Comparison of Placebo Effect between Asian and Caucasian Type 2 Diabetic Patients: A Meta-Analysis

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Abstract

Background: Placebo was defined as any therapy that is used for its nonspecific psychological and physiologic effect but has no specific pharmacologic impact on the condition being treated. Besides medication therapies, studies have found that the optimal dietary approach as well as physical activity and education are useful to control hyperglycemia in patients with type 2 diabetes (T2DM). The aim of this study was to evaluate the placebo effects of antidiabetic therapies in Asian and Caucasian T2DM patients and make a comparison between the two ethnicities.
Methods: A search using the MEDLINE database, EMBASE, and Cochrane Database was performed, from when recording began until December 2016. The main concepts searched in English were sulfonylurea (SU); alpha glucosidase inhibitors (AGI); metformin (MET); thiazolidinediones (TZD); dipeptidyl peptidase-4 inhibitors (DPP-4i); sodium-glucose cotransporter 2 inhibitors (SGLT2i); glucagon-like peptide-1 receptor agonist (GLP-1RA); type 2 diabetes (T2DM); placebo controlled; and randomized controlled trials. Using the Cochrane instrument, we evaluated the adequacy of randomization, allocation concealment procedures, and blinding.
Results: This study included 63 studies with a total of 7096 Asian patients involved and 262 studies with a total of 27,477 Caucasian patients involved. In Caucasian population, the use of placebo led to significant reductions of glycosylated hemoglobin (HbA1c), −0.683% (P = 0.008) in SU monotherapy treatment, −0.193% (P = 0.001) in DPP-4i treatment, and −0.230% (P < 0.001) in SGLT2i treatment, respectively. In Asian population, the use of placebo resulted in significant decreases of HbA1c, −0.162% (P = 0.012) in DPP-4i treatment and −0.269% (P = 0.028) in GLP-1RA add-on therapy, respectively. The placebo also significantly reduced body weight. In Caucasian population, placebo use resulted in 0.833 kg (P = 0.006) weight loss by SU treatment and 0.953 kg (P = 0.006) weight loss by GLP-1RA treatment. In Asian population, the placebo led to a weight change of 0.612 kg (P < 0.001) by GLP-1RA analog treatment. The changes of HbA1c and weight due to the placebo effect in other treatments were not significant in both Asian and Caucasian population. Comparisons of the placebo effect on HbA1c change and weight change in each treatment group indicated that no significant difference was found between Asian and Caucasian population.
Conclusions: The overall differences of the placebo effect on HbA1c changes as well as on body weight changes were not significant between Asian and Caucasian T2DM patients. The placebo effect on HbA1c changes and weight changes was not associated with baseline age, gender, baseline body mass index, baseline HbA1c, duration of diabetes, or study duration.

Key words: Asian; Caucasian; Placebo; Type 2 Diabetes Mellitus

Introduction

Placebo was defined as any therapy that is used for its nonspecific psychological and physiologic effect but has no specific pharmacologic impact on the condition being treated.[1] Besides medication therapies, studies have found that the optimal dietary approach as well as physical activity and education are useful to control hyperglycemia in patients with type 2 diabetes (T2DM).[2] Several reviews reported that increasing physical activity and exercise improved glucose control in people with T2DM, yielding an average reduction of glycosylated hemoglobin (HbA1c) of between 0.4% and

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.235107

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Received: 07-02-2018 **Edited by:** Yuan-Yuan Ji
How to cite this article: Guo W, Nie L, Wang XR, Xu ML, Yang WJ, Gao XY, Cai XL, Ji LN. Comparison of Placebo Effect between Asian and Caucasian Type 2 Diabetic Patients: A Meta-Analysis. Chin Med J 2018;131:1605-12.

0.6%.[3-5] Hence, the knowledge of placebo effects is important to evaluate the efficacy of a new drug to determine its real effective in glucose control or body weight control. It is also useful for blind trials to evaluate the effect difference between treatment groups and placebo groups. Moreover, in randomized controlled trails (RCTs) or observational studies, it is useful for testing the placebo-corrected efficacy in glucose control even if the control group was an active antidiabetic drug.[1,6,7]

With the increasing prevalence of T2DM in Asian population and the unmet need for improving glucose control,[8-10] the placebo-controlled RCTs of novel agents have been carried out in both Asian and Caucasian patients with T2DM. It was suggested that the placebo response in clinical trials represents more than just regression to the mean and passage of time;[11] well-learned and definitely understood placebo effect are likely to be related to better design and execution of diabetes trials in Asian and Caucasian populations.[12,13]

Due to the lower body mass index (BMI) and other different demographics of Asian patients compared with that of Caucasian patients[9,14] and the complicate genetic and pharmacogenetic ethnic background[15,16] or variable response to antidiabetic treatment,[17-19] the placebo effect of glucose control and body weight control between the two ethnicities might be different. The exact placebo effect in T2DM treatment has not been evaluated comprehensively so far, especially in Asian and Caucasian patients. If the trial was done mainly in Caucasian population (>50%), it would be classified as Caucasian group, if the trial was done mainly in Asian population (>50%), it would be classified as Asian group.[17-19] Therefore, the aim of this study was to evaluate the placebo effects of antidiabetic therapies in Asian and Caucasian T2DM patients and make comparison between the two ethnicities.

Methods

Search strategy

A search using the MEDLINE database, EMBASE, and Cochrane Database was performed, from when recording began to December 2016. The strategy was performed using the following terms in English: sulfonylurea (SU); alpha glucosidase inhibitors (AGIs); metformin (MET); thiazolidinediones (TZD); dipeptidyl peptidase-4 inhibitors (DPP-4i); sodium-glucose cotransporter 2 inhibitors (SGLT2i); glucagon-like peptide-1 receptor analogues (GLP-1RA); type 2 diabetes (T2DM); placebo controlled; and randomized controlled trials. The search was conducted from June 2014 to October 2016. This meta-analysis was registered as CRD42014009373.

Study selection

To evaluate the placebo effects of antidiabetic therapies in T2DM patients, the inclusion criteria were therefore listed as follows: (1) placebo-controlled, randomized trials; (2) included T2DM participants; (3) the study duration ≥12 weeks; (4) the levels of HbA1c changed from baseline were measured in the placebo group; and (5) the ethnicity was reported in the trial.

According to the inclusion criteria, two authors (Nie L, Xu ML) independently screened the studies one by one. If there is any disagreement, a third author (Wang XR) will be consulted. Using the Cochrane instrument, we evaluated the adequacy of randomization, allocation concealment procedures, and blinding.[20]

Data extraction

The following data were independently extracted using a standardized form. Study titles and authors, study design, the number of individuals in placebo group, patients' age, gender, BMI, diabetes duration, baseline HbA1c, duration of follow-up, and the changes of HbA1c and body weight in placebo group were all documented. If there is any disagreement, it would be resolved by discussion with another author (Yang WJ).

Definition of Asian and Caucasian

All the data would be divided according to the ethnicity of the population included. If the trial involved more than 50% Caucasian population of all patients, it would be classified as in Caucasian group; if the trial was done mainly in Asian population (>50%), it would be classified as in Asian group.[17-19]

Statistical analysis

To compare the baseline variables between Asian and Caucasian population, data were expressed as mean ± standard deviation and were compared using *t*-test. A two-sided $P < 0.05$ was considered statistically significant. The primary end point of this meta-analysis was absolute HbA1c change relative to baseline in placebo treatment group in Asian and Caucasian T2DM patients. The mean difference (MD) in the placebo group was calculated as the change from baseline and 95% confidence interval (*CI*) was also shown. The measures of effect for all continuous variables were the differences from baseline to end point. When the standard deviations (SDs) for these differences were missing, we calculated the SD of the difference with the following formula:[21]

$$SD_{\text{paired difference}}^{2} = SD_{\text{pretreatment value}}^{2} + SD_{\text{posttreatment value}}^{2} - 2 \times r \times SD_{\text{pretreatment value}} \times SD_{\text{posttreatment value}}$$

We used a conservative correlation coefficient (r) of 0.4.

$$SD_{\text{paired difference}} = \sqrt{SD_{\text{paired difference}}^{2}}$$

Treatment effects were estimated by random-effect or fixed-effect pairwise meta-analysis. Higgins I^2 statistics were used to quantify the percentage of the total variance in the summary estimate due to between-study heterogeneity. Publication bias was assessed via a funnel plot vision. Meta-regression analysis was also made for the association analysis between placebo effect in HbA1c changes and baseline characteristics. Statistical testing was two-sided, with $P < 0.05$ considered statistically significant. All statistical analyses were performed with the STATA statistical software package (Version 11.0, StataCorp, College Station, TX, USA). We conducted this study according to the PRISMA guidelines.[22]

Results

Outlines of the studies included

Figure 1 indicates the study selection process. This study included 63 studies with a total of 7096 Asian patients involved and 262 studies with a total of 27,477 Caucasian patients recruited. In SU treatment group, there were 22 studies conducted in Caucasian population, but no study was found to recruit Asians. In MET treatment group, there was one study conducted in Asians and 16 studies conducted in Caucasians. There were eight studies in Asians and 35 studies in Caucasians with AGI treatment and 12 studies in Asians and 72 studies in Caucasians with TZD treatment. In DPP-4i treatment, there were 23 studies in Asians and 46 studies in Caucasians. In SGLT2i treatment, there were 11 studies in Asians and 38 studies in Caucasians.

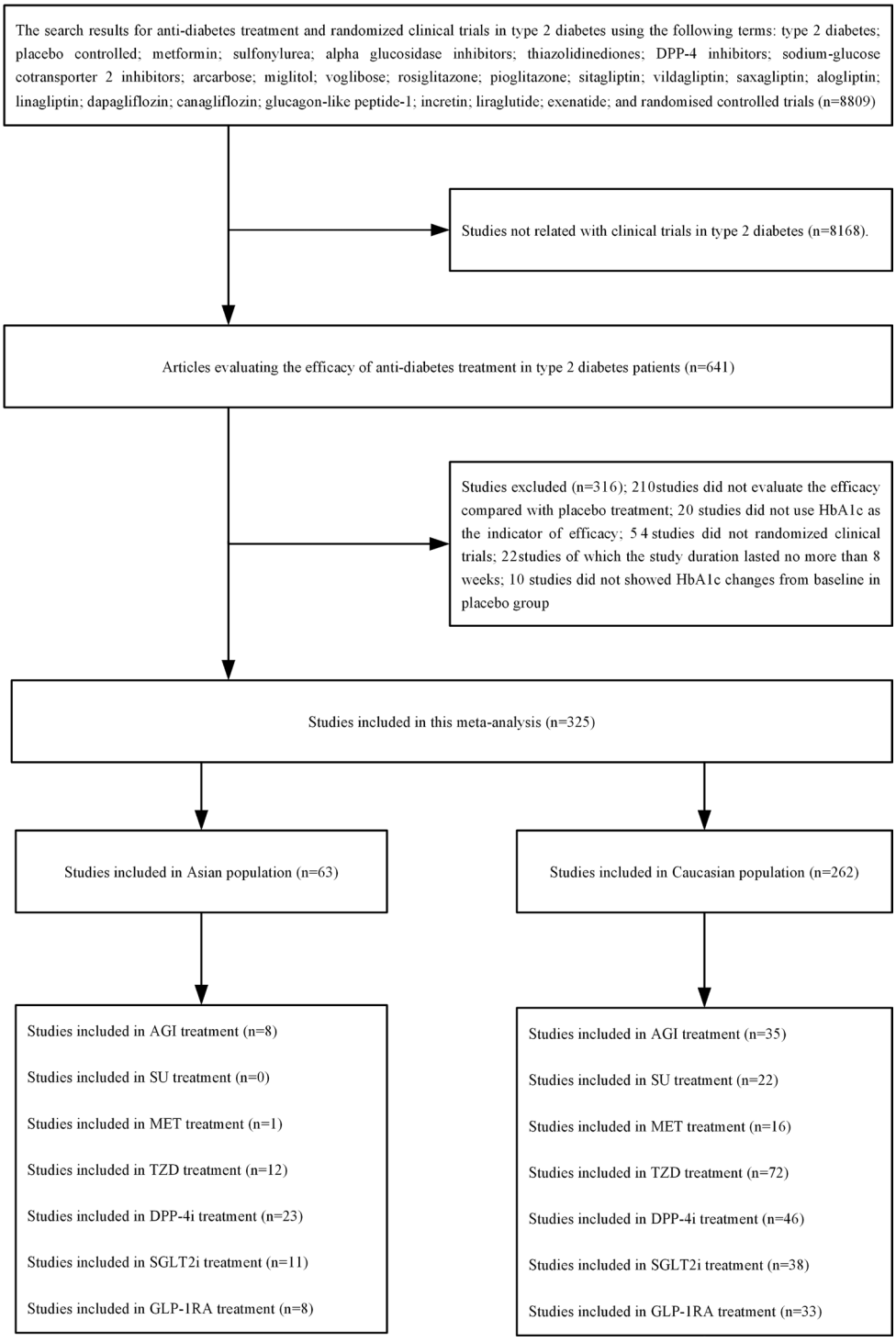

Figure 1: The flowchart of included studies. AGI: Alpha glucosidase inhibitor; SU: Sulfonylurea; MET: Metformin; TZD: Thiazolidinedione; DPP4i: Dipeptidyl peptidase-4 inhibitors; SGLT2i: Sodium-glucose cotransporter 2 inhibitors; GLP-1RA: Glucagon-like peptide-1 receptor agonist.

Table 1: Baseline characteristics of patients receiving placebo treatment compared between Asian population and Caucasian population in each kind of antidiabetic agents

Variables	Asian (n=63)	Caucasian (n=262)	t	P
SU				
Number of studies	0	22		
Age (years)	/	57.1 ± 4.3	/	/
Male (%)	/	42	/	/
Baseline BMI (kg/m^2)	/	30.1 ± 2.7	/	/
DM duration (years)	/	6.6 ± 3.1	/	/
Baseline HbA1c (%)	/	8.60 ± 1.12	/	/
MET				
Number of studies	1	16		
Age (years)	56.0 ± 2.8	57.0 ± 2.3	−0.580	0.568
Male (%)	44	42	−0.206	0.839
Baseline BMI (kg/m^2)	30.0 ± 1.4	30.5 ± 2.0	−0.334	0.742
DM duration (years)	3.0 ± 0.0	7.4 ± 3.2	−1.912	0.077
Baseline HbA1c (%)	8.00 ± 0.00	8.61 ± 1.40	−0.601	0.554
AGI				
Number of studies	8	35		
Age (years)	55.6 ± 3.7	59.4 ± 4.1	−2.353	0.025
Male (%)	54	43	−1.786	0.086
Baseline BMI (kg/m^2)	24.0 ± 0.0	29.6 ± 2.4	−3.279	0.001
DM duration (years)	8.2 ± 5.2	6.4 ± 2.9	1.119	0.273
Baseline HbA1c (%)	9.13 ± 0.84	8.16 ± 1.24	2.069	0.046
TZD				
Number of studies	12	72		
Age (years)	55.5 ± 5.0	57.7 ± 3.5	−1.744	0.086
Male (%)	44	41	−0.680	0.499
Baseline BMI (kg/m^2)	24.2 ± 1.8	31.1 ± 2.2	−8.798	<0.001
DM duration (years)	7.2 ± 3.0	7.0 ± 3.4	0.129	0.898
Baseline HbA1c (%)	8.64 ± 1.12	8.24 ± 1.05	1.138	0.262
DPP-4i				
Number of studies	23	46		
Age (years)	56.6 ± 3.3	57.1 ± 5.0	−0.423	0.673
Male (%)	40	46	2.945	0.004
Baseline BMI (kg/m^2)	25.3 ± 1.1	30.6 ± 1.5	−15.516	<0.001
DM duration (years)	5.9 ± 2.8	6.4 ± 3.7	−0.551	0.584
Baseline HbA1c (%)	8.24 ± 0.78	8.22 ± 0.46	0.127	0.899
SGLT2i				
Number of studies	11	38		
Age (years)	56.7 ± 4.1	57.6 ± 4.2	−0.633	0.530
Male (%)	37	46	2.906	0.005
Baseline BMI (kg/m^2)	26.9 ± 1.9	31.3 ± 1.9	−6.247	<0.001
DM duration (years)	5.9 ± 2.4	7.8 ± 4.8	−1.093	0.282
Baseline HbA1c (%)	8.00 ± 0.0	8.05 ± 0.4	−0.394	0.695
GLP-1RA				
Number of studies	8	33		
Age (years)	56.6 ± 2.7	55.7 ± 1.9	1.122	0.269
Male (%)	41	48	1.541	0.131
Baseline BMI (kg/m^2)	26.8 ± 3.6	33.0 ± 1.8	−7.177	<0.001
DM duration (years)	8.1 ± 3.3	6.6 ± 3.2	1.233	0.225
Baseline HbA1c (%)	8.22 ± 0.44	8.00 ± 0.35	1.610	0.115

Data are given as the mean ± SD. P values indicated the significance of the comparisons between Asian and Caucasian. SU: Sulfonylurea; BMI: Body mass index; DM: Diabetes mellitus; HbA1c: Glycosylated hemoglobin; MET: Metformin; AGI: Alpha glucosidase inhibitor; TZD: Thiazolidinedione; DPP-4i: Dipeptidyl peptidase-4 inhibitor; SGLT2i: Sodium-glucose cotransporter 2 inhibitor; GLP-1RA: Glucagon-like peptide-1 receptor agonist; SD: Standard deviation; /: No reported data.

