test for overall effect Li 2014 A Subtotal (95% CI) Heterogeneity: Tau ² Test for overall effect 1.4.3 SAXA vs sulfo Goke 2013 Schernthaner 2015 Subtotal (95% CI) Heterogeneity: Tau ² Test for overall effect 1.4.5 SAXA vs acart	-19.4 = 84.35; Ci : Z = 0.82 liptin -33 -10.8 = 59.21; Ci : Z = 0.02 gliptin -33 -33 = 3.83; Ch : Z = 1.72 mylureas -9 -13.2 = 1.25; Ch : Z = 6.18	34.9 hi ² = 5.5: (P = 0.4' 22.4 29 hi ² = 8.7: (P = 0.9i 22.4 18.8 i ² = 1.17; (P = 0.0i 32.8 18.5 i ² = 1.35; (P < 0.0i	146 283 3, df = 1) 66 397 463 397 463 38, df = 8) 66 60 0 126 50 126 46 126 47 4 344 764 764 4, df = 1 0001)	-20.6 1 (P = (-26.8 -16.16 1 (P = (-43.9 -36.6 (P = 0. (P = 0. (P = 0.	36 0.02); ² 14.3 29 0.003); 15.6 28); ² = 32.8 18.4 25); ² =	137 279 = 82% 61 392 453 12 89' 63 57 120 = 14% 420 339 759 = 26%	50.4% 100.0% 47.5% 52.5% 100.0% 26.3% 73.7% 100.0% 33.7% 66.3% 100.0%	1.20[-7.07, 9.47] -5.92[-19.98, 8.14] -6.20[-12.69, 0.29] 5.36[1.31, 9.41] -0.13[-11.44, 11.18] 10.90[-0.77, 22.57] 3.60[-2.65, 9.85] 5.52[-0.78, 11.81] 7.00[2.56, 11.44] 10.10[7.33, 12.87] 9.05[6.18, 11.93]	
Subtotal (95% CI) Heterogeneity: Tau ² , Test for overall effect 1.4.2 SAXA vs sitag Li 2014 A Scheen 2010 Subtotal (95% CI) Heterogeneity: Tau ² , Test for overall effect 1.4.3 SAXA vs vida Li 2014 A Subtotal (95% CI) Heterogeneity: Tau ² , Test for overall effect 1.4.4 SAXA vs sulfo Goke 2013 Schernthaner 2015 Subtotal (95% CI) Heterogeneity: Tau ² , Test for overall effect 1.4.5 SAXA vs acart Du 2017 Ly 2013	-19.4 = 84.35; Ci :: Z = 0.82 liptin -10.8 = 59.21; Ci :: Z = 0.02 gliptin -33 = 3.83; Ch :: Z = 1.72 onylureas -9 -13.2 = 1.25; Ch :: Z = 6.18	34.9 hi ² = 5.5: (P = 0.4' 22.4 29 hi ² = 8.7: (P = 0.9i 22.4 18.8 i ² = 1.17; (P = 0.0i 32.8 18.5 i ² = 1.35; (P < 0.0i	146 283 3, df = 1) 66 397 463 397 463 38, df = 8) 66 60 0 126 50 126 46 126 47 4 344 764 764 4, df = 1 0001)	-20.6 1 (P = (-26.8 -16.16 1 (P = (-43.9 -36.6 (P = 0. -16 (P = 0. -18.19	36 0.02); ² 14.3 29 0.003); 15.6 28); ² = 32.8 18.4 25); ² =	137 279 = 82% 61 392 453 1 ² = 89 ⁴ 63 57 120 = 14% 420 339 759	50.4% 100.0% 47.5% 52.5% 100.0% 26.3% 73.7% 100.0% 33.7% 66.3%	1.20 [-7.07, 9.47] -5.92 [-19.98, 8.14] -6.20 [-12.69, 0.29] 5.36 [1.31, 9.41] -0.13 [-11.44, 11.18] 10.90 [-0.77, 22.57] 3.60 [-2.65, 9.85] 5.52 [-0.78, 11.81] 7.00 [2.56, 11.44] 10.10 [7.33, 12.87]	
Subtotal (95% cf) Heterogeneity: Tau ² Test for overall effect 1.4.2 SAXA vs sitag Li 2014 A Scheen 2010 Subtotal (95% cf) Heterogeneity: Tau ² Test for overall effect Li 2014 B Subtotal (95% cf) Heterogeneity: Tau ² Test for overall effect 1.4.4 SAXA vs suida Schernthaner 2015 Subtotal (95% cf) Heterogeneity: Tau ² Test for overall effect 1.4.5 SAXA vs acart Du 2017 Lx 2013 Subtotal (95% cf)	-19.4 = 84.35; C :: Z = 0.82 liptin = 33 -10.8 = 59.21; C :: Z = 0.02 gliptin -33 -33 = 3.83; Ch :: Z = 1.72 onylureas -13, 2 = 1.25; Ch :: Z = 6.18 osse -17.83 -36	$\begin{array}{c} 34.9 \\ hi^{\mu}=5.5; \\ (P=0.4 \\ 29 \\ hi^{\mu}=8.7i \\ (P=0.9) \\ 22.4 \\ 18.8 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ (P=0.0) \\ 32.8 \\ 18.5 \\ (P=0.0) \\ 36.12 \\ 14.9 \end{array}$	146 283 3, df = 1) 66 397 463 3, df = 8) 66 60 126 df = 1 9) 420 344 764 df = 1 0001) 2388 90 328	-20.6 1 (P = (-26.8 -16.16 1 (P = (-43.9 -36.6 (P = 0. (P = 0. -18.19 -34.2	36 0.02); ² 14.3 29 0.003); 41.9 15.6 28); ² = 32.8 18.4 25); ² = 36.5 14.9	137 279 = 82% 61 392 453 57 120 = 14% 420 339 759 = 26% 243 90 333	50.4% 100.0% 47.5% 52.5% 100.0% % 26.3% 73.7% 100.0% 33.7% 66.3% 100.0% 31.0%	1.20 [-7.07, 9.47] -5.92 [-19.96, 8.14] -6.20 [-12.69, 0.29] 5.36 [1.31, 9.41] -0.13 [-11.44, 11.18] 10.90 [-0.77, 22.57] 3.60 [-2.65, 9.85] 5.52 [-0.78, 11.81] 7.00 [2.56, 11.44] 10.10 [7.33, 12.87] 9.05 [6.18, 11.93] 0.36 [-6.13, 6.85]	
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Fig 3. Mean change of FPG from baseline (a. saxagliptin vs placebo; b. saxagliptin vs active comparators).