Moreover, there were eight studies in Asian population and 33 studies in Caucasian population with GLP-1RA treatment compared with placebo [Supplementary Tables S1 and S2].

Table 2: Placebo effect on HbA1c changes in the antidiabetic treatment between Asian and Caucasian population

Variables	Asian					Caucasian					Differences‡
	n	MD	95% *CI*	*P**	I^2 (%)	*n*	MD	95% *CI*	*P*†	I^2 (%)	
SU											
Total	0	/	/	/	/	25	0.187	−0.144–0.518	0.269	77.7	/
Mono	0	/	/	/	/	11	0.683	0.181–1.185	0.008	61.9	/
Addon	0	/	/	/	/	14	−0.286	−0.721–0.149	0.197	60.7	/
MET											
Total	2	0.140	−1.330–1.611	0.852	0.0	23	0.127	−0.360–0.613	0.610	68.3	0.013
Mono	2	0.140	−1.330–1.611	0.852	0.0	15	0.404	−0.112–0.919	0.125	85.3	−0.264
Addon	0	/	/	/	/	8	−0.375	−1.374–0.624	0.462	70.9	/
AGI											
Total	8	−0.070	−0.562–0.421	0.779	0.0	35	0.014	−0.275–0.304	0.923	92.4	−0.084
Mono	2	−0.301	−0.921–0.319	0.341	0.0	20	0.128	−0.285–0.541	0.545	92.4	−0.429
Addon	6	−0.014	−0.607–0.578	0.962	0.0	15	−0.066	−0.464–0.332	0.746	88.3	0.052
TZD											
Total	11	−0.036	−0.962–0.890	0.939	0.0	66	0.130	−0.174–0.433	0.402	79.3	−0.166
Mono	2	0.203	−2.328–2.735	0.875	0.0	33	0.403	−0.091–0.898	0.110	76.7	−0.200
Addon	9	−0.105	−1.048–0.838	0.827	0.0	33	−0.016	−0.399–0.367	0.934	82.2	−0.089
DPP-4i											
Total	28	−0.162	−0.289–−0.035	0.012	88.9	54	−0.193	−0.311–−0.075	0.001	94.2	0.031
Mono	10	−0.041	−0.191–0.108	0.588	91.8	16	0.091	−0.128–0.311	0.415	62.6	−0.132
Addon	18	−0.211	−0.379–−0.044	0.013	80.0	38	−0.288	−0.427–−0.149	0.000	95.3	0.077
SGLT2i											
Total	10	−0.047	−0.543–0.449	0.853	87.2	43	−0.230	−0.340–−0.121	0.000	88.5	0.183
Mono	9	0.053	−0.398–0.504	0.818	79.5	8	0.033	−0.565–0.632	0.913	42.4	0.020
Addon	1	/	/	/	/	35	−0.257	−0.361–−0.154	0.000	90.6	/
GLP-1RA											
Total	9	−0.214	−0.448–0.021	0.074	81.3	34	−0.172	−0.383–0.038	0.109	72.1	−0.042
Mono	3	0.048	−0.670–0.765	0.897	18.5	9	−0.091	−0.502–0.321	0.666	0.0	0.139
Addon	6	−0.269	−0.509–−0.029	0.028	85.0	25	−0.188	−0.427–0.050	0.122	79.0	−0.081

**P* value represented the significance of placebo effect on HbA1c changes from baseline in Asian population; †*P* value represented the significance of placebo effect on HbA1c changes from baseline in Caucasian population. ‡All differences of HbA1c changes between Asian and Caucasian populations were without significance. MD: Mean difference; *CI*: Confidence interval; SU: Sulfonylurea; MET: Metformin; AGI: Alpha glucosidase inhibitor; TZD: Thiazolidinedione; DPP-4i: Dipeptidyl peptidase-4 inhibitor; SGLT2i: Sodium-glucose cotransporter 2 inhibitor; GLP-1RA: Glucagon-like peptide-1 receptor agonist; Mono: Monotherapy; Addon: Add-on therapy; *n*: Number of treatment arms included; /: No reported data.

Baseline characteristics of the patients received placebo treatment in different studies are shown in Table 1. Baseline BMI was significantly different between Asian and Caucasians in the treatment of AGIs, TZDs, DPP-4i, SGLT2i, and GLP-1RAs, but not in the treatment of MET. Other characteristics such as baseline age, gender, duration of diabetes, and baseline HbA1c were comparable between Asian and Caucasian populations in most kinds of antidiabetic treatment.

Methodological quality

All studies were double-blindly designed with placebo controlled. The heterogeneity was assessed for each hypoglycemic treatment. When the $I^2 > 50\%$, the random-effect model was used, and when the $I^2 \leq 50\%$, the fixed-effect model was used. The publication bias assessed via visual inspection of the funnel plot suggested no significant risk of publication bias. The risk of bias in each study was evaluated according to the Cochrane instrument in both Asian population and Caucasian population [Supplementary Figures S1 and S2].

Placebo effect in glycosylated hemoglobin between Asian and Caucasian population in antidiabetic treatment

In SU treatment group, the use of placebo led to a nonsignificant HbA1c change from baseline (MD, 0.187%; 95% *CI*, −0.144–0.518%; $P = 0.269$) in Caucasian population. There was no study in Asian population. In MET treatment group, the placebo effect led to a nonsignificant HbA1c change of 0.127% (95% *CI*, −0.360–0.613%; $P = 0.610$) in Caucasian population and also a nonsignificant HbA1c change of 0.140% (95% *CI*, −1.330–1.611%; $P = 0.852$) in Asian population. In AGI treatment group, the placebo effect resulted in an HbA1c change of 0.014% without significance (95% *CI*, −0.275–0.304%; $P = 0.923$) in Caucasians and resulted in a nonsignificant HbA1c change of −0.070% (95% *CI*, −0.562–0.421%; $P = 0.779$) in Asians. In TZD treatment group, the placebo effect led to a nonsignificant HbA1c change of 0.130% (95% *CI*, −0.174–0.433%; $P = 0.402$) in Caucasians as well as a nonsignificant HbA1c change

Table 3: Placebo effect on body weight changes in the antidiabetic treatment between Asian and Caucasian population

Variables	Asian					Caucasian					Differences‡
	n	MD	95% *CI*	*P**	I^2 (%)	*n*	MD	95% *CI*	*P*†	I^2 (%)	
SU											
Total	0	/	/	/	/	10	−0.833	−1.423–−0.243	0.006	99.5	/
Mono	0	/	/	/	/	6	−0.947	−1.810–−0.084	0.032	99.8	/
Addon	0	/	/	/	/	4	−0.647	−1.301–0.007	0.053	77.4	/
MET											
Total	0	/	/	/	/	8	−0.686	−2.823–1.451	0.529	0.0	/
Mono	0	/	/	/	/	6	−0.950	−3.624–1.723	0.486	0.0	/
Addon	0	/	/	/	/	2	0.346	−0.597–1.288	0.472	88.9	/
AGI											
Total	3	0.145	−1.543–1.834	0.866	0.0	12	−0.594	−1.607–0.420	0.251	0.0	0.739
Mono	1	/	/	/	/	9	−0.699	−1.733–0.335	0.185	0.0	/
Addon	2	0.136	−2.341–2.612	0.914	0.0	3	−0.330	−2.759–2.099	0.790	0.0	0.466
TZD											
Total	4	−0.348	−1.494–0.797	0.551	0.0	19	0.018	−0.945–0.982	0.970	67.4	−0.366
Mono	1	/	/	/	/	7	−0.582	−1.161–−0.003	0.049	73.4	/
Addon	3	−0.322	−1.567–0.923	0.612	0.0	12	0.122	−1.003–1.247	0.832	71.3	−0.444
DPP-4i											
Total	13	−0.345	−0.854–0.164	0.184	45.1	34	−0.058	−0.407–0.290	0.743	85.9	−0.287
Mono	6	−0.468	−0.989–0.054	0.079	29.3	10	−0.304	−0.720–0.112	0.152	87.7	−0.164
Addon	7	−0.242	−1.070–0.587	0.567	30.4	24	0.030	−0.419–0.479	0.896	85.4	−0.272
SGLT2i											
Total	10	−0.399	−1.286–0.488	0.378	9.3	41	−0.512	−2.882–1.859	0.672	69.5	0.113
Mono	9	−0.375	−1.447–0.696	0.492	33.3	8	−0.975	−12.230–10.279	0.865	0.0	0.600
Addon	1	/	/	/	/	33	−0.453	−2.711–1.805	0.694	74.9	/
GLP-1RA											
Total	8	−0.612	−0.884–−0.339	<0.001	38.8	28	−0.953	−1.626–−0.280	0.006	83.2	0.341
Mono	3	−0.767	−1.270–−0.264	0.003	0.0	7	−1.388	−1.804–−0.973	<0.001	85.3	0.621
Addon	5	−0.570	−0.888–−0.252	<0.001	63.8	21	−0.882	−1.662–−0.102	0.027	82.3	0.312

**P* value represented the significance of placebo effect on body weight changes from baseline in Asian population; †*P* value represented the significance of placebo effect on body weight changes from baseline in Caucasian population. ‡All differences of body weight changes between Asian and Caucasian populations were without significance. MD: Mean difference; *CI*: Confidence interval; SU: Sulfonylurea; MET: Metformin; AGI: Alpha glucosidase inhibitor; TZD: Thiazolidinedione; DPP-4i: Dipeptidyl peptidase-4 inhibitor; SGLT2i: Sodium-glucose cotransporter 2 inhibitor; GLP-1RA: Glucagon-like peptide-1 receptor agonist; Mono: Monotherapy; Addon: Add-on therapy; *n*: Number of treatment arms included; /: No reported data.

of −0.036% (95% *CI*, −0.962–0.890%; *P* = 0.939) in Asians. In DPP-4i treatment group, the placebo effect led to a significant decrease in HbA1c (MD, −0.193%; 95% *CI*, −0.311–−0.075%; *P* = 0.001) in Caucasian population and also a significant reduction of HbA1c (MD, −0.162%; 95% *CI*, −0.289–−0.035%; *P* = 0.012) in Asian population. In SGLT2i treatment group, the placebo effect resulted in a significant decrease in HbA1c (MD, −0.230%; 95% *CI*, −0.340–−0.121%; *P* < 0.001) in Caucasians while it resulted in a nonsignificant HbA1c change of − 0.047% (95% *CI*, −0.543–0.449%; *P* = 0.853) in Asian population. In GLP-1RA treatment group, the placebo effect led to an HbA1c change of −0.172% (95% *CI*, −0.383–0.038%; *P* = 0.109) without significance in Caucasians and also a nonsignificant HbA1c change of −0.214% (95% *CI*, −0.448–0.021%; *P* = 0.074) in Asians [Table 2]. Comparisons of the placebo effect in HbA1c changes relative to baseline indicated that no significant difference was found between Asian and Caucasian population in MET, AGI, TZD, DPP-4i, SGLT-2i, and GLP-1RA treatment. Since no studies of Asian population in SU treatment, it was concerned lack of evidence for comparing the Asian and Caucasian population in this category [Table 2 and Supplementary Figures S3-S15].

Placebo effect in body weight between Asian and Caucasian population in antidiabetic treatment

In SU treatment group, the placebo effect resulted in a significant weight decrease (MD, −0.833 kg; 95% *CI*, −1.423–−0.243 kg; *P* = 0.006) in Caucasian population. No data were found with placebo effect in Asians. In MET treatment group, the placebo effect resulted in a nonsignificant weight change of −0.686 kg (95% *CI*, −2.823–1.451 kg; *P* = 0.529) in Caucasian population. No data were found with placebo effect in Asian population. In AGI treatment group, the placebo effect resulted in a nonsignificant weight change of −0.594 kg (95% *CI*, −1.607–0.420 kg; *P* = 0.251) in Caucasians and also a nonsignificant body weight change of 0.145 kg (95% *CI*, −1.543–1.834 kg; *P* = 0.866) in Asians. In TZD treatment group, the placebo effect led to a weight change of 0.018 kg without significance (95% *CI*, −0.945–0.982 kg; *P* = 0.970)

in Caucasians and also a nonsignificant body weight change of −0.348 kg (95% *CI*, −1.494–0.797 kg; *P* = 0.551) in Asians. In DPP-4i treatment group, the placebo effect led to a weight change of −0.058 kg without significance (95% *CI*, −0.407–0.290 kg; *P* = 0.743) in Caucasian population and a nonsignificant body weight change of −0.345 kg (95% *CI*, −0.854–0.164 kg; *P* = 0.184) in Asian population. In SGLT2i treatment group, the placebo treatment led to a weight change of −0.512 kg without significance (95% *CI*, −2.882–1.859 kg; *P* = 0.672) in Caucasians and also a nonsignificant body weight change of −0.399 kg (95% *CI*, −1.286–0.488 kg; *P* = 0.378) in Asian population. In GLP-1RA treatment group, weight change in placebo effect was −0.953 kg with significance (95% *CI*, −1.626–−0.280 kg; *P* = 0.006) in Caucasians, and in Asians, the placebo effect was associated with a significant body weight reduction (MD, −0.612 kg; 95% *CI*, −0.884–−0.339 kg; *P* < 0.001). Comparisons of the placebo effect in body weight changes from baseline indicated that no significant difference was found between Asian and Caucasian population in AGI, TZD, DPP-4i, SGLT-2i, and GLP-1RA treatment. Since no studies of Asian population in SU and MET treatment, it was concerned lack of evidence for comparing the Asian and Caucasian population in those treatments [Table 3 and Supplementary Figures S16-S27].

Associated factors with placebo effect

Meta-regression analysis indicated that, in each antidiabetic treatment group, the HbA1c changes in placebo treatment were not associated with the baseline age, gender, BMI, baseline HbA1c, DM duration, or study duration, respectively. There was also no association between HbA1c change and weight change from baseline. Meta-regression analysis also suggested that the weight change was not associated with the baseline age, gender, baseline BMI, duration of diabetes, study duration, baseline HbA1c, and the HbA1c changes from baseline in each antidiabetic treatment [Supplementary Table S3].

Discussion

With the aim of comparisons between Asian and Caucasian population of the placebo effect, this meta-analysis indicated that the overall difference of the placebo effect in HbA1c changes from baseline was not significant, and the difference of the placebo effect in body weight changes from baseline between the two populations was neither significant in the seven kinds of antidiabetic treatments in T2DM. However, it is clear that there was a reduction of HbA1c and body weight due to placebo in each population. These data were based on a large dataset of placebo treatment including 63 studies in Asians and 262 studies in Caucasians. Moreover, placebo effect on HbA1c change or body weight change was not associated with baseline age, gender, BMI, baseline HbA1c, duration of diabetes, and study duration both in Asians and Caucasians.

The term "'placebo effect" was first introduced by Graves in 1920.[23] A placebo treatment may be administered through ingestion, injection, inhalation, insertion into a body cavity, or topical application. Placebo effect in T2DM might be associated with the optimal dietary treatment as well as physical activity and exercise for the glucose control and body weight control, besides medication therapy. Some evidence indicated that the dietary treatment for the glucose control might reduce HbA1c by 0.12~0.5% and also associated with weight change by −0.84~1.39 kg.[24-26] Physical activity and exercise were also suggested to improve the glucose control in people with T2DM with an average decrease in HbA1c by 0.4~0.6%.[3-5] All the above may contribute to the placebo effect on glucose control and body weight control. In this meta-analysis, we summarized the exact placebo effect in Caucasian population as well as in Asian population with different treatments for T2DM.

So far, mechanisms that underlie placebo effect are still not clearly understood. As Shapiro *et al.* indicated,[6] the reasons might fall within one of the three general categories. First, patient variables might be associated with placebo effect, including the attitude toward the physician, the treatment, and the illness, as well as including the levels of anxiety and expectation. However, in this meta-analysis, we could not collect these data from published trials to make further comparisons. Second, the physician variables may be another factor, including the doctor's credibility, enthusiasm, authority, empathy, and sympathy, which was also lack of evidence in this study. Third, there might be associated with situational variables, including the location and form of treatment. However, in this study, we compared placebo effect in glucose control and body weight change between Caucasian and Asian population in all the seven kinds of antidiabetic treatments but found no significant difference. Other possible reasons for placebo effect, as indicated by Gowdey[2] in his review of placebo pharmacology, the influence of expectations might play a role, which could not be confirmed in our study because of no evidence. Besides medication therapy, mechanisms for placebo effect in T2DM might be associated with the optimal dietary approach as well as physical activity to control hyperglycemia in T2DM.[2] Several reviews and meta-analyses[3,4,24] indicated that diet and exercise could produce significant improvements in glucose control in people with T2DM. The difference of diet approach between Asian and Caucasian population was reported as the different composition of diet; however, with the rapid development of Asian, the western diet became more and more popular in Asian countries and the difference became smaller and smaller. The difference of physical activity between the two ethnicities was seldom reported and studied; therefore, all the above possible causes or mechanisms that might be associated with the placebo effect in T2DM treatments may not be significantly different between Caucasian and Asian population.

In a recently reported review, Kaptchuk and Miller[7] suggested that the therapeutic benefits associated with placebo effects did not alter the pathophysiology of diseases beyond their symptomatic manifestations. The observation from our mate-analysis supported the above conclusion. Ulteriorly, we proposed that the placebo effect in HbA1c changes and body weight changes of anti-diabetes treatment were comparable between Caucasians and Asians although there were evidence indicating that the pathophysiology of insulin secretion and insulin resistance was not the same between the two

ethnicities.[9,14] What's more, meta-regression analysis from our study also indicated that the placebo effect on HbA1c changes as well as on weight changes from baseline was not associated with baseline factors although the baseline BMI levels were significantly lower in Asians than that in Caucasians.

Certainly, as a meta-analysis, our meta-analysis has some limitations that we will better list here. First, the inclusion criteria and the baseline characteristics such as age, BMI, and duration of diabetes were different across studies, which caused a high level of heterogeneity. However, with the aim of comparisons between Asian and Caucasian population of the placebo effect, we used the random-effect model for analysis when the level of heterogeneity was high and also performed sensitivity analysis. We had also made meta-regression analysis to find if the baseline characteristics were the associated factors. Second, the data on placebo effects on glucose control or body weight control in each trial were used as the parameters in this meta-analysis, but not the pooled, patient-level data, which should be more useful to make a conclusion. However, these data are seldom available because most trials are sponsored by the industry. Therefore, we used the parameters in each trial as surrogates. Third, since no studies of Asian population in SU and MET treatments when we made comparisons of the placebo effect on HbA1c and body weight changes from baseline, it is concerned lack of evidence for comparing the Asian and Caucasian patients in those categories. Moreover, publication bias may also have effects on the results of placebo effects in this meta-analysis; however, a funnel plot assessment was carried out to minimize the risk of publication bias.

In a word, our results from this meta-analysis should be interpreted cautiously. The overall difference of the placebo effect on HbA1c changes as well as on body weight changes was not significant between Asian and Caucasian T2DM patients, but it is clear that there was a reduction of HbA1c and body weight due to placebo in each population. The placebo effect was not associated with baseline age, gender, baseline BMI, baseline HbA1c, duration of diabetes, or study duration.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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亚洲与欧美人群2型糖尿病患者的安慰剂效应比较

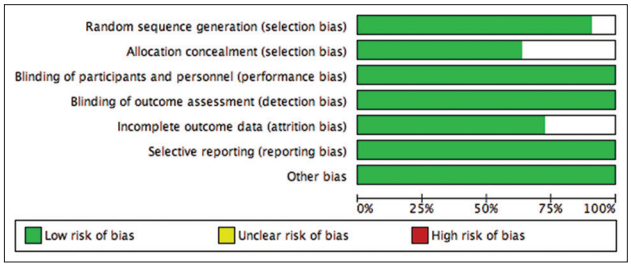
摘要

背景：安慰剂效应被理解为非特定心理及生理效应，而无特定药理学效应。有证据显示，在2型糖尿病治疗方面，安慰剂效应源自于减少总热量的摄入以及减轻体重。本荟萃分析的目的是系统评价在亚洲与欧美2型糖尿病患者人群中的安慰剂效应，并比较安慰剂效应在两人种之间的差异。

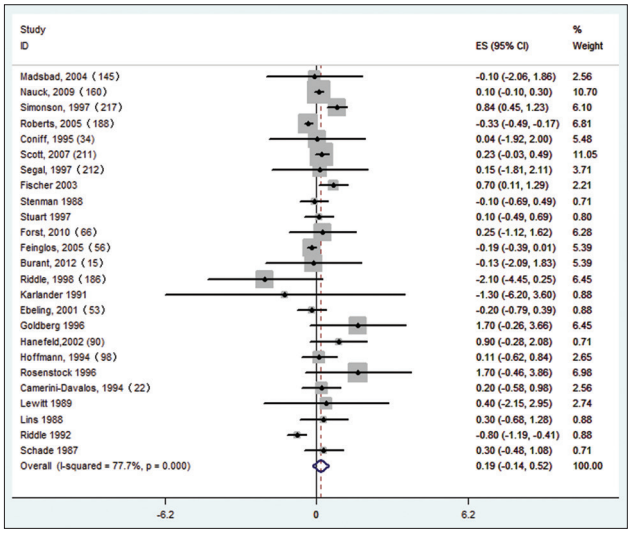
方法：在MEDLINE、EMBASE、Cochrane等数据库中进行文献检索，检索截止时间2016年11月。检索关键词为英文，包括：磺脲类(SU)、α-糖苷酶抑制剂(AGI)、二甲双胍(MET)、噻唑烷二酮类(TZD)、二肽基肽酶-4抑制剂(DPP-4i)、钠葡萄糖协同转运蛋白2抑制剂(SGLT2i)、胰高血糖素样肽受体激动剂(GLP-1RA)、2型糖尿病(T2DM)、空白对照、随机对照试验。应用Cochrane协作网对临床随机分组、对照、双盲研究进行质量评估。

结果：本荟萃分析共纳入63项亚洲人群研究（7096名患者）和262项欧美人群研究（27477名患者）。在欧美人群中，安慰剂的使用带来了糖化血红蛋白（HbA1c）的显著下降，其中SU单药治疗组-0.683% (P=0.008)、DPP-4i组-0.193% (P=0.001)及SGLT2i组-0.230%(P=0.000)。在亚洲人群中，安慰剂的使用在DPP-4i组及GLP-1RA联合治疗组也带来了HbA1c的显著下降，分别为-0.162% (P=0.012)、-0.269% (P=0.028)。安慰剂效应同时带来了显著的体重减轻，在欧美人群中，安慰剂所致的体重下降在SU组为-0.833kg (P=0.006)、GLP-1RA组为-0.953kg (P=0.006)。在亚洲人群中，安慰剂所致的体重下降在GLP-1RA组为-0.612kg (P=0.000)。安慰剂效应对HbA1c变化及体重变化的影响在两个人群中的其它治疗组均无显著变化。各治疗组间的比较显示，安慰剂所致的HbA1c及体重变化在亚洲与欧美2型糖尿病人群中无明显差异。

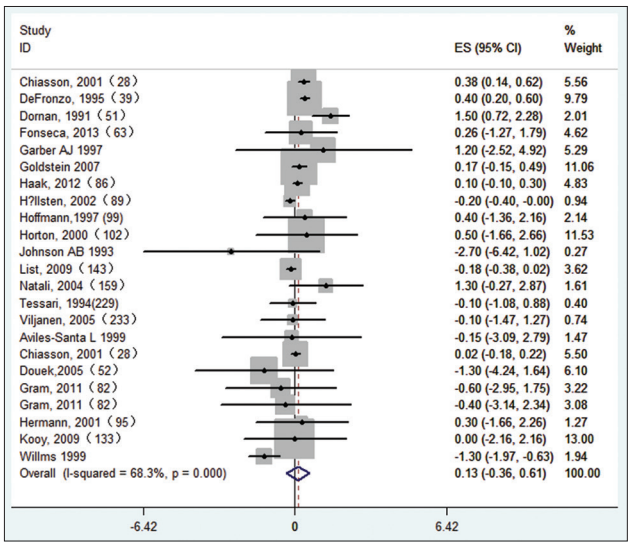
结论：安慰剂效应对HbA1c变化及体重变化的影响在亚洲与欧美2型糖尿病人群中无显著差异，且与年龄、性别、基线体重指数（BMI）、基线HbA1c、糖尿病病程及研究时长无明显相关性。



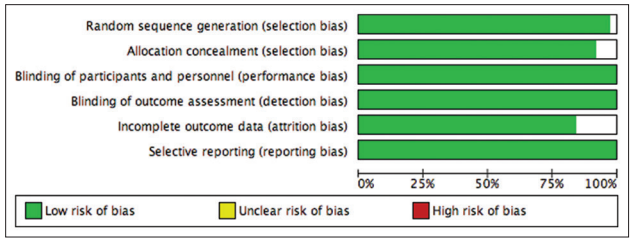
Supplementary Figure S1: Evaluation of the risk of bias of the studies included in Asian population.



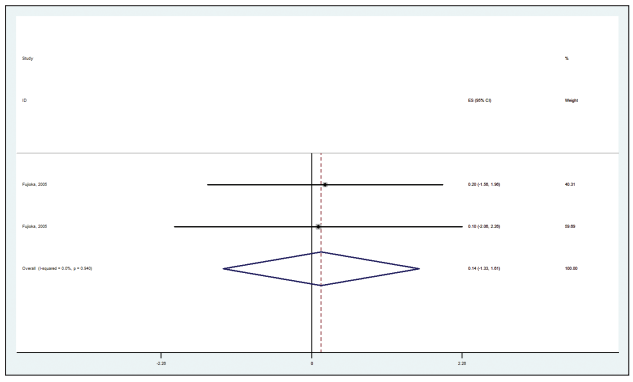
Supplementary Figure S3: Placebo effect on HbA1c changes in sulfonylurea treatment group in Caucasian population.



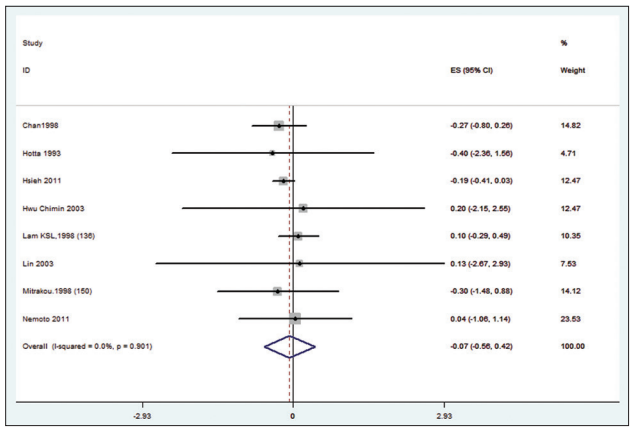
Supplementary Figure S5: Placebo effect on HbA1c changes in metformin treatment group in Caucasian population.



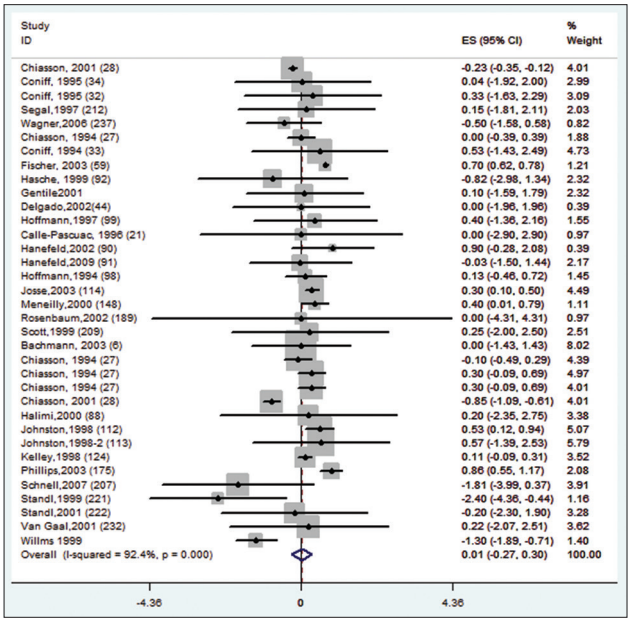
Supplementary Figure S2: Evaluation of the risk of bias of the studies included in Caucasian population.



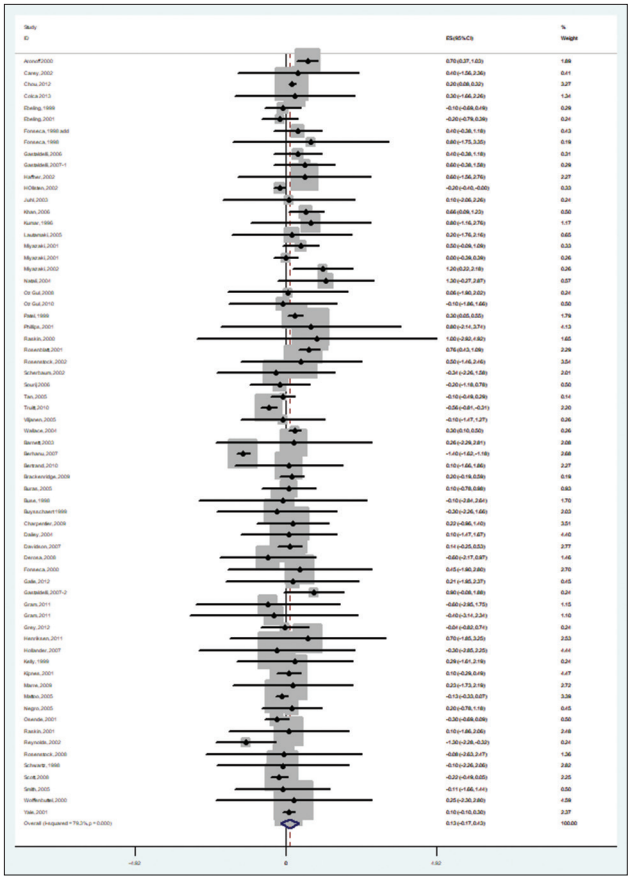
Supplementary Figure S4: Placebo effect on HbA1c changes in metformin treatment group in Asian population.



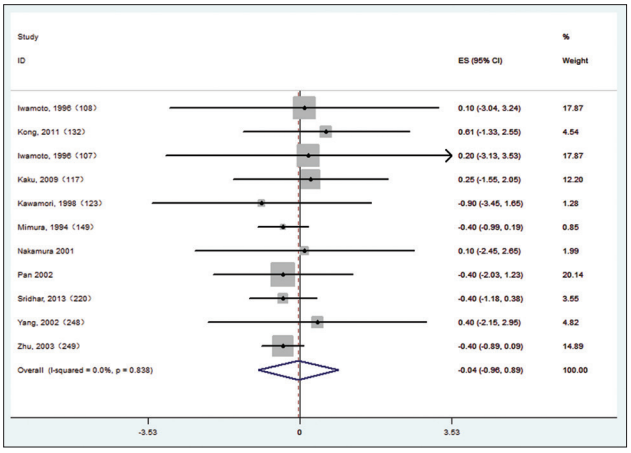
Supplementary Figure S6: Placebo effect on HbA1c changes in alpha glucosidase inhibitors treatment group in Asian population.



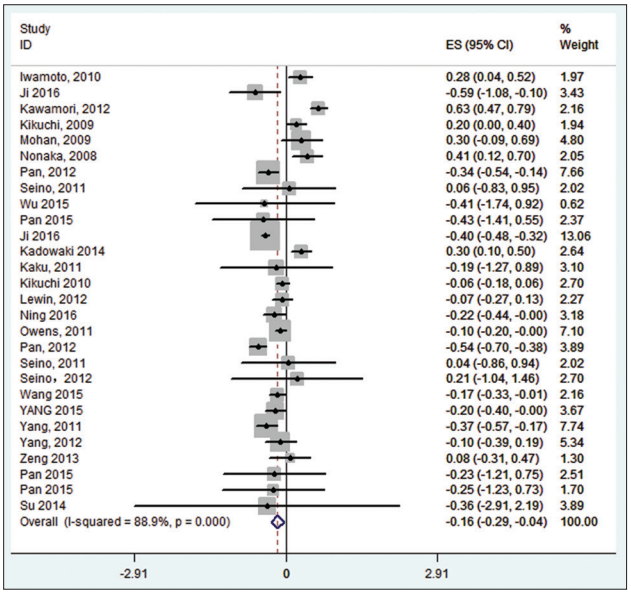
Supplementary Figure S7: Placebo effect on HbA1c changes in alpha glucosidase inhibitors treatment group in Caucasian population.



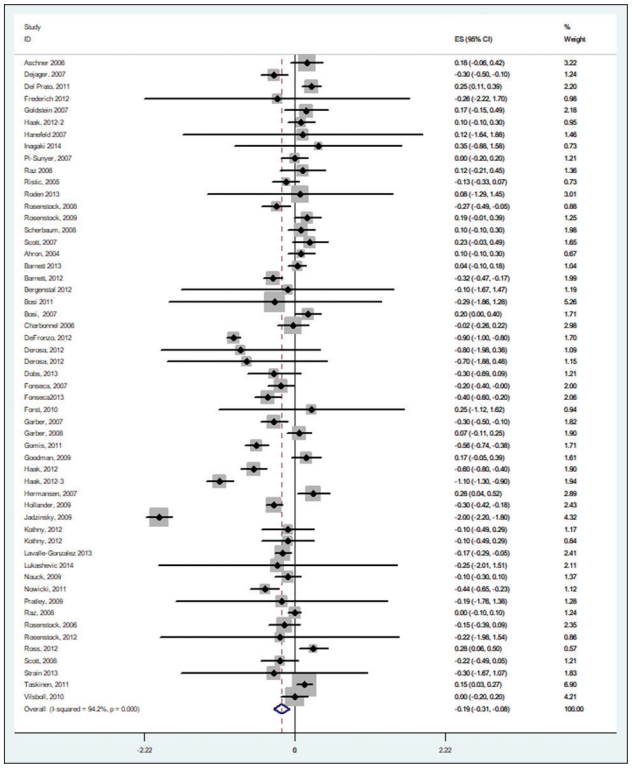
Supplementary Figure S9: Placebo effect on HbA1c changes in thiazolidinediones treatment group in Caucasian population.