(WMD -0.13 mg/dL, 95% CI -11.44 to 11.18; *p* = 0.98) and vildaglitpin (WMD 5.52 mg/dL, 95% CI -0.78 to 11.81; *p* = 0.09).

Non-glycemic outcomes

Overall and serious adverse events. Generally, the incidences of overall (*versus* placobo: RR 1.01, 95% CI 0.97 to 1.05; p = 0.77; Fig 4a) and severe (*versus* placobo: RR 1.01, 95% CI 0.96 to 1.06; p = 0.78; S3 Fig) treatment-related adverse events did not increase in the treatment of saxagliptin. Moreover, saxagliptin significantly reduced overall adverse events compared with acarbose (RR 0.71, 95% CI 0.57 to 0.89; p = 0.03; Fig 4b) and liraglutide (RR 0.41, 95% CI 0.24 to 0.71; p = 0.001) when added to metformin.

Hypoglycemia. Compared with placebo, saxaglitpin significantly but slightly increased the incidences of hypoglycemia (RR 1.13, 95% CI 1.05 to 1.21; p = 0.0009; Fig 5a). Compared with sulfonylureas, saxaglitpin significantly reduced the risk of hypoglycemia by 95% (RR 0.05, 95% CI 0.01 to 0.23; p = 0.0002; Fig 5b). No significant differences were observed in comparison with other active comparators, including other DPP-4 inhibitors.