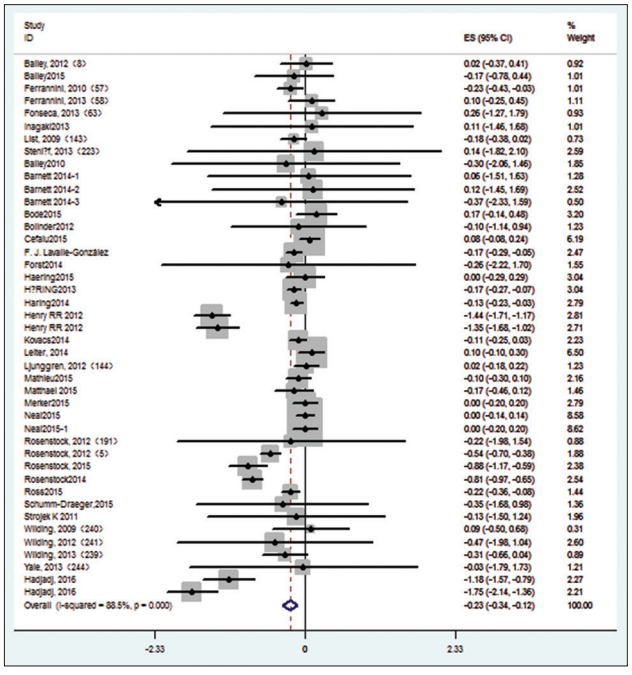
Supplementary Figure S8: Placebo effect on HbA1c changes in thiazolidinediones treatment group in Asian population.



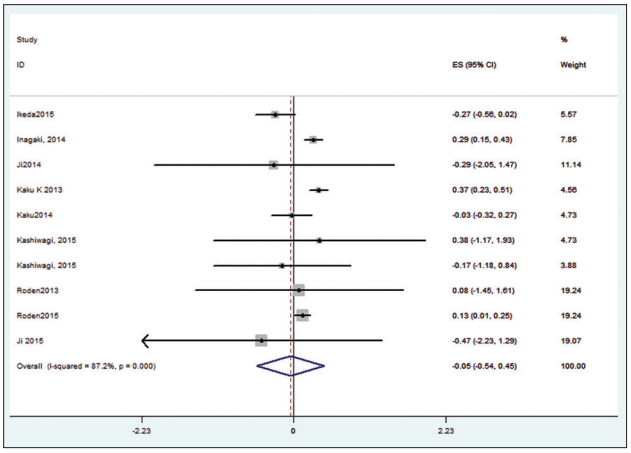
Supplementary Figure S10: Placebo effect on HbA1c changes in DPP-4 inhibitors treatment group in Asian population.



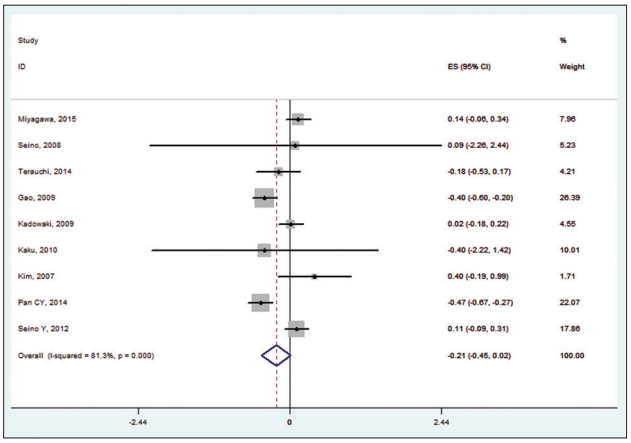
Supplementary Figure S11: Placebo effect on HbA1c changes in DPP-4 inhibitors treatment group in Caucatian population.



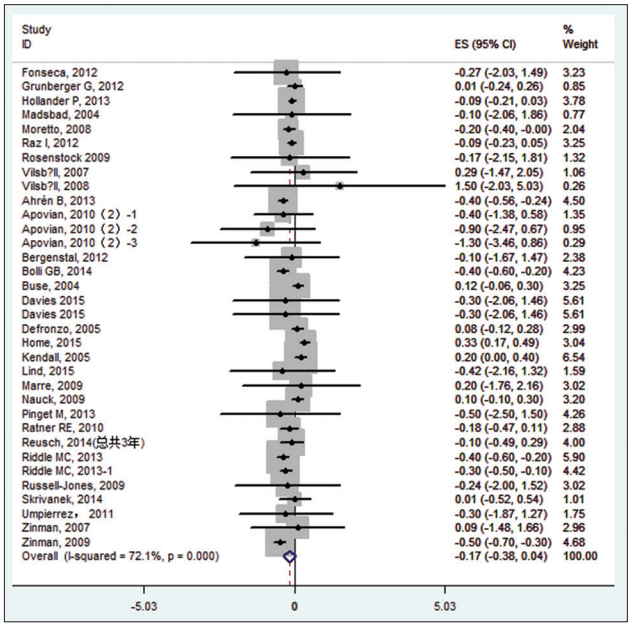
Supplementary Figure S13: Placebo effect on HbA1c changes in sodium-glucose cotransporter 2 inhibitors treatment group in Caucatian population.



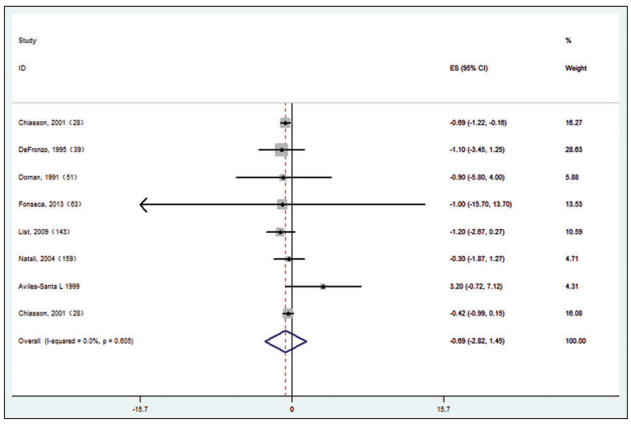
Supplementary Figure S12: Placebo effect on HbA1c changes in sodium-glucose cotransporter 2 inhibitors treatment group in Asian population.



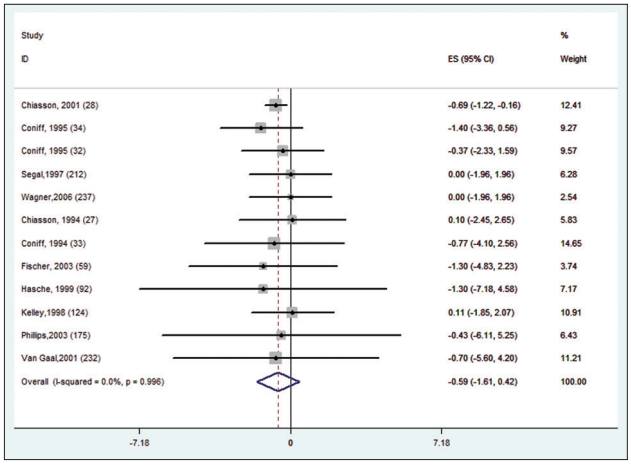
Supplementary Figure S14: Placebo effect on HbA1c changes in glucagon-like peptide-1 analogs treatment group in Asian population.



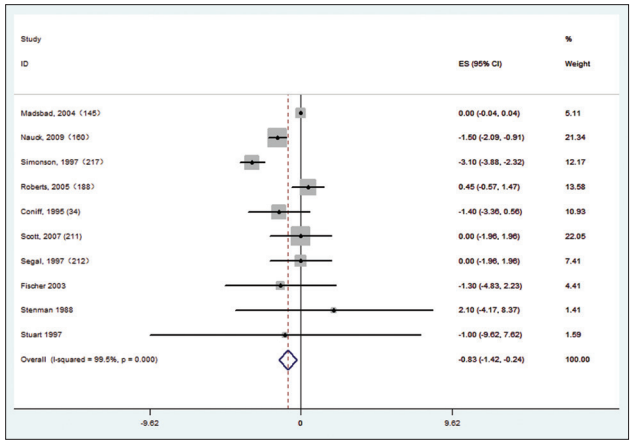
Supplementary Figure S15: Placebo effect on HbA1c changes in glucagon-like peptide-1 analogs treatment group in Caucasian population.



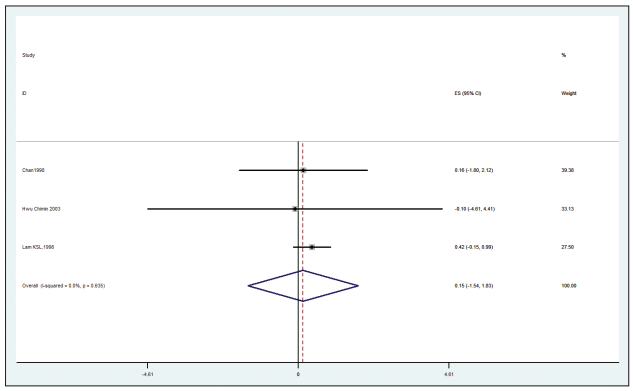
Supplementary Figure S17: Placebo effect on weight changes in metformin treatment group in Caucatian population.



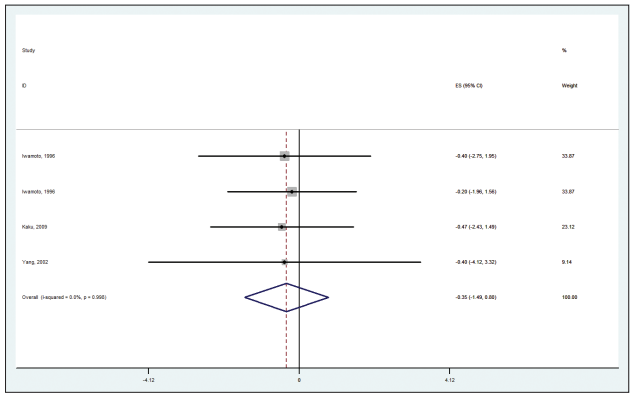
Supplementary Figure S19: Placebo effect on weight changes in alpha glucosidase inhibitors treatment group in Caucasian population.



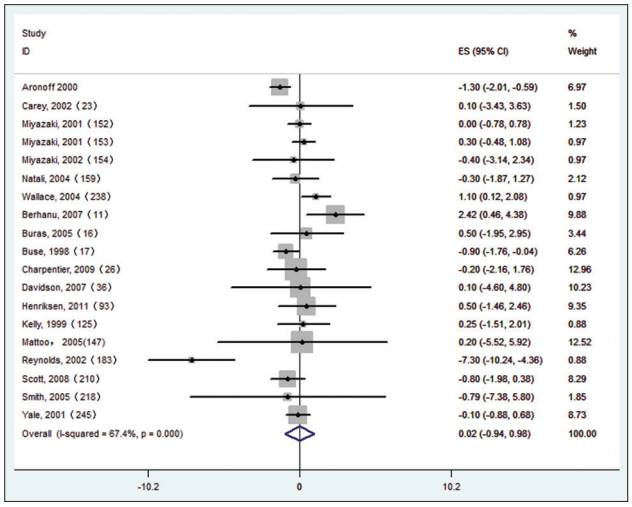
Supplementary Figure S16: Placebo effect on weight changes in sulfonylurea treatment group in Caucasian population.



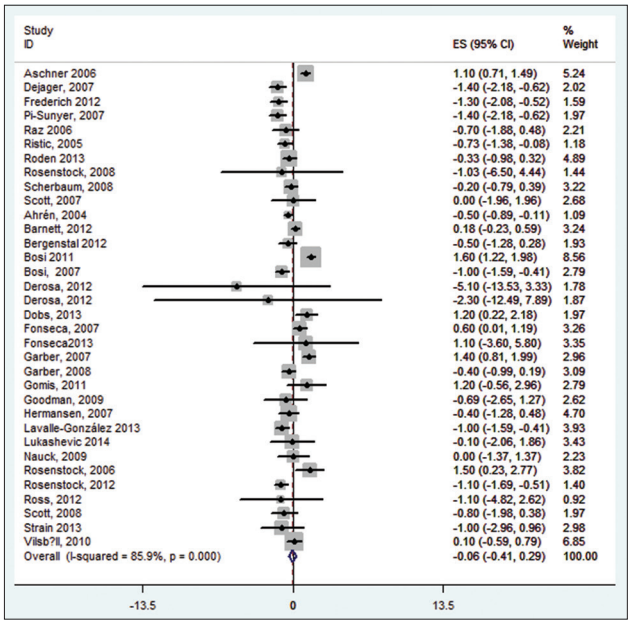
Supplementary Figure S18: Placebo effect on weight changes in alpha glucosidase inhibitors treatment group in Asian population.



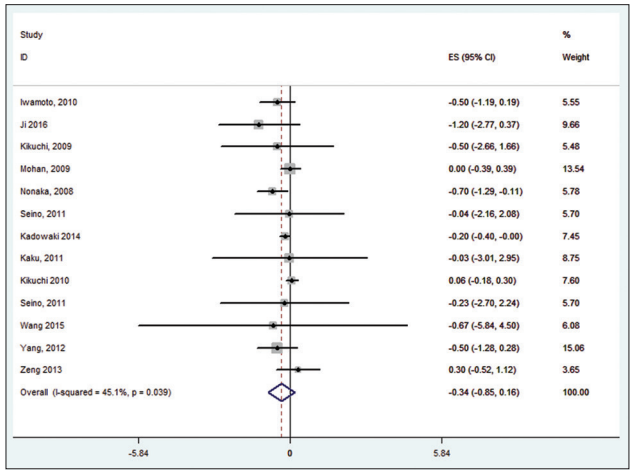
Supplementary Figure S20: Placebo effect on weight changes in thiazolidinediones treatment group in Asian population.



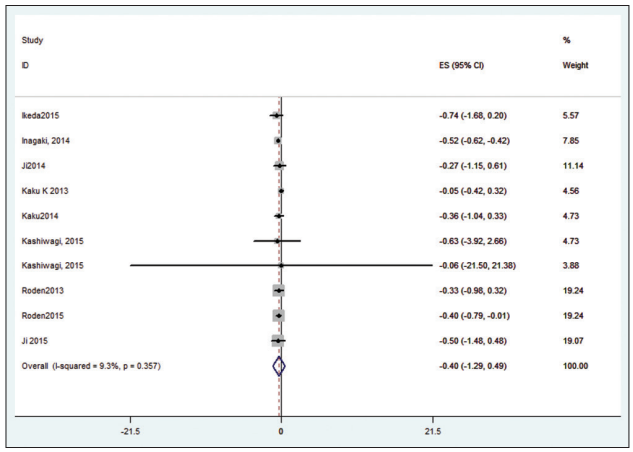
Supplementary Figure S21: Placebo effect on weight changes in thiazolidinediones treatment group in Caucasian population.



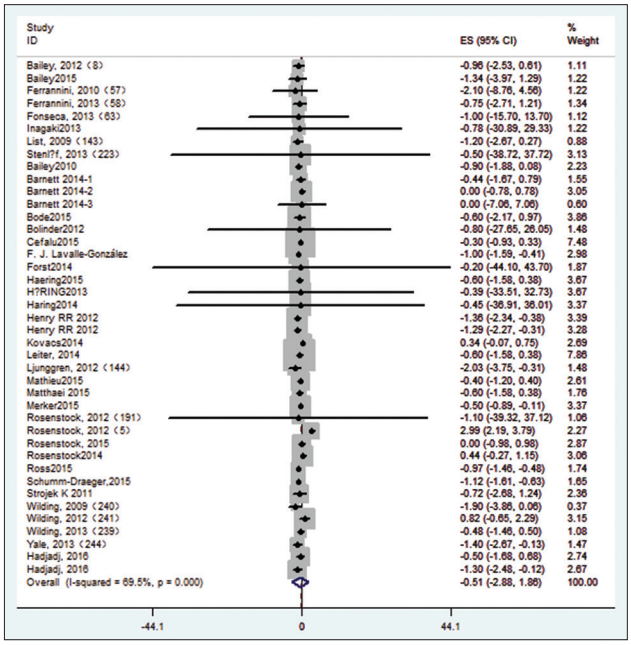
Supplementary Figure S23: Placebo effect on weight changes in DPP-4 inhibitors treatment group in Caucasian population.



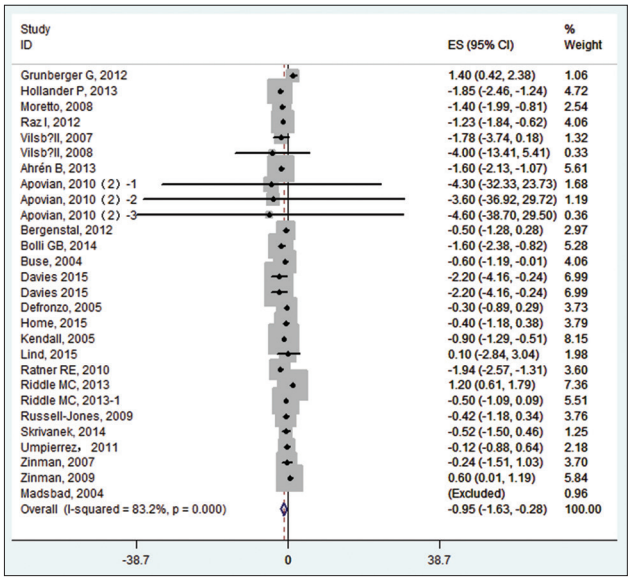
Supplementary Figure S22: Placebo effect on weight changes in DPP-4 inhibitors treatment group in Asian population.



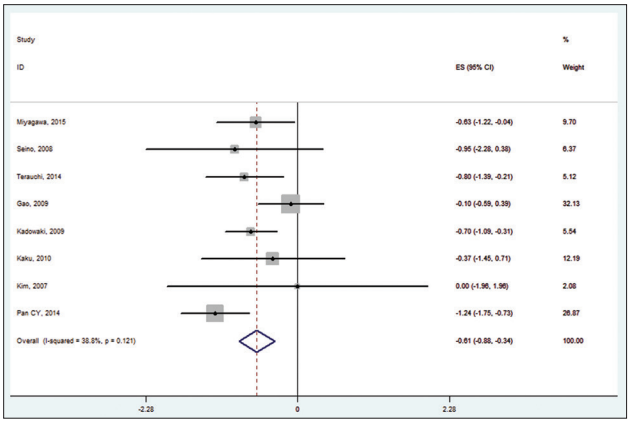
Supplementary Figure S24: Placebo effect on weight changes in sodium-glucose cotransporter 2 inhibitors treatment group in Asian population.



Supplementary Figure S25: Placebo effect on weight changes in sodium-glucose cotransporter 2 inhibitors treatment group in Caucasian population.



Supplementary Figure S27: Placebo effect on weight changes in glucagon-like peptide-1 analogs treatment group in Caucasian population.



Supplementary Figure S26: Placebo effect on weight changes in glucagon-like peptide-1 analogs treatment group in Asian population.

Supplementary Table S1: Studies in Asian population

Author, year	Study duration	Treatment group	Number of patients	Age (years)	Men (%)	BMI (kg/m^2)	DM duration (years)	Baseline HbA1c (%)
MET versus placebo, monotherapy								
Fujioka, 2005	24 weeks	Placebo	79	58 ± 11	63	28.9 ± 3.5	3.2 ± 2.6	7.9 ± 0.9
Fujioka, 2005	16 weeks	Placebo	117	54 ± 10	49	30.7 ± 4.1	2.7 ± 2.7	8.3 ± 1.1
AGI versus placebo, monotherapy								
Chan, 1998	24 weeks	Placebo	63	54 (10)	50.8	/	2.1 ± 3.4	/
Hotta, 1993	24 weeks	Placebo	20	47.9	22.2	/	4.4	10.3
AGI versus placebo, add-on therapy								
Hsieh, 2011	24 weeks	Placebo + SU	53	59 ± 10.7	51.4	/	/	8.11 ± 0.77
Hwu Chii-Min, 2003	18 weeks	Placebo + ins	53	54.7 ± 8.6	/	/	10.9 ± 6.1	
Lin BJ, 2003	24 weeks	Placebo + SU	32	55.4 ± 8.5	37.5	/	5	8.99 ± 0.95
Lam KSL, 1998	24 weeks	Placebo	44	56.9 ± 1.3	43.2	24.1 ± 0.4	10.1 ± 0.8	9.4 ± 0.1
Nemoto, 2011	12 weeks	Placebo + ins	100	/	/	/	/	/
TZD versus placebo, monotherapy								
Iwamoto, 1996	12 weeks	Placebo	126	57.4 ± 9.3	53.2	24.7 ± 3.4	7.5 ± 5.4	8.51 ± 1.46
Kong, 2011	12 weeks	Placebo	32	54.0 ± 8.5	59.4	25.53 ± 4.03	5.85 ± 3.89	7.35 ± 0.62
Nakamura, 2001	6 months	Placebo	14	/	/	/	/	/
TZD versus placebo, add-on therapy								
Hwang, 2008	12 months	Placebo+ SU	46	53.4 ± 9.7	45.7	26.6 ± 2.5	/	/
Iwamoto, 1996	12 weeks	Placebo + SU	126	58.7 ± 8.0	42.9	23.3 ± 3.1	/	8.98 ± 1.45
Kaku, 2009	28 weeks	Placebo + MET	86	53 ± 7.5	57	25.4 ± 3.6	5.6 ± 5.0	7.55 ± 0.9
Kawamori, 1998	12 weeks	Placebo	9	60.6 ± 10.0	55.6	22.0 ± 3.0	11.9 ± 8.1	8.7 ± 1.3
Mimura, 1994	3 months	Placebo	6	58 ± 2.1	50	21.3 ± 1.4	/	9.7 ± 0.3
Pan, 2002	12 weeks	Placebo + SU + MET	142	/	/	/	/	8.5 ± 1.12
Sridhar, 2013	24 weeks	Placebo + glimepiride + MET	25	44.0 ± 7.2	100	25.1 ± 3.2	2.9 ± 2.1	6.8 ± 0.4
Yang, 2002	6 months	Placebo + SU	34	57.8 ± 8.9	38.2	25.84 ± 3.50	/	9.7 ± 1.4
Zhu, 2003	24 weeks	Placebo + SU	105	58.8 ± 7.7	46	25.1 ± 2.8	7.6	9.8 ± 1.3
DPP-4 inhibitor versus placebo, monotherapy								
Iwamoto, 2010	12 weeks	Placebo	73	60.2 ± 8.0	68.5	24.1 ± 3.2	6.4 ± 5.5	7.74 ± 0.93
JI 2016	24 weeks	Placebo	127	51.7 ± 10.2	61.7	26.0 ± 3.5	1.1 ± 0.2	8.7 ± 1.1
Kawamori, 2012	12 weeks	Placebo	80	59.7 ± 8.9	71.3	24.3 ± 3.4	/	7.95 ± 0.67
Kikuchi, 2009	12 weeks	Placebo	72	60.4 ± 8.1	63.9	24.6 ± 3.1	7.1 ± 5.5	7.4 ± 0.8
Mohan, 2009	18 weeks	Placebo	178	50.9 ± 9.3	60	24.9 ± 3.4	1.9 ± 1.6	8.8 ± 1.1
Nonaka, 2008	12 weeks	Placebo	76	55.0 ± 8.0	66	25.1 ± 3.2	4.1 ± 4.6	7.7 ± 0.9
Pan, 2012	24 weeks	Placebo	284	51.6 ± 10.3	54.6	25.9 ± 3.7	1.2 ± 2.6	8.2 ± 0.8
Pan 2015	16 weeks	Placebo	88	53.2 ± 9.0	57.1	25.8 ± 3.0	2.0 ± 2.5	7.86 ± 0.79
Seino, 2011	12 weeks	Placebo	75	59.1 ± 10.47	74.7	24.39 ± 3.69	6.83 ± 6.07	7.85 ± 0.89
Wu 2015	24 weeks	Placebo	23	51.2 ± 7.5	50	24.11 ± 2.28		8.00 ± 0.69
DPP-4 inhibitor versus placebo, add-on therapy								
Ji 2016	24 weeks	Placebo + MET	484	56.2 ± 10.8	49.6	25.1 ± 3.2	4.1 ± 4.3	7.2 ± 0.04
Kadowaki, 2014	12 weeks	Placebo + glimepiride	98	60.3 ± 7.8	67.3	24.6 ± 3.6	8.3 ± 6.2	8.4 ± 0.8
Kaku, 2011	12 weeks	Placebo + PIO	115	60.1 ± 9.7	76/39	26.4 ± 4.4	6.7 ± 5.3	7.92 ± 0.85
Kikuchi, 2010	12 weeks	Placebo + glimepiride	100	60.3 ± 10.1	69	24.4 ± 2.6	9.8 ± 6.4	8 ± 0.8
Lewin, 2012	18 weeks	Placebo + SU	84	56.2 ± 10.2	61.9	28.2 ± 5.1	/	8.6 ± 0.7
Ning 2016	24 weeks	Placebo + ins	118	58.5 ± 9.33	46.6	25.7 ± 2.68	11.4 ± 6.53	8.6 ± 0.93
Owens, 2011	24 weeks	Placebo + MET + SU	263	57.6 ± 9.7	48.3	28.2 ± 4.5	/	8.14 ± 0.05
Pan, 2012	24 weeks	Placebo + MET	144	54.5 ± 9.68	45.8	25.46 ± 3.09	5.15 ± 4.58	8.01 ± 0.82
Pan 2015	16 weeks	Placebo + MET	93	53.4 ± 9.4	48.9	25.5 ± 3.9	5.5 ± 3.9	7.98 ± 0.75
Pan 2015	16 weeks	Placebo + PIO	63	51.8 ± 10.4	62.9	26.1 ± 3.0	4.9 ± 4.7	7.96 ± 0.82
Seino, 2011	12 weeks	Placebo + voglibose	75	62.3 ± 10.5	48/27	24.42 ± 4.20	7.52 ± 6.03	8.12 ± 1.19

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Supplementary Table S1: Contd...

Author, year	Study duration	Treatment group	Number of patients	Age (years)	Men (%)	BMI (kg/m²)	DM duration (years)	Baseline HbA1c (%)
DPP-4 inhibitor versus placebo, add-on therapy								
Seino, 2012	24 weeks	Placebo + MET	100	52.1 ± 8.05	72	26.14 ± 4.58	6.04 ± 4.36	8.00 ± 0.86
Wang 2015	24 weeks	Placebo + MET	80	56.5 ± 8.7	50	25.8 ± 4.0		8.00 ± 0.80
Yang 2015	24 weeks	Placebo + glimepiride	136	58.7 ± 9.3	58.1	25.0 ± 2.8	6.9 ± 4.1	10.6 ± 2.3
Yang, 2011	24 weeks	Placebo + MET	287	54.4 ± 10.1	48.7	26.1 ± 3.5	5.1 ± 4.0	7.9 ± 0.8
Yang, 2012	24 weeks	Placebo + MET	198	55.1 ± 9.8	55	25.3 ± 3.6	7.3 ± 4.6	8.5 ± 0.9
Zeng 2013	24 weeks	Placebo + MET + SU	48	57.0 ± 8.9	52.1	25.6 ± 3.4		8.10 ± 0.84
SGLT2i versus placebo, monotherapy								
Ikeda, 2015	12 weeks	Placebo	66	53.9 ± 11.12	54.5	30.37 ± 5.466		7.88 ± 0.694
Inagaki, 2013	12 weeks	Placebo	75	57.7 ± 11.0	72.0	26.41 ± 4.34		7.99 ± 0.77
Inagaki, 2014	24 weeks	Placebo	93	58.2 ± 11.0	64.5	25.85 ± 4.39		8.04 ± 0.70
Ji, 2014	24 weeks	Placebo	132	49.9 ± 10.87	65.9	25.93 ± 3.64		8.35 ± 0.95
Kaku, 2013	12 weeks	Placebo	54	58.4 ± 10.0	79.6	/		8.12 ± 0.71
Kaku, 2014	24 weeks	Placebo	56	56.8 ± 9.9	66.1	26.00 ± 4.11		8.41 ± 0.78
Kashiwagi, 2015	24 weeks	Placebo	46	65.7 ± 6.93	78.3	24.96 ± 3.362		7.55 ± 0.526
Kashiwagi, 2015	24 weeks	Placebo	56	57.7 ± 9.24	58.9	25.47 ± 3.092		8.38 ± 0.738
Roden, 2013	24 weeks	Placebo	228	54.9 ± 10.9	54	28.7 ± 6.2		7.91 ± 0.78
SGLT2i versus placebo, add-on therapy								
Ji, 2015	18 weeks	Placebo	226	55.8 ± 9.4	55.6	25.5 ± 3.6		7.9 ± 0.9
Roden, 2015	76 weeks	Placebo	228	54.9 ± 10.9	53.9	28.7 ± 6.2		7.91 ± 0.78
GLP-1RA versus placebo, monotherapy								
Miyagawa, 2015	26 weeks	Placebo	70	57.7 ± 8.3	79	25.2 ± 3.2		8.20 ± 0.83
Seino, 2008	14 weeks	Placebo	46	57.5 ± 8.7	63	23.77 ± 2.63		8.43 ± 1.02
GLP-1RA versus placebo, add-on therapy								
Gao, 2009	12 weeks	Placebo + MET/SU	232	54 ± 9	41	26.1 ± 3.4		8.3 ± 1.0
Kadowaki, 2009	12 weeks	Placebo + SU	40	60.5 ± 10.2	75	25.8 ± 4.6		8.1 ± 0.7
Kaku, 2010	24 weeks	Placebo + SU	88	58.6 ± 9.7	65	24.9 ± 4.0		8.45 ± 0.99
Kim, 2007	15 weeks	Placebo	15	55 ± 9	36	36 ± 6		8.6 ± 1.4
Pan CY, 2014	24 weeks	Placebo + MET ± SU	194	55.1 ± 10.5	46.9	27.1 ± 3.8		7.85 ± 0.71
Seino Y, 2012	24 weeks	Placebo + basal ins ± SU	157	58.0 ± 10.1	51	25.2 ± 3.9		8.52 ± 0.78

Data are given as the mean ± SD. BMI: Body mass index; DM: Diabetes mellitus; HbA1c: Glycosylated hemoglobin; MET: Metformin; AGI: Alpha glucosidase inhibitors; TZD: Thiazolidinediones; DPP-4: Dipeptidyl peptidase-4 inhibitors; SGLT2i: Sodium-glucose cotransporter 2 inhibitors; GLP-1RA: Glucagon-like peptide-1 analogs; SD: Standard deviation; PIO: Pioglitazone; /: No reported data; ins: Insulin.

Supplementary Table S2: Studies in Caucasian population

Author, year	Study duration	Treatment group	Number of patients	Age (years)	Men (%)	BMI (kg/m²)	DM duration (years)	Baseline HbA1c (%)
SU versus placebo, monotherapy								
Coniff, 1995	36 weeks	Placebo	62	56.3	52	29.9	5.5	7.1
Ebeling, 2001	6 months	Placebo	10	/	/	31.9 ± 1.5	/	8.6 ± 0.2
Fischer, 2003	16 weeks	Placebo	25	58.6 ± 6.3	68	/	6.4 ± 0.9	8.3 ± 0.2
Goldberg, 1996	14 weeks	Placebo	74	60.4	64.9	/	6	7.8
Hanefeld, 2002	16 weeks	Placebo	8	59 ± 1.6	75	27.2 ± 1.1	6.8 ± 1.6	8.7 ± 0.6
Hoffmann, 1994	24 weeks	Placebo	30	56.9 ± 6.7	40	26.8 ± 1.5	1.0 ± 0.9	8.29 ± 0.37
Madsbad, 2004	12 weeks	Placebo	29	57 ± 9.4	69	30.3 ± 4.2	3.8 ± 3.4	7.8 ± 0.9
Rosenstock, 1996	14 weeks	Placebo	79	61.1 ± 9.7	67	/	6	8.0 ± 1.1
Scott, 2007	12 weeks	Placebo	125	55.3 ± 9.7	62.4	31.6 ± 5.8	4.7 ± 4.2	7.9 ± 1.0
Segal, 1997	24 weeks	Placebo	42	59	57.1	29.1	/	8.25
Simonson, 1997	16 weeks	Placebo	69	60.2	76.8	29.7	7.5	8.3 ± 0.2

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Supplementary Table S2: Contd...