Body weight. In comparison with placebo, treatment with saxaglipitin was associated with a significant but slight increase of body weight (WMD 0.42 kg, 95% CI 0.26 to 0.59; p < 0.00001; S4a Fig). Saxagliptin was inferior to liraglutide (WMD 5.10 kg, 95% CI 1.66 to 8.54; p = 0.004; S4b Fig) and dapagliflozin (WMD 2.40 kg, 95% CI 1.69 to 3.11; p < 0.00001). However, treatment with saxagliptin was associated with significantly less effect on body weight than sulfonylureas (WMD –2.34 kg, 95% CI –3.31 to –1.36; p < 0.00001). In comparison with other DPP-4 inhibitors, changes in body weight were similar.

Other adverse events. The incidences of pancreatitis (RR 1.13, 95% CI 0.65 to 1.96; p = 0.66; S5a Fig) and heart failure (RR 0.99, 95% CI 0.89 to 1.10; p = 0.85; S5b Fig) did not differ significantly between saxagliptin and controls (placebo and sulfonylureas). The risk of arthralgia did not differ significantly between saxagliptin, saxagliptin and placebo (RR 1.02, 95% CI 0.92 to 1.13; p = 0.66; S5c Fig), Compared with sitagliptin, saxagliptin could significantly reduced the risk of arthralgia (RR 0.20, 95% CI 0.04 to 0.90; p = 0.04; S5d Fig), but not compared with other active treatments. Treatment with saxagliptin was not associated with any increased risks of upper respiratory tract infection, urinary tract infection and nasopharyngitis compared with both placebo and active comparators (p > 0.05). See S5e–S5j Fig. for forest plots of adverse events above.

Discussion

This meta-analysis of the available literature on saxagliptin aimed to assess its clinical efficacy and safety in patients with type 2 diabetes. The findings of the analysis indicate that treatment with saxagliptin can lead to significant decreases of HbA1c and FPG compared with placebo, both when given as monotherapy or add-on therapy to other treatments, including metformin, sulfonylureas, thiazolidinediones, dapagliflozin and insulin. Mean placebo-adjusted HbA1c and FPG levels in saxagliptin add-on therapy were lowered by comparable amounts to saxagliptin monotherapy. When combined with submaximal-dose metformin, saxagliptin significantly increased the proportion of patients achieving HbA1c <7% compared with acarbose and uptitrated metformin. Generally, efficacy on glycemic control of saxagliptin was similar to sitaglitpin and vildagliptin, while inferior to liraglutide and dapagliflozin. More direct comparisons with other active comparators in future trials may provide further evidence of the efficacy of saxagliptin in comparison with other active treatments.

Saxagliptin is generally well tolerated, with no increased risk of overall and serious adverse events as monotherapy and combination therapy. Additionally, saxagliptin group experienced