Author, year	Study duration	Treatment group	Number of patients	Age (years)	Men (%)	BMI (kg/m²)	DM duration (years)	Baseline HbA1c (%)
SU versus placebo, add-on therapy								
Burant, 2012	12 weeks	Placebo	61	52.9 ± 11.3	43	31.2 ± 5.0	5.6 ± 4.8	8.46 ± 1.07
Camerini-Davalos, 1994	3 years	Placebo + ins	29	46.4 ± 2.0	/	24.3 ± 0.4	14.1	10.3 ± 0.3
Feinglos, 2005	16 weeks	Placebo + MET	61	58.8 ± 10.0	41	32.1 ± 4.9	4.6	7.64
Forst, 2010	12 weeks	Placebo + MET	71	60.1 ± 8.1	62	32.2 ± 4.2	6.2 ± 5.1	8.4 ± 0.7
Karlander, 1991	325 days	Placebo + ins	/	/	/	/	/	10.3
LeWitt, 1989	6 months	Placebo + ins	/	/	/	/	/	/
Lins, 1988	12 weeks	Placebo + ins	10	60 ± 3	60	/	/	10.7 ± 0.5
Nauck, 2009	26 weeks	Placebo + MET	121	56 ± 9	60	31.6 ± 4.4	8 ± 6	8.4 ± 1.1
Riddle, 1992	16 weeks	Placebo + ins	10	/	/	/	/	/
Riddle, 1989	4 months	Placebo + ins	10	/	/	/	/	/
Riddle, 1998	24 weeks	Placebo + ins	73	58 ± 8	54.8	33.7 ± 5.4	7 ± 4	9.9
Roberts, 2005	26 weeks	Placebo + MET + SU	77	56.4 ± 10.0	62.3	32.76 ± 5.11	7.9 ± 4.9	8.15 ± 0.65
Schade, 1987	4 months	Placebo + ins	8	/	/	/	/	/
Stenman, 1988	4 months	Placebo + ins	8	/	/	/	/	/
Stuart, 1997	12 weeks	Placebo + ins	9	/	/	/	/	7.4 ± 0.3
Clark JCM, 1997	/	Placebo	/	/	/	/	/	/
MET versus placebo, monotherapy								
Chiasson, 2001	36 weeks	Placebo	83	57.7 ± 9.9	67.5	31.1 ± 4.4	5.1 ± 4.9	8.1 ± 0.7
DeFronzo, 1995	29 weeks	Placebo	146	53 ± 1	42.5	29.2 ± 0.3	6.0 ± 0.6	8.2 ± 0.2
Dornan, 1991	8 months	Placebo	30	55 ± 1	/	30 ± 1	/	11.8 ± 0.4
Fonseca, 2013	12 weeks	PBO	69	53.4 ± 9.7	46.4	30.9 ± 5.5	4.64 ± 5.93	7.84 ± 0.78
Garber, 1997	14 weeks	Placebo	79	55 ± 11	56	/	/	9.9 ± 1.9
Grant, 1996	6 months	Placebo	23	/	/	/	/	/
Goldstein, 2007	24 weeks	Placebo	165	/	/	/	/	8.68 ± 1.00
Hällsten, 2002	26 weeks	Placebo	14	57.7 ± 1.9	71.4	30.3 ± 1.2	/	6.3 ± 0.1
Haak, 2012	24 weeks	Placebo	72	55.7 ± 11.0	50	28.6 ± 5.2	/	8.7 ± 1.0
Horton, 2000	24 weeks	Placebo	172	59.6 ± 10.9	60.5	29.2 ± 3.9	4.6 ± 4.7	8.3 ± 1.1
Johnson, 1993	12 weeks	Placebo	4	/	/	/	/	/
List, 2009	12 weeks	PBO	54	53 ± 11	56	32 ± 5	/	7.9 ± 0.9
Nagi, 1993	12 weeks	Placebo	/	/	/	/	/	/
Natali, 2004	16 weeks	PBO	22	58 ± 9	81.8	30.2 ± 3.1	3.4 ± 3.4	7.6 ± 0.8
Tessari, 1994	4 weeks	Placebo	6	60 ± 3	33.3	28 ± 1	/	6.7 ± 0.3
Viljanen, 2005	26 weeks	Placebo	11	58.7 ± 8.3	81.8	29.8 ± 4.1	/	6.2 ± 0.7
MET versus placebo, add-on therapy								
Avilés-Santa, 1999	24 weeks	Placebo + ins	22	54.6 ± 7.8	45.5	/	10.1 ± 4.7	9.1 ± 1.5
Douek, 2005	12 months	Placebo + ins	91	58 ± 7.7	62.6	31.5 ± 4.3	10 ± 5.2	10.0 ± 1.5
Gram, 2011	2 years	Placebo + ins	46	55.8 ± 7.7	71.7	34.0 ± 6.0	7.3 ± 4.3	8.7 ± 1.3
		Placebo + ASP	48	57.1 ± 8.5	47.9	33.7 ± 5.0	9.1 ± 5.5	8.5 ± 1.2
Hermann, 2001	12 months	Placebo + ins	19	58.1 ± 9.7	63.2	32.6 ± 3.8	13	8.7 ± 1.0
Kooy, 2009	4.3 years	Placebo + ins	194	59 ± 11	50	30 ± 5	12 ± 8	7.9 ± 1.2
Willms, 1999	12 weeks	Placebo + SU	29	59.2 ± 9.4	58.6	/	10.0 ± 6.4	10.6 ± 1.6
AGI versus placebo, monotherapy								
Calle-Pascuac, 1996	16 weeks	Placebo	20	/	/	35.9 ± 7.6	/	6.4 ± 1.3
Chiasson, 1994	1 year	Placebo	39	/	/	28.8 ± 0.5	/	/
Chiasson, 2001	36 weeks	Placebo	83	57.7 ± 9.9	67.5	31.1 ± 4.5	5.1 ± 4.9	8.1 ± 0.7
Coniff, 1994	36 weeks	Placebo	98	55.6 ± 1.0	45	31.5	3	6.65
Coniff, 1995	16 weeks	Placebo	64	54	58	32	5	8.67
Coniff, 1995	36 weeks	Placebo	62	56.3	52	29.9	5.5	7.1
Delgado, 2002	4 months	Placebo	8	/	/	34.4 ± 2.8	/	7.5 ± 0.6
Derosa, 2011	7 months	Placebo	92	/	48.9	26.8 ± 0.9	/	6.7 ± 0.5

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Supplementary Table S2: Contd...

Author, year	Study duration	Treatment group	Number of patients	Age (years)	Men (%)	BMI (kg/m²)	DM duration (years)	Baseline HbA1c (%)
AGI versus placebo, monotherapy								
Fischer, 2003	16 weeks	Placebo	25	58.6 ± 6.3	/	27.0 ± 0.7	6.4 ± 0.9	8.3 ± 0.2
Gentile, 2001	28 weeks	Placebo	48	/	/	/	/	8.7 ± 0.9
Hanefeld, 2002	16 weeks	Placebo	8	59 ± 1.6	75	27.2 ± 1.1	6.8 ± 1.6	8.7 ± 0.6
Hanefeld, 2009	20 weeks	Placebo	45	59.92 ± 10.0	/	30.78 ± 3.70	/	6.09 ± 0.66
Hasche, 1999	24 months	Placebo	48	/	/	26.2 ± 2.4	/	8.7 ± 0.9
Hoffmann, 1997	24 weeks	Placebo	32	60.2 ± 8.6	38	26.3 ± 2.2	3.6 ± 2.8	9.4 ± 0.9
Hoffmann, 1994	24 weeks	Placebo	30	56.9 ± 6.7	40	26.8 ± 1.5	12.1 ± 10.8	8.29 ± 0.37
Johnston, 1998	1 year	Placebo	105	56.9 ± 1.3	51	32.0 ± 0.9	4.5 ± 0.7	8.62 ± 0.18
Johnston, 1998-2	1 year	Placebo	120	53.9	/	30.6	4.8	8.53
Josse, 2003	12 months	Placebo	99	70.3 ± 0.5	/	28.6 ± 0.4	4.8 ± 0.5	7.3 ± 0.1
Kirkman, 2006	5 years	Placebo	110	53.7 ± 11.7	34.6	35.2 ± 7.1	/	6.33 ± 0.63
Meneilly, 2000	12 months	Placebo	23	70 ± 1	/	28.0 ± 1.0	/	7 ± 0.2
Rosenbaum, 2002	22 weeks	Placebo	20	62 ± 9.7	40	31.7 ± 3.9	6.8	6.3 ± 2.1
Segal, 1997	24 weeks	Placebo	42	59	57.1	29.1	/	8.25
Scott, 1999	16 weeks	Placebo	52	57 ± 8	65	29.0 ± 3.0	2.17 ± 1.42	6.89 ± 0.85
Wagner, 2006	12 weeks	Placebo	17	54 (50–58)	82.3	28.7 (25.6–30.30)	4 (2–5)	6.6 (6.1-7.1)
AGI versus placebo, add-on therapy								
Bachmann, 2003	78 weeks	Placebo + SU	166	63.3 ± 7.2	43.3	29.0 ± 2.9	8 ± 12.5	9.38 ± 0.73
Chiasson, 1994	1 year	Placebo + MET	/	/	/	29.4 ± 0.6	/	/
		Placebo + SU	/	/	/	27.8 ± 0.4	/	/
		Placebo + ins	/	/	/	30.2 ± 0.5	/	/
Chiasson, 2001	36 weeks	Placebo + MET	83	57.9 ± 8.6	73.5	30.7 ± 5.1	7.5 ± 7.4	8.2 ± 0.9
Halimi, 2000	6 months	Placebo + MET	70	55 ± 10	62.8	29.7 ± 3.3	9 ± 7.5	8.5 ± 1.1
Kelley, 1998	24 weeks	Placebo + ins	73	60.8	48	31.1	12.3	8.69
Mitrakou, 1998	24 weeks	Placebo + ins	60	57.4 ± 5.8	61.7	24.5 ± 3.4	7.9 ± 3.2	9.9 ± 0.4
Phillips, 2003	24 weeks	Placebo + MET	43	62.39 ± 8.02	76.7	30.09 ± 2.85	6.06 ± 5.32	7.82 ± 0.83
Schnell, 2007	20 weeks	Placebo + ins	81	62.3 ± 7.4	/	29.9 ± 4.5	9.6 ± 5.1	9.4 ± 1
Standl, 1999	24 weeks	Placebo + ins	24	62.9 ± 9.4	/	24.1 ± 2.0	12.2 ± 5.7	11.0 ± 1.2
Standl, 2001	24 weeks	Placebo + SU + MET	68	61 ± 8	54.4	27.9 ± 3.5	9	8.84 ± 0.66
Willms, 1999	12 weeks	Placebo + SU	29	59.2 ± 9.4	58.6	/	10.0 ± 6.4	10.6 ± 1.6
Van Gaal, 2001	32 weeks	Placebo + MET	75	57.9 ± 8.5	49.3	29.7 ± 3.9	6	8.4 ± 1
TZD versus placebo, monotherapy								
Aronoff, 2000	26 weeks	Placebo	79	/	/	/	/	10.4 ± 0.22
Caballero, 2003	12 weeks	Placebo	/	/	/	/	/	/
Caballero, 2003	/	Placebo	/	/	/	/	/	/
Caballero, 2003	/	Placebo	/	/	/	/	/	/
Carey, 2002)	16 weeks	Placebo	17	57.9 ± 10.7	76.5	31.3 ± 3.6	3.1 ± 3.3	7.1 ± 1.4
Chou, 2012	26 weeks	Placebo	137	55.4 ± 12.32	48.9	30.1 ± 5.43	4.9 ± 6.13	7.7 ± 0.54
Ebeling, 1999	16 weeks	Placebo	12	63.5 ± 2.8	50	33.1 ± 1.0	14.3 ± 1.9	8.8 ± 0.3
Ebeling, 2001	6 months	Placebo	10	/	/	31.9 ± 1.5	/	8.6 ± 0.2
Fonseca, 1998	6 months	Placebo	79	/	/	/	/	/
Fonseca, 1998	26 weeks	Placebo	8	52.6 ± 7.5	37.5	39.6 ± 13.4	/	10.1 ± 1.43
Gastaldelli, 2006	12 weeks	Placebo	13	56 ± 2	61.5	30.2 ± 1.0	3 ± 1	8.2 ± 0.4
Gastaldelli, 2007-1	4 months	Placebo	12	56 ± 2	66.7	29.8 ± 1.2	2 ± 1	8.1 ± 0.4
Haffner, 2002	26 weeks	Placebo	95	59.8 ± 10.5	61.1	30.1 ± 3.9	4.5 ± 4.8	8.7 ± 1.5
Hällsten, 2002	26 weeks	Placebo	14	57.7 ± 1.9	71.4	30.3 ± 1.2	/	6.3 ± 0.1
Herz, 2003	16 weeks	Placebo	99	58.0 ± 10.7	49.5	31.7 ± 4.5	1.5 ± 2.5	/
Juhl, 2003	13 weeks	Placebo	10	54 ± 9	60	31.7 ± 1.9	/	6.8 ± 1.0
Khan, 2006	26 weeks	Placebo	21	54.8 ± 8.65	28.6	32.0 ± 4.23	/	8.62 ± 0.323
Kumar, 1996	12 weeks	Placebo	49	57	73.5	28.9 ± 4.6	7	7.2
Lautamäki, 2005	16 weeks	Placebo	27	63.2 ± 7.4	70.4	29.6 ± 3.4	6.8 ± 5.9	7.1 ± 0.9

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Supplementary Table S2: Contd...

Author, year	Study duration	Treatment group	Number of patients	Age (years)	Men (%)	BMI (kg/m²)	DM duration (years)	Baseline HbA1c (%)
TZD versus placebo, monotherapy								
Miyazaki, 2001	12 weeks	Placebo	14	/	/	30.1 ± 1.0	/	8.3 ± 0.4
Miyazaki, 2001	16 weeks	Placebo	11	/	/	29.5 ± 1.3	/	7.9 ± 0.3
Miyazaki, 2002	26 weeks	Placebo	11	58 ± 3	27.3	32.8 ± 1.6	/	8.6 ± 0.5
Miyazaki, 2007	3 months	Placebo	14	56 ± 2	64.3	30 ± 1	/	8.3 ± 0.4
Natali, 2004	16 weeks	Placebo	22	58 ± 9	81.8	30.2 ± 3.1	3.4 ± 3.4	7.6 ± 0.8
Ozgul, 2008	12 weeks	Placebo	10	/	/	29.2 ± 2.3	/	6.39 ± 1.1
Ozgul, 2010	12 weeks	Placebo	21	/	/	29.6 ± 4.1	/	7.3 ± 0.9
Patel, 1999	12 weeks	Placebo	75	56.8 ± 11.50	69.3	28.9 ± 3.98	4.2	9.1
Phillips, 2001	16 weeks	Placebo	173	57.7 ± 9.2	68.8	29.1 ± 4.2	6.6 ± 6.9	8.9 ± 1.5
Raskin, 2000	8 weeks	Placebo	69	60.06 ± 9.39	59.4	30.44 ± 4.15	5.6 ± 5.19	8.7 ± 1.63
Rosenblatt, 2001	16 weeks	Placebo	96	55.2 ± 10.0	56.2	30.7 ± 5.0	/	10.42 ± 1.70
Rosenstock, 2002	16 weeks	Placebo	148	58	59	20-38	0.2-37.9	8.2 ± 1.2
Scherbaum, 2002	26 weeks	Placebo	84	59.1	56	29.2	5.6	8.75
Sourij, 2006	12 weeks	Placebo	21	/	/	/	/	6.1 ± 0.5
Tan, 2005	24 weeks	Placebo	6	/	/	30.8 ± 1.04	/	7.52 ± 0.38
Truitt, 2010	26 weeks	Placebo	92	55.3 ± 9.3	51.1	32.2 ± 5.8	6.7 ± 5.6	8.21 ± 0.98
Viljanen, 2005	26 weeks	Placebo	11	58.7 ± 8.3	81.8	29.8 ± 4.1	6.2 ± 0.7	6.2 ± 0.7
Wallace, 2004	12 weeks	Placebo	11	62.6 ± 10.0	72.7	28.9 ± 2.8	2.5	6.7 ± 0.9
TZD versus placebo, add-on therapy								
Barnett, 2003	26 weeks	Placebo + SU	87	54.1	75	26.4	6.5	9.06 ± 1.03
Berhanu, 2007	20 weeks	Placebo + ins ± MET	112	52.5 ± 11.07	41.1	31.8 ± 6.2	8.5 ± 5.43	8.6 ± 0.13
Bertrand, 2010	12 months	Placebo	95	65.9 ± 6.9	92	29.5 ± 4.6	8.4 ± 6.9	6.9 ± 0.8
Brackenridge, 2009	3 months	Placebo ± MET	8	60.8 ± 3.45	87.5	32.0 ± 1.56	2.9 ± 0.4	6.6 ± 0.14
Buras, 2005	12 weeks	Placebo	39	57 ± 9	66.7	32.6 ± 5.0	8 ± 9	7.9 ± 1.4
Buse, 1998	26 weeks	Placebo + ins	71	57 ± 11	49	34.5 ± 7.2	/	9.0 ± 1.4
Buysschaert, 1999	16 weeks	Placebo + SU	85	60	51.8	/	7.77	8.5
Charpentier, 2009	7 months	Placebo	147	59.2 ± 9.6	66.2	29.2 ± 3.1	12.1 ± 7.9	8.2 ± 0.6
Colca, 2013	12 weeks	Placebo	56	53	48	/	/	7.98
Dailey, 2004	24 weeks	Placebo + glyburide/MET	184	57 ± 10	61	32 ± 5	9 ± 6	8.1 ± 0.8
Davidson, 2007	24 weeks	Placebo + RSG	116	53 ± 10.4	48.3	31.9 ± 5.6	6.2 ± 5.3	9.4 ± 1.4
Derosa, 2008	6 months	Placebo + MET	61	54 ± 3	47.5	28.4 ± 1.7	4 ± 1	8.0 ± 0.9
Einhorn, 2000	16 weeks	Placebo + MET	160	55.7 ± 9.92	60	32.12 ± 5.5	9.75 ± 1.3	/
Fonseca, 2000	26 weeks	MET + placebo	113	58.8 ± 9.2	74.3	30.3 ± 4.4	7.3 ± 5.7	8.6 ± 1.3
Galle, 2012	6 months	Placebo + ins	19	69.6 ± 9.4	68.4	30.3 ± 4.6	12.4 ± 8.2	7.7 ± 0.9
Gastaldelli, 2007-2	4 months	Placebo + SU	10	55 ± 4	40	29.9 ± 1.4	5 ± 2	8.3 ± 0.4
Gastaldelli, 2009	16 weeks	Placebo	10	62 ± 2	/	29.7 ± 0.8	/	/
Gòmez-Pérez, 2002	26 weeks	MET + placebo	34	53.4 ± 7.5	29.4	28.5 ± 3.9	9.1 ± 5.6	/
Gram, 2011	2 years	Placebo + ins	46	55.8 ± 7.7	71.7	34.0 ± 6.0	7.3 ± 4.3	8.7 ± 1.3
		Placebo + ASP	48	57.1 ± 8.5	47.9	33.7 ± 5.0	9.1 ± 5.5	8.5 ± 1.2
Grey, 2012	6 months	Placebo	10	57.9 ± 15.2	50	33.2 ± 4.1	/	7.1 ± 1.0
Henriksen, 2011	26 weeks	Placebo + ins	106	60.9 ± 7.8	62	33.9 ± 5.5	12.6 ± 7.3	8.5 ± 1.3
Hollander, 2007	24 weeks	Placebo + ins	186	53.8 ± 10.2	46.2	33.0 ± 6.5	12.6 ± 8.6	9.1 ± 1.3
Kelly, 1999	12 weeks	Placebo	10	58.6 ± 7.5	80	28.6 ± 3.76	/	8.38 ± 1.52
Kipnis, 2001	16 weeks	Placebo + SU	187	56.9 ± 8.9	58	32.0 ± 4.9	/	9.9 ± 0.2
Lebovitz, 2001	/	Placebo	1842	/	/	/	/	/
Marre, 2009	26 weeks	Placebo + SU	114	54.7 ± 10.0	47	30.3 ± 5.4	6.5	8.4 ± 1.0
Mattoo, 2005	6 months	Placebo + ins	147	58.9 ± 6.9	42.9	31.8 ± 5.0	13.4 ± 6.1	8.79 ± 0.10
Negro, 2005	12 months	Placebo + MET	19	59 ± 8	63.2	28.7 ± 1.9	6.6 ± 2.9	8.1 ± 0.5

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Supplementary Table S2: Contd...