	Experimen	tal	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup			Events		Weight	M-H, Random, 95% 0	M-H, Random, 95% Cl
Barnett 2013	202	304	108	151	6.0%	0.93 [0.82, 1.06]	
Chacra 2011	427	501	237	267	12.8%	0.96 [0.91, 1.02]	
Chen 2017	96	234	101	231	2.8%	0.94 [0.76, 1.16]	
Dou 2017	100	215	99	210	3.1%	0.99 [0.81, 1.21]	
Frederich 2012	65	148	22	74	0.9%	1.48 [1.00, 2.19]	· · · · · ·
Hollander 2011	309	381	145	184	9.1%	1.03 [0.94, 1.13	
Kadowaki 2017	73	117	61	115	2.6%	1.18 [0.94, 1.47]	
Kumar 2014	51	107	48	106	1.7%	1.05 [0.79, 1.40]	
Matthaei 2016	89	153	94	162	3.5%	1.00 [0.83, 1.21]	
Moses 2014	81	129	91	128	4.0%	0.88 [0.74, 1.05]	
Nowicki 2011	49	85	46	85	1.9%	1.07 [0.82, 1.39]	
Pan 2012	124	284	102	284	3.0%	1.22 [0.99, 1.49]	
Pfutzner 2011	211	320	224	328	7.5%	0.97 [0.87, 1.08]	
Rosenstock 2008	58	102	38	67	1.9%	1.00 [0.77, 1.31]	
Rosenstock 2013	183	208	77	95	7.4%	1.09 [0.97, 1.21]	
Rosenstock 2013	332	383	142	179	9.6%	1.09 [1.00, 1.19]	
Rosenstock 2015	87	179	87	179	2.8%	1.00 [0.81, 1.24	
Scirica 2013		3280	3641	8212		0.95 [0.92, 0.99	
White 2014	19	74	34	86	0.7%	0.65 [0.41, 1.04]	
Yang 2011	125	283	119	287	3.4%	1.07 [0.88, 1.29]	
	40	407		44420	400.00/	4 04 10 07 4 05	L
Total (95% CI)		487	EE10	11430	100.0%	1.01 [0.97, 1.05]	Ĭ
Total events Heterogeneity: Tau² = (6185	1 62 4	5516		2), 12 - 400	,	
Test for overall effect: 2			1 - 19 (1	0.0	5), 1 = 407	0	0.5 0.7 1 1.5 2
rest for overall effect. 2	L - 0.29 (F -	0.77)					Favours [saxagliptin] Favours [place
Ъ)							
(b)	Experiment		Contro	-		Risk Ratio	Risk Ratio
Study or Subgroup					Woight	M-H, Random, 95% CI	M-H, Random, 95% Cl
1.6.1 SAXA vs metfor		otal	vents	Total	weight	M-H, Kandolli, 95 /8 CI	MI-H, Kalidolli, 55/8 Cl
Fonseca 2012	21	138	16	144	41.7%	1.37 [0.75, 2.51]	_
Hermans 2012	27	147	22	139	58.3%	1.16 [0.69, 1.94]	
Subtotal (95% CI)		285	~~~		100.0%	1.24 [0.84, 1.84]	
Total events	48		38				
Heterogeneity: Tau ² =		.17. df		0.68):	$^{2} = 0\%$		
Test for overall effect: 2			. (.	,,			
		,					
1.6.2 SAXA vs sulfon	ylureas						
Goke 2013	45	428	142	430	51.9%	0.32 [0.23, 0.43]	
Schernthaner 2015	26	359	28	359	48.1%	0.93 [0.56, 1.55]	
Subtotal (95% CI)		787		789	100.0%	0.53 [0.19, 1.52]	
Total events	71		170				
Heterogeneity: Tau ² =			lf = 1 (P	= 0.000	5); l ² = 92%	6	
Test for overall effect: 2	Z = 1.18 (P =	0.24)					
4.0.0.04.84	. 41						
1.6.3 SAXA vs sitagli		100			100.00/		
Scheen 2010		403 403	30		100.0% 100.0%	0.69 [0.40, 1.19]	
Subtotal (95% CI)		403	20	398	100.0%	0.69 [0.40, 1.19]	
Total events Heterogeneity: Not app	21		30				
Test for overall effect: 2		0 19)					
rest for overall effect.	2 – 1.34 (P –	0.18)					
1.6.4 SAXA vs vildagl	iptin						
Li 2014 B	13	60	15	57	100.0%	0.82 [0.43, 1.57]	— —
Subtotal (95% CI)		60			100.0%	0.82 [0.43, 1.57]	
Total events	13		15			- /	
Heterogeneity: Not app							
Test for overall effect:		0.56)					
	`	,					
1.6.5 SAXA vs acarbo	se						
Du 2017		231	109		100.0%	0.71 [0.57, 0.89]	
Subtotal (95% CI)		231			100.0%	0.71 [0.57, 0.89]	◆
Total events	78		109				
Heterogeneity: Not app							
Test for overall effect: 2	Z = 2.94 (P =	0.003)					
4.0.0.0474	161 l						
1.6.6 SAXA vs dapagi		470	07	470	400.001	4 00 10 00 4 6 1	
Rosenstock 2015		176 176	87		100.0% 100.0%	1.09 [0.89, 1.34]	
Subtotal (95% CI)		170	07	179	100.0%	1.09 [0.89, 1.34]	T
Total events	93		87				
Heterogeneity: Not app Test for overall effect: 2		0.420					
rest for overall effect:	≤ = 0.80 (P =	0.42)					
1.6.7 SAXA vs liraglu	tide						
Li 2014 B	13	60	32	61	100.0%	0.41 [0.24, 0.71]	
Subtotal (95% CI)	15	60	52		100.0%	0.41 [0.24, 0.71]	
Total events	13		32				-
Heterogeneity: Not app			02				
Test for overall effect: 2		0.001)					
							0.05 0.2 1 5

Fig 4. Overall adverse events (a. saxagliptin vs placebo; b. saxagliptin vs active comparators).

Study or Subgroup	Experime Events		Cont Events		Weight	Risk Ratio M-H, Fixed, 95% C	Risk Ratio I M-H, Fixed, 95% Cl
Barnett 2013	23	304	10	151	11.2%	1.14 [0.56, 2.34]	
Chacra 2011	8	253	9	267	7.3%	0.94 [0.37, 2.39]	
Chacra 2011	13	248	9	267	7.2%		
Chen 2017	50	234	54	231	45.4%		
Dou 2017	1	215	4	210	3.4%		-
Fonseca 2012	2	138	0	144	0.4%	5.22 [0.25, 107.68]	
Hollander 2011	2	195	1	184	0.9%	1.89 [0.17, 20.64]	
Hollander 2011	0	186	1	184	1.3%	0.33 [0.01, 8.04]	
Kadowaki 2017	24	117	17	115	14.3%		+
Matthaei 2016	4	162	2	153			
	2		0				
Moses 2014		129		128	0.4%		
Pfutzner 2011	0	320	2	328	2.1%		
Rosenstock 2013	3	192	1	179	0.9%	2.80 [0.29, 26.64]	
Rosenstock 2013	2	191	1	179	0.9%	1.87 [0.17, 20.49]	
White 2014	0	74	1	86	1.2%	0.39 [0.02, 9.35]	· · · · ·
Yang 2011	3	283	2	287	1.7%	1.52 [0.26, 9.04]	
Total (95% CI)		3241		3093	100.0%	1.10 [0.87, 1.38]	•
Total events	137		114				ĺ
Heterogeneity: Chi ² = ²	10.08, df = 1	5 (P =	0.81): l²	= 0%			
Test for overall effect:	Z = 0.80 (P =	= 0.42)					0.01 0.1 1 10 Favours [saxagliptin] Favours [placeb
b)	Experimen	tal	Contro	I		Risk Ratio	Risk Ratio
Study or Subgroup	Events 1				Veight	M-H, Random, 95% CI	M-H, Random, 95% Cl
1.8.1 SAXA vs metfor			_				
Fonseca 2012	2	138	0	144	29.2%	5.22 [0.25, 107.68]	
Hermans 2012	2	147	2	139	70.8%	0.95 [0.14, 6.62]	
Subtotal (95% CI)	4	285		283 1	00.0%	1.56 [0.30, 8.01]	
Total events Heterogeneity: Tau ² = 0 Test for overall effect: 2	0.00; Chi ² = 0		2 = 1 (P =	0.35); l [:]	= 0%		
1.8.2 SAXA vs sulfony							
Goke 2013	0	428	39	430	25.1%	0.01 [0.00, 0.21]	
Schernthaner 2015	4	359	55		74.9%	0.07 [0.03, 0.20]	
Subtotal (95% CI)		787		789 1	00.0%	0.05 [0.01, 0.23]	
Total events Heterogeneity: Tau ² = 0 Test for overall effect: 2				0.21); l [:]	= 35%		
1.8.3 SAXA vs acarbo	se						
Du 2017	3	231	4	230	77.5%	0.75 [0.17, 3.30]	
Lv 2013	1	90	1		22.5%	1.00 [0.06, 15.74]	
Subtotal (95% CI)	•	321			00.0%	0.80 [0.22, 2.95]	
Total events	4		5				-
Heterogeneity: Tau ² = 0 Test for overall effect: 2	0.00; Chi ² = 0			0.85); I ²	= 0%		
1.8.4 SAXA vs repagli							
Xia 2014	2	120	5	120 1		0.40 [0.08, 2.02]	
Subtotal (95% CI)		120		120 1	00.0%	0.40 [0.08, 2.02]	
Total events	2		5				
Heterogeneity: Not app Test for overall effect: 2		0.27)					
4.0.5.CAVA							
1.8.5 SAXA vs vildagl		60	-	E0 -	00.001	0 56 10 44 0 6 1	
Li 2014 B Subtotal (95% CI)	3	62 62	5		00.0% 00.0%	0.56 [0.14, 2.24]	
Subtotal (95% CI) Total events	3	02	-	50	00.070	0.56 [0.14, 2.24]	
I otal events Heterogeneity: Not app			5				
Test for overall effect: 2		0.41)					
1.8.6 SAXA vs dapagl	iflozin						
Rosenstock 2015	2	176	2	179 1	00.0%	1.02 [0.14, 7.14]	
Subtotal (95% CI)	2	176	2		00.0%	1.02 [0.14, 7.14]	
Total events	2		2		/ 0		
Heterogeneity: Not app	licable		2				
Test for overall effect: 2	∠ = 0.02 (P =	0.99)					
	tide						
1.8.7 SAXA vs liraglut		60	4		00.0%	0.76 [0.18, 3.26]	
1.8.7 SAXA vs liraglut Li 2014 B	3				00.0%	0.76 [0.18, 3.26]	
1.8.7 SAXA vs liraglut Li 2014 B Subtotal (95% Cl)		60		61 1	00.070		-
1.8.7 SAXA vs liraglut Li 2014 B Subtotal (95% CI) Total events	3		4	61 1	00.070		_
1.8.7 SAXA vs liraglut Li 2014 B Subtotal (95% CI) Total events Heterogeneity: Not app	3 Ilicable	60	4	61 1	00.070		
1.8.7 SAXA vs liraglut Li 2014 B Subtotal (95% CI) Total events	3 Ilicable	60	4	61 1	00.070		
1.8.7 SAXA vs liraglut Li 2014 B Subtotal (95% CI) Total events Heterogeneity: Not app	3 Ilicable	60	4	61 1	00.070		