Author, year	Study duration	Treatment group	Number of patients	Age (years)	Men (%)	BMI (kg/m²)	DM duration (years)	Baseline HbA1c (%)
TZD versus placebo, add-on therapy								
Osende, 2001	3 months	Placebo	21	57.0 ± 1.7	52.4	31.5 ± 2.1	/	9.2 ± 0.2
Raskin, 2001	26 weeks	Placebo + ins	104	55.6 ± 10.3	55.8	32.7 ± 6.2	11.7 ± 6.2	8.9 ± 1.1
Reynolds, 2002	6 months	Placebo + ins	/	/	/	36.3 ± 1.8	/	9.8 ± 0.5
Rosenstock, 2008	26 weeks	Placebo + glimepiride 3 mg/d	57	65 ± 9	60	29.1 ± 4.5	6.6 ± 3.9	7.9 ± 1.3
Scheen, 2009	34.5 months	Placebo +MET	261	60.3 ± 7.9	67	32.0 ± 5.3	5.6 ± 5.4	7.6 ± 1.2
		Placebo + SU	493	62.9 ± 7.8	71	29.9 ± 4.3	6.9 ± 6.1	7.7 ± 1.4
Schwartz, 1998	26 weeks	Placebo + ins	118	56 ± 10	51	35.0 ± 6.3	10 ± 4	9.4 ± 1.1
Smith, 2005	24 weeks	Placebo	21	53.1 ± 9.3	47.6	31.9 ± 5.0	/	6.46 ± 0.72
Wolffenbuttel, 2000	26 weeks	Placebo + SU	192	61.9 ± 9.1	57.3	28.1 ± 4.1	8	9.21 ± 1.30
Yale, 2001	24 weeks	Placebo + MET + SU	99	60 ± 0.9	58	30.0 ± 0.4	10.8 ± 0.6	9.7 ± 0.1
DPP-4 inhibitor versus placebo, monotherapy								
Aschner, 2006	24 weeks	Placebo	244	/	/	/	/	8.03 ± 0.82
DeFronzo, 2008	26 weeks	Placebo	64	/	/	/	/	/
de Jager, 2007	24 weeks	Placebo	94	52.2 ± 11.2	47.9	32.6 ± 5.6	1.6 ± 2.5	8.4 ± 0.8
Goldstein, 2007	24 weeks	Placebo	165	/	/	/	/	8.68 ± 1.00
Haak, 2012	24 weeks	Placebo	72	55.7 ± 11.0	50	28.6 ± 5.2	/	8.7 ± 1.0
Pi-Sunyer, 2007	24 weeks	Placebo	92	52.0 ± 12.0	54.3	32.7 ± 6.4	2.5 ± 3.7	8.5 ± 0.8
Prato, 2011	24 weeks	Placebo	167	54.4 ± 10.3	47.3	29.08 ± 4.84	/	8.0 ± 0.07
Raz I, 2006	18 weeks	Placebo	103	/	/	/	/	8.05 ± 0.9
Ristic, 2005	12 weeks	Placebo	55	54.6 ± 10.6	56.9	31.6 ± 4.41	2.28 ± 2.99	7.76 ± 0.83
Rosenstock, 2009	24 weeks	Placebo	95	53.91 ± 12.32	49.5	30.93 ± 4.26	2.3 ± 2.7	7.9 ± 0.9
Rosenstock, 2008	12 weeks	Placebo	67	55.2 ± 9.8	63	31.1 ± 4.46	1.8	8.0 ± 0.88
Scherbaum, 2008	52 weeks	Placebo	150	62.8 ± 11.0	59.3	30.0 ± 4.9	2.7 ± 3.2	6.8 ± 0.4
Scott, 2007	12 weeks	Placebo	125	55.3 ± 9.7	62.4	31.6 ± 5.8	4.7 ± 4.2	7.9 ± 1.0
Strain, 2013	24 weeks	Placebo	139	74.4 ± 4	38.1	30.5 ± 4.8	10.6 ± 6.9	7.9 ± 0.7
DPP-4 inhibitor versus placebo, add-on therapy								
Ahrén, 2004	12 weeks	Placebo + MET	51	55.7 ± 11.0	66.7	30.2 ± 3.6	5.5 ± 3.7	7.8 ± 0.7
Barnett, 2012	24 weeks	Placebo + ins	151	57.3 ± 9.27	45	31.8 ± 4.76	12.2 ± 7.37	8.6 ± 0.86
Bosi, 2007	24 weeks	Placebo + MET	130	54.5 ± 10.3	53.1	33.2 ± 6.1	6.2 ± 5.3	8.3 ± 0.9
Charbonnel, 2006	24 weeks	Placebo + MET	226	/	/	/	/	8.03 ± 0.82
DeFronzo, 2009	24 weeks	Placebo + MET	179	/	/	/	/	/
DeFronzo, 2012	26 weeks	Placebo + MET	129	55.2 ± 9.9	47.3	30.6 ± 4.8	6.0 ± 5.0	8.5 ± 0.6
		Placebo + PIO 15 mg + MET	130	54.1 ± 9.5	46.9	31.3 ± 5.0	5.7 ± 4.8	8.5 ± 0.7
		Placebo + PIO 30 mg + MET	129	56.1 ± 9.4	48.8	31.4 ± 5.4	7.6 ± 7.1	8.5 ± 0.7
		Placebo + PIO 45 mg + MET	129	54.5 ± 9.7	41.1	30.7 ± 4.7	5.7 ± 4.2	8.5 ± 0.7
Derosa, 2012	12 months	Placebo + MET	87	54.8 ± 7.9	51	28.9 ± 2.0	5.4 ± 2.3	8.0 ± 0.7
Derosa, 2010	12 months	Placebo + PIO/glimepiride	/	/	/	/	/	/
Derosa, 2012	12 months	Placebo + MET	83	52.4 ± 7.1	51.8	27.8 ± 1.4	6.3 ± 3.9	8.2 ± 0.7
Dobs, 2013	18 weeks	Placebo + MET + RSG	92	54.8 ± 9.5	60	30.8 ± 5.6	9.4 ± 6.8	8.7 ± 1.0
Fonseca, 2007	24 weeks	Placebo + ins	152	58.9 ± 10.8	54.6	32.9 ± 5.9	14.9 ± 8.4	8.4 ± 1.1
Forst, 2010	12 weeks	Placebo	71	60.1 ± 8.1	62	32.2 ± 4.2	6.2 ± 5.1	8.4 ± 0.7
Garber, 2007	24 weeks	Placebo + PIO	138	54.8 ± 10.6	50.7	32.3 ± 5.8	4.8 ± 4.6	8.7 ± 1.2
Garber, 2008	24 weeks	Placebo + SU	144	57.9 ± 10.5	58.3	31.0 ± 5.5	7.8 ± 5.8	8.5 ± 1.0
Goldstein, 2007	24 weeks	Placebo + MET 500 mg bid	178	/	/	/	/	8.90 ± 1.00
		Placebo + MET 1000 mg bid	177	/	/	/	/	8.68 ± 0.91
Gomis, 2011	24 weeks	Placebo + PIO	130	57.1 ± 10.1	65.4	29.7 ± 4.8	/	8.58 ± 0.08
Goodman, 2009	24 weeks	Placebo + MET	122	54.5 ± 9.7	67.2	31.7 ± 4.3	/	8.7 ± 1.1

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Supplementary Table S2: Contd...

Author, year	Study duration	Treatment group	Number of patients	Age (years)	Men (%)	BMI (kg/m²)	DM duration (years)	Baseline HbA1c (%)
DPP-4 inhibitor versus placebo, add-on therapy								
Haak, 2012	24 weeks	Placebo + MET 500 mg bid	144	52.9 ± 10.4	56.9	28.9 ± 4.8	/	8.7 ± 0.9
		Placebo + MET 1000 mg bid	147	55.2 ± 10.6	53.1	29.5 ± 5.3	/	8.5 ± 0.9
Hermansen, 2007	24 weeks	Placebo + glimepiride/ placebo + glimepiride + MET	219	56.5 ± 9.6	53.4	30.7 ± 6.3	9.3 ± 6.8	8.34 ± 0.74
Hollander, 2009	24 weeks	Placebo + TZD	184	54.0 ± 10.1	46.2	30.3 ± 5.8	5.1 ± 5.4	8.2 ± 1.1
Jadzinsky, 2009	24 weeks	Placebo + MET	328	51.8 ± 10.7	49.7	30.2 ± 4.9	1.7 ± 3.1	9.4 ± 1.3
Kothny, 2012	52 weeks	Placebo	89	69.3 ± 7.2	61.8	30.1 ± 5.0	/	7.9 ± 1.0
		Placebo	64	65.4 ± 10.5	51.6	30.0 ± 4.7	/	7.5 ± 1.1
Lukashevich, 2014	24 weeks	Placebo + MET + glimepiride	160	55.0 ± 11.1	45%	28.0 ± 4.5	7.5 ± 6.1	8.8 ± 0.9
Nauck, 2009	26 weeks	Placebo + MET	104	56 ± 11	48	32 ± 6	6 ± 5	8.0 ± 0.9
Nowicki, 2011	12 weeks	Placebo + ins/OADs	85	66.2 ± 9.1	48.2	30.2 ± 6.8	18.2 ± 8.5	8.1 ± 1.1
Pratley, 2009	24 weeks	Placebo + PIO	97	55.2 ± 10.8	54.6	33.2 ± 6.2	/	8.0 ± 0.8
Raz, 2008	18 weeks	Placebo + MET	94	56.1 ± 9.5	41.5	30.4 ± 5.3	7.3 ± 5.3	9.1 ± 0.8
Rosenstock, 2006	24 weeks	Placebo + PIO	178	56.9 ± 11.1	57.9	31.0 ± 5.0	6.1 ± 5.7	8.0 ± 0.8
Ross, 2012	12 weeks	Placebo + MET	43	59.9 ± 10.7	47.7	28.7 ± 5.5	/	7.92 ± 0.74
Scott, 2008	18 weeks	Placebo + MET	92	55.3 ± 9.3	59	30.0 ± 4.5	5.4 ± 3.7	7.7 ± 0.9
Taskinen, 2011	24 weeks	Placebo + MET	523	56.6 ± 10.9	57	30.05 ± 5.01	/	8.02 ± 0.88
Vilsbøll, 2010	24 weeks	Placebo + ins	319	57.2 ± 9.3	53	31 ± 5	12 ± 6	8.6 ± 0.9
SGLT2i versus placebo, monotherapy								
Bailey, 2012	24 weeks	Placebo	68	53.5 ± 11.08	54.4	32.47 ± 4.91	1.1 ± 1.95	7.8 ± 1.12
Bailey, 2015	102 weeks	Placebo	75	52.7 ± 10.3	41.3	/	2.1 ± 3.1	7.84 ± 0.87
Ferrannini, 2010	24 weeks	Placebo	75	52.7 ± 10.3	41.3	32.3 ± 5.5	/	7.84 ± 0.87
Ferrannini, 2013	12 weeks	Placebo	82	58	54.9	28.8	/	7.8 ± 0.8
Fonseca, 2013	12 weeks	Placebo	69	53.4 ± 9.7	46.4	30.9 ± 5.5	4.64 ± 5.93	7.84 ± 0.78
Inagaki, 2013	12 weeks	Placebo	75	57.7 ± 11.0	72.0	26.41 ± 4.34	/	7.99 ± 0.77
List, 2009	12 weeks	Placebo	54	53 ± 11	56	32 ± 5	/	7.9 ± 0.9
Stenlöf, 2013	26 weeks	Placebo	192	55.7 ± 10.9	45.8	31.8 ± 6.2	4.2 ± 4.1	8.0 ± 1.0
SGLT2i versus placebo, add-on therapy								
Bailey, 2010	24 weeks	Placebo + MET	137	53.7 ± 10.3	55	31.8 ± 5.3	5.8 ± 5.1	8.11 ± 0.96
Bailey, 2013	102 weeks	Placebo + MET	137	/	/	/	/	8.12 ± 0.96
Barnett, 2014	52 weeks	Placebo (CKD, 2)	95	62.6 ± 8.1	58.9	30.8 ± 5.6	/	8.09 ± 0.80
		Placebo (CKD, 3)	187	65.1 ± 8.2	56.7	30.3 ± 5.3	/	8.09 ± 0.80
		Placebo (CKD, 4)	37	62.9 ± 11.9	51.4	31.8 ± 6.0	/	8.16 ± 0.99
Bode, 2015	104 weeks							
Bolinder, 2012	24 weeks	Placebo + MET	91	60.8 ± 6.9	59.2	31.7 ± 3.9	5.5 ± 5.3	7.16 ± 0.53
Cefalu, 2015	52 weeks	Placebo + OAD/ins	459	63.0 ± 7.7	68.6	32.9 ± 6.1	12.3 ± 8.2	8.08 ± 0.80
Draeger, 2015	16 weeks	Placebo + MET	101	58.5 ± 9.4	46.5	31.74 ± 4.69	5.53 ± 4.23	7.94 ± 0.85
Forst, 2014	26 weeks	Placebo + MET + PIO	115	58.3 ± 9.6	66.1	32.5 ± 6.4	10.1 ± 6.6	8.0 ± 1.0
Häring, 2015	76 weeks	Placebo + MET + SU	225	56.9 ± 9.2	49.8	27.9 ± 4.9	/	8.1 ± 0.8
Hakjadj, 2016	24 weeks							
Häring, 2013	24 weeks	Placebo + MET + SU	225	56.9 ± 9.2	50	27.9 ± 4.9	/	8.15 ± 0.83
Häring, 2014	24 weeks	Placebo + MET	207	56.0 ± 9.7	56	28.7 ± 5.2	/	7.90 ± 0.88
Henry, 2012	24 weeks	Dapagliflozin 5 mg/d + placebo	203	52.3 ± 10.2	45.3	/	1.6 ± 3.1	9.1 ± 1.4
		Placebo + MET	201	51.8 ± 9.8	47.3	/	1.6 ± 2.6	9.2 ± 1.3
		Dapagliflozin 10 mg/d + placebo	219	51.1 ± 11.5	47.9	/	2.1 ± 3.8	9.1 ± 1.3
		Placebo + MET	208	52.7 ± 10.4	46.6	/	1.9 ± 4.0	9.1 ± 1.3
Kovacs, 2014	24 weeks	Placebo + PIO + MET	165	54.6 ± 10.5	44.2	29.3 ± 5.4	/	8.2 ± 0.92
Lavalle-González, 2013	26 weeks	Placebo + MET	183	55.3 ± 9.8	51.4	31.1 ± 6.1	6.8 ± 5.3	8.0 ± 0.9

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Supplementary Table S2: Contd...