Fig 5. Hypoglycemia (a. saxagliptin vs placebo; b. saxagliptin vs active comparators).

less overall adverse events than acarbose and liraglutide groups when combined with metformin, indicating its favorable safety profile in patients with T2D. Compared with sulfonylureas, saxagliptin had a significant better effect on hypoglycemia and body weight gain. Treatment of saxagliptin was shown to be with a minimal increase of hypoglycemia, which mainly depending on the result from the included Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus -Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial. Patients in that trial were permitted various concomitant antihyperglycaemic therapies at the doctor's discretion. A post-hoc analysis [52] of SAVOR-TIMI 53 trial found that hypoglycemia rates (any or major) were increased with saxagliptin in patients taking sulfonylureas, not in those taking insulin. A pooled analysis also found that saxagliptin was not associated with increased reported or confirmed hypoglycemia when use of sulfonylurea was excluded [53]. Thus, lower doses of sulfonylureas might be required to reduce risk of hypoglycaemia. Saxagliptin improves the sensitivity of pancreatic islets (α - and β -cells) to glucose, inhibits the production of glucagon, and stimulates the secretion of insulin in a glucose-dependent manner. Consequently, it may still be an appropriate agent for patients with relatively higher risk of hypoglycemia.

The potential safety issue of heart failure risk that arose from SAVOR-TIMI 53 and the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAM-INE) trials led to the US FDA's recommendation [54] to consider discontinuing saxagliptin and alogliptin for patients if heart failure develops. However, according to our meta-analysis, risk of heart failure was similar with saxagliptin and comparators, with almost identical rates of heart failure in both groups. The result was opposite to previous systematic reviews and meta analyses, among which increased risk of heart failure was found in the treatment of saxagliptin individually or DPP-4 inhibitors as an integrity. Until now, there is no identified pathophysiology for the increased risk of heart failure by saxagliptin treatment. On the contrary, previous preclinical and mechanistic studies of DPP-4 inhibitors suggest additional nonglycemic beneficial actions on blood vessels and the heart, via both GLP-1-dependent and GLP-1-independent effects [55,56]. Positive effects of DPP-4 inhibitors on the myocardium have also been described in patients with ischemic heart disease [57].

US FDA had warned that DPP-4 inhibitors may cause serious arthralgia in August 2015, raising safety issues concerning the entire drug class and encouraging healthcare professionals and patients to pay attention [58]. In a search of the FDA Adverse Event Reporting System database, FDA has identified 33 cases of serious arthralgia reported with the use of DPP-4 inhibitors between October 2006 and December 2013. However, the current finding from our meta-analysis showed no safety signal for increased risk of arthralgia in the saxagliptin treatment, and a possible better effect than sitagliptin. Furthermore, there was no increased risk of pancreatitis and infections as supported by our studies, which was also consistent with previous meta-analyses [59–62]. Postmarketing safety surveillance of saxagliptin will provide further data on the incidences of adverse events.

In contrast to GLP-1 receptor agonists, saxagliptin does not mimic infused GLP-1 in its effects on subjective satiety or gastric volume, which have been associated with noticeable weight loss. Overall, saxagliptin appears to be associated with only modest changes in body weight. In comparison with placebo, saxagliptin was associated with a slight gain in body weight, which is of limited clinical significance. However, in comparison with sulfonylureas, saxagliptin had a significant advantage on body weight (-2.34 kg).

In the US and Europe, saxagliptin has been approved for use in patients with type 2 diabetes, both as monotherapy and in combination with metformin, a sulfonylurea, thiazolidinedione, or insulin, and also in combination with metformin plus insulin. However, in some countries like China, it is currently only approved for use as monotherapy or in combination with metformin. Our systematic review has demonstrated significant advantages of saxagliptin in achieving glycemic control when added to sulfonylureas, thiazolidinediones, or insulin, with similar or better safety profiles. These results will help administrators in China and other countries make evidence-based decisions.

This systematic review and meta-analysis of RCTs focused on the efficacy and safety of saxagliptin in the treatment of T2D. The sample size of nearly 30,000 patients enabled the demonstration of reliable results and the comparisons to most classes of oral antidiabetic drugs, by which the knowledge around the comparative efficacy and safety was enriched. However, there are some limitations in this study. Firstly, the follow-up periods of some included trials were relatively short, which limited the observation of longtime outcomes among some comparisons. Secondly, two trials included in the meta-analysis, which comparing saxagliptin with vildagliptin, sitagliptin and (or) liraglutide, were found to have possible high risk of performance and detection bias. This potential bias may reduce the credibility of corresponding results. Interpretations of these findings must be made with caution. More head-to-head trials between saxagliptin and active comparators are still needed to further confirm the efficacy and safety of saxagliptin compared with other classes of antidiabetic drugs.

In conclusion, Generally, saxagliptin has similar efficacy compared with most oral antidiabetic drugs, while may be more effective than acarbose. Saxagliptin is safe in the treatment of T2D, especially having a better safety profile than acarbose and sulfonylureas.

Supporting information

S1 Text. PRISMA checklist. (DOC)

S1 Fig. Risk of bias of included trials (a. graph; b. summary). (EPS)

S2 Fig. Patients achieved HbA1c $<\!7\%$ (a. saxagliptin vs placebo; b. saxagliptin vs active comparators).

(EPS)

S3 Fig. Serious adverse events. (EPS)

S4 Fig. Body weight (a. saxagliptin vs placebo; b. saxagliptin vs active comparators). (EPS)

S5 Fig. Other adverse events [a. pancreatitis; b. heart failure; c. arthralgia (saxagliptin vs placebo); d. arthralgia (saxagliptin vs active comparators); e. upper respiratory tract infection (saxagliptin vs placebo); f. upper respiratory tract infection (saxagliptin vs active comparators); g. urinary tract infection (saxagliptin vs placebo); h. urinary tract infection (saxagliptin vs active comparators); i. nasopharyngitis (saxagliptin vs placebo); j. nasopharyngitis (saxagliptin vs active comparators)]. (EPS)

Author Contributions

Conceptualization: Peng Men, Hui-lin Tang, Suo-di Zhai.

Investigation: Peng Men.

Methodology: Peng Men, Hui-lin Tang.

Project administration: Suo-di Zhai.

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Writing – review & editing: Xiao-tong Li, Suo-di Zhai.

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