Author, year	Study duration	Treatment group	Number of patients	Age (years)	Men (%)	BMI (kg/m²)	DM duration (years)	Baseline HbA1c (%)
SGLT2i versus placebo, add-on therapy								
Leiter, 2014	24 weeks	Placebo	482	63.6 ± 7.0	67.0	32.7 ± 5.7	13.0 ± 8.4	8.1 ± 0.8
Ljunggren, 2012	50 weeks	Placebo + MET	91	60.8 ± 6.9	56	31.7 ± 3.9	5.5 ± 5.3	7.16 ± 0.53
Mathieu, 2015	24 weeks	Placebo + MET	160	55.06 ± 9.6	47.5	32.26 ± 5.3	8.06 ± 6.6	8.176 ± 0.98
Matthaei, 2015	24 weeks	Placebo + MET + SU	109	60.9 ± 9.2	55.6	32 ± 4.6	9.6 ± 6.2	8.24 ± 0.87
Merker, 2015	76 weeks	Placebo + MET	207	56.0 ± 9.7	56	28.7 ± 5.2	/	7.9 ± 0.9
Neal, 2015	18 weeks	Placebo + ins	636	63	66	33.1 ± 6.5	16.0 ± 7.8	8.3 ± 0.9
	52 weeks	Placebo + ins	639	63	66	33.1 ± 6.5	16.0 ± 7.8	8.3 ± 0.9
Rosenstock, 2012	12 weeks	Placebo + MET	65	53.3 ± 7.8	48	30.6 ± 4.6	6.4 ± 5.0	7.75 ± 0.83
Rosenstock, 2012	48 weeks	Placebo + PIO	139	53.5 ± 11.4	51.1	/	5.07 ± 5.05	8.34 ± 1.00
Rosenstock, 2014	52 weeks	Placebo + ins	188	55.3 ± 10.1	40	34.7 ± 4.3	/	8.33 ± 0.72
Rosenstock, 2015	24 weeks							
Ross, 2015	16 weeks	Placebo + MET	207	/	/	/	/	7.69 ± 0.07
Strojek, 2011	24 weeks	Placebo + glimepiride 4 mg/d	145	60.3 ± 10.16	49	/	7.4 ± 5.7	8.15 ± 0.74
Wilding, 2009	12 weeks	Placebo + ins	23	58.4 ± 6.5	69.6	34.8 ± 4.6	13.8 ± 7.3	8.4 ± 0.9
Wilding, 2012	48 weeks	Placebo + ins	193	58.8 ± 8.6	49.2	33.1 ± 5.9	13.5 ± 7.3	8.47 ± 0.77
Wilding, 2013	12 weeks	Placebo + MET	66	57.3 ± 8.6	54.5	32.0 ± 4.8	5.7 ± 3.2	7.68 ± 0.60
Yale, 2013	26 weeks	Placebo	90	68.2 ± 8.4	63.3	33.1 ± 6.5	16.4 ± 10.1	8.0 ± 0.9
GLP-1RA versus placebo, monotherapy								
Buse, 2004	30 weeks	Placebo	123	55 ± 11	62.6	34 ± 5	5.7 ± 4.7	8.7 ± 1.2
Fonseca, 2012	12 weeks	Placebo	122	54.1 ± 11.0	49.2	31.8 ± 6.7	1.4	8.07 ± 0.9
Grunberger G, 2012	12 weeks	Placebo	32	55.0 ± 9.3	56.3	32.1 ± 5.2	3.9 ± 4.7	7.4 ± 0.6
Hollander P, 2013	24 weeks	Placebo	143	54 ± 10	61	36.5 ± 4.8	4.9 ± 4.1	7.55 ± 0.84
Madsbad, 2004	12 weeks	Placebo	29	57 ± 9.4	69	30.3 ± 4.2	3.8 ± 3.4	7.8 ± 0.9
Moretto, 2008	24 weeks	Placebo	77	53 ± 9	55	32 ± 5	1 ± 2	7.8 ± 0.9
Raz I, 2012	24 weeks	Placebo	123	55.8 ± 8.5	37	32.1 ± 5.3	2.3 ± 1.9	7.6 ± 1.0
Rosenstock, 2009	16 weeks	Placebo	50	/	/	/	/	7.8 ± 0.9
Terauchi, 2014	12 weeks	Placebo	37	51.7 ± 9.7	78.4	27.4 ± 4.5	4.7 ± 4.5	8.0 ± 0.6
Vilsbøll, 2007	14 weeks	Placebo	40	57.7 ± 8.2	47.5	30.4 ± 4.0	5	8.2 ± 0.7
Vilsbøll, 2008	14 weeks	Placebo	10	55.4 ± 6.7	80	30.3 ± 4.3	1.8 ± 0.8	8.1 ± 0.3
GLP-1RA versus placebo, add-on therapy								
Ahrén B, 2013	24 weeks	Placebo + MET	170	55.0 ± 9.4	47.6	33.1 ± 6.5	5.9 ± 4.7	8.1 ± 0.9
Apovian, 2010	24 weeks	Placebo + MET	51	55.0 ± 7.9	39	33.6 ± 4.6	3.9 ± 3.2	7.2 ± 0.5
		MET + SU + placebo	36	55.1 ± 9.9	31	34.3 ± 4.0	7.6 ± 6.9	7.9 ± 0.9
		Exenatide + placebo	11	55.3 ± 11.3	54	33.8 ± 4.3	4.3 ± 2.8	7.7 ± 1.1
Bergenstal, 2012	24 weeks	Placebo + MET	90	56.1 ± 10.1	52	32.5 ± 5.5	5.5 ± 3.9	8.03 ± 0.83
Bolli GB, 2014	24 weeks	Placebo + MET	160	58.2 ± 9.8	45	32.4 ± 5.5	6.2 ± 4.7	8.0 ± 0.8
Buse, 2004	30 weeks	Placebo + SU	123	55 ± 11	62.6	34 ± 5	5.7 ± 4.7	8.7 ± 1.2
Davies, 2015	56 weeks	Placebo	211	54.7 ± 9.8	45.8	37.4 ± 7.1	6.7 ± 5.07	7.9 ± 0.8
DeFronzo, 2005	30 weeks	Placebo + NET	113	54 ± 9	59.3	34 ± 6	6.6 ± 6.1	8.2 ± 1.0
Home, 2015	156 weeks	Placebo + MET + glimepiride	115	55.7 ± 9.6	60.9	31.8 ± 4.9	9.3 ± 6.1	8.26 ± 0.98
Kendall, 2005	30 weeks	Placebo + MET + SU	247	56 ± 10	55.9	34 ± 5	9.4 ± 6.2	8.5 ± 1.0
Lind, 2015	24 weeks							
Marre, 2009	26 weeks	Placebo + glimepiride 2–4 mg/d	114	54.7 ± 10.0	47	30.3 ± 5.4	6.5	8.4 ± 1.0
Nauck, 2009	26 weeks	Placebo + MET	121	56 ± 9	60	31.6 ± 4.4	8 ± 6	8.4 ± 1.1
Pinget M, 2013	24 weeks	Placebo + PIO ± MET	161	55.3 ± 9.5	51	34.4 ± 7.0	8.1 ± 5.6	8.1 ± 0.8
Ratner, 2010	13 weeks	Placebo	109	56.3 ± 9.2	56	31.7 ± 4.2	7.1 ± 5.4	7.53 ± 0.6
Reusch, 2014	52 weeks	Placebo + PIO ± MET	151	54.9 ± 9.40	58.3	34.7 ± 5.6	7.9 ± 6.1	8.1 ± 0.9

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Supplementary Table S2: Contd...

Author, year	Study duration	Treatment group	Number of patients	Age (years)	Men (%)	BMI (kg/m²)	DM duration (years)	Baseline HbA1c (%)
GLP-1RA versus placebo, add-on therapy								
Riddle MC, 2013	24 weeks	Placebo + ins + MET ± TZD	223	56 ± 10	51	31.7 ± 6.0	8.7 ± 5.8	7.6 ± 0.5
Riddle MC, 2013-1	24 weeks	Placebo + ins ± MET	167	57 ± 10	49	32.6 ± 6.3	12.4 ± 6.3	8.4 ± 0.8
Russell-Jones, 2009	26 weeks	Placebo + MET + glimepiride	114	57.5 ± 9.6	49	31.3 ± 5.0	9.4 ± 6.2	8.3 ± 0.9
Skrivanek, 2014	52 weeks	Placebo + MET	38	53 ± 11	32	32 ± 4	7 ± 6	8.1 ± 1.1
Umpierrez, 2011	16 weeks	Placebo	66	56 ± 12	44	33.9 ± 4.3	7.5 ± 5.4	8.05 ± 0.8
Zinman, 2007	16 weeks	Placebo + TZD ± MET	112	53.7 ± 10.2	57.1	34.0 ± 5.0	8.2 ± 5.8	7.9 ± 0.8
Zinman, 2009	26 weeks	Placebo + MET 1 g bid + RSG 4 mg bid	177	55 ± 10	62	33.9 ± 5.2	9 ± 6	8.4 ± 1.2

Data are given as the mean ± SD. BMI: Body mass index; DM: Diabetes mellitus; HbA1c: Glycosylated hemoglobin; SU: Sulfonylurea; MET: Metformin; TZD: Thiazolidinediones; AGI: Alpha glucosidase inhibitors; DPP-4: Dipeptidyl peptidase-4 inhibitors; SGLT2i: Sodium-glucose cotransporter 2 inhibitors; GLP-1RA: Glucagon-like peptide-1 analogs; CKD: Chronic kidney disease; SD: Standard deviation; PIO: Pioglitazone; PBO: Placebo; ASP: Insulin Aspart; OADs: Oral hypoglycemic drugs; RSG: Rosiglitazone; ins: Insulin.

Supplementary Table S3: Meta-regression analysis for placebo effect

Variables	Asian			Caucasian		
	Coefficient	95% *CI*	*P*	Coefficient	95% *CI*	*P*
SU						
HbA1c change						
Total group						
Age	/	/	/	0.056	−0.014–0.125	0.109
Sex	/	/	/	0.017	−0.001–0.349	0.063
BMI	/	/	/	−0.091	−0.196–0.014	0.083
Duration of diabetes	/	/	/	0.015	−0.073–0.104	0.721
Study duration	/	/	/	−0.000	−0.009–0.008	0.935
Baseline HbA1c	/	/	/	−0.166	−0.393–0.061	0.144
Baseline weight	/	/	/	/	/	/
Weight change	/	/	/	−0.193	−0.370–−0.017	0.034
Weight change						
Total group						
Age	/	/	/	−0.417	0.997–0.163	0.142
Sex	/	/	/	−0.056	−0.183–0.072	0.359
BMI	/	/	/	0.426	−0.560–1.412	0.354
Duration of diabetes	/	/	/	−0.213	−0.839–0.414	0.467
Study duration	/	/	/	−0.010	−0.154–0.135	0.888
Baseline HbA1c	/	/	/	−0.065	−2.681–2.550	0.958
Baseline weight	/	/	/	0.033	−0.259–0.326	0.801
HbA1c change	/	/	/	−2.994	−4.365–−1.624	0.000
MET						
HbA1c change						
Total group						
Age	/	/	/	−0.075	−0.214–0.064	0.272
Sex	/	/	/	−0.001	−0.021–0.029	0.938
BMI	/	/	/	−0.075	−0.257–0.107	0.395
Duration of diabetes	/	/	/	−0.192	−0.341–−0.042	0.016
Study duration	/	/	/	0.002	−0.009–0.012	0.761
Baseline HbA1c	/	/	/	0.084	−0.141–0.310	0.446
Baseline weight	/	/	/	−0.035	−0.096–0.027	0.250
Weight change	/	/	/	−0.106	−0.343–0.132	0.356
Weight change						
Total group						

Contd...

Supplementary Table S3: Contd...

Variables	Asian			Caucasian		
	Coefficient	95% *CI*	*P*	Coefficient	95% *CI*	*P*
Age	/	/	/	0.072	−0.230–0.373	0.618
Sex	/	/	/	0.013	−0.035–0.060	0.573
BMI	/	/	/	−0.080	−0.974–0.814	0.849
Duration of diabetes	/	/	/	0.335	−0.316–0.985	0.282
Study duration	/	/	/	0.006	−0.049–0.062	0.805
Baseline HbA1c	/	/	/	0.302	−0.937–1.540	0.609
Baseline weight	/	/	/	0.135	−0.044–0.314	0.128
HbA1c change	/	/	/	−0.061	−1.257–1.134	0.914
AGI						
HbA1c change						
Total group						
Age	0.004	−0.120–0.127	0.946	0.017	−0.052–0.086	0.607
Sex	−0.016	−0.065–0.033	0.450	−0.005	−0.035–0.237	0.700
BMI	/	/	/	−0.019	−0.142–0.104	0.756
Duration of diabetes	0.025	−0.190–0.240	0.765	−0.108	−0.227–0.010	0.071
Study duration	−0.017	−0.130–0.095	0.718	0.007	−0.008–0.022	0.356
Baseline HbA1c	0.130	−0.240–0.500	0.423	−0.301	−0.572–−0.031	0.030
Baseline weight	/	/	/	0.017	−0.031–0.066	0.467
Weight change	1.143	−3–789–6.074	0.424	−0.178	−0.408–0.052	0.121
Weight change						
Total group						
Age	0.104	−1.373–1.581	0.791	0.023	−0.305–0.351	0.881
Sex	/	/	/	0.001	−0.066–0.068	0.978
BMI	/	/	/	−0.055	−0.528–0.418	0.808
Duration of diabetes	0.671	−38.678–37.336	0.860	0.079	−0.222–0.380	0.576
Study duration	0.083	−1.578–1.745	0.849	−0.017	−0.074–0.041	0.549
Baseline HbA1c	0.297	−5.280–5.874	0.840	0.109	−0.876–1.095	0.817
Baseline weight	/	/	/	−0.018	−0.092–0.056	0.614
HbA1c change	0.593	−11.369–12.556	0.851	0.097	−1.807–2.002	0.915
TZD						
HbA1c change						
Total group						
Age	−0.004	−0.073–0.065	0.899	0.026	−0.031–0.084	0.356
Sex	−0.001	−0.020–0.019	0.938	0.005	−0.008–0.018	0.472
BMI	0.036	−0.182–0.255	0.706	−0.090	−0.186–0.006	0.066
Duration of diabetes	−0.021	−0.276–0.233	0.826	−0.040	−0.097–0.016	0.158
Study duration	0.002	−0.058–0.062	0.947	−0.011	−0.027–0.004	0.150
Baseline HbA1c	−0.056	−0.368–0.256	0.695	0.052	−0.091–0.196	0.468
Baseline weight	−0.007	−0.241–0.228	0.940	−0.022	−0.054–0.010	0.175
Weight change	−0.219	−2.345–1.906	0.789	−0.004	−0.150–0.143	0.960
Weight change						
Total group						
Age	0.040	−0.593–0.673	0.868	0.039	−0.178–0.256	0.716
Sex	−0.135	−0.237–0.210	0.875	0.006	−0.038–0.050	0.787
BMI	−0.114	−1.688–1.460	0.850	−0.332	−0.599–−0.065	0.016
Duration of diabetes	/	/	/	−0.018	−0.207–0.171	0.848
Study duration	−0.012	−0.215–0.191	0.879	−0.059	−0.015–0.041	0.241
Baseline HbA1c	0.117	−2.087–2.322	0.890	−0.594	−1.080–−0.108	0.018
Baseline weight	/	/	/	−0.155	−0.244–−0.065	0.001
HbA1c change	−0.273	−19.846–19.301	0.971	0.360	−0.770–1.490	0.521
DPP-4i						
HbA1c change						
Total group						
Age	0.046	−0.000–0.092	0.050	0.018	−0.010–0.046	0.198

Contd...

Supplementary Table S3: Contd...

Variables	Asian			Caucasian		
	Coefficient	95% *CI*	*P*	Coefficient	95% *CI*	*P*
Sex	0.025	0.013–0.037	0.000	0.011	−0.009–−.032	0.269
BMI	−0.098	−0.224–0.027	0.118	0.032	−0.072–0.136	0.537
Duration of diabetes	0.024	−0.037–0.086	0.409	0.007	−0.034–0.049	0.723
Study duration	−0.044	−0.061–−0.027	0.000	−0.004	−0.018–0.009	0.514
Baseline HbA1c	−0.060	−0.238–0.118	0.492	−0.418	−0.669–−0.166	0.002
Baseline weight	−0.030	−0.077–0.017	0.186	0.015	−0.027–0.056	0.476
Weight change	0.322	−0.046–0.692	0.081	0.039	−0.102–0.179	0.583
Weight change						
Total group						
Age	0.009	−0.061–0.080	0.779	0.035	−0.073–0.144	0.511
Sex	−0.010	−0.056–0.037	0.658	0.026	−0.033–0.086	0.376
BMI	−0.106	−0.664–0.453	0.690	0.004	−0.307–0.315	0.981
Duration of diabetes	0.034	−0.058–0.126	0.433	0.109	0.003–0.215	0.044
Study duration	0.003	−0.052–0.058	0.918	0.029	−0.006–0.065	0.106
Baseline HbA1c	0.139	−0.496–0.774	0.644	0.558	−0.269–1.386	0.180
Baseline weight	−0.081	−0.210–0.039	0.157	−0.010	−0.120–0.100	0.850
HbA1c change	−0.283	−1.316–0.751	0.564	−0.915	−2.651–0.821	0.293
SGLT2i						
HbA1c change						
Total group						
Age	0.055	−0.021–0.131	0.134	0.074	0.038–0.110	0.000
Sex	0.013	−0.007–0.033	0.176	0.024	0.004–0.044	0.023
BMI	−0.059	−0.179–0.061	0.283	−0.006	−0.091–0.079	0.885
Duration of diabetes	−0.081	−0.333–0.171	0.462	0.046	0.010–0.083	0.015
Study duration	0.001	−0.010–0.0112	0.881	0.004	−0.003–0.011	0.270
Baseline HbA1c	0.264	−0.926–1.454	0.623	−0.793	−1.067–−0.518	0.000
Baseline weight	/	/	/	/	/	/
Weight change	0.589	−0.264–1.442	0.150	/	/	/
Weight change						
Total group						
Age	0.005	−0.104–0.113	0.920	−0.016	−0.102–0.070	0.711
Sex	0.014	−0.011–0.395	0.226	−0.027	−0.078–0.025	0.299
BMI	0.023	−0.106–0.152	0.683	−0.009	−0.162–0.144	0.903
Duration of diabetes	−0.093	−0.345–0.159	0.402	0.015	−0.112–0.142	0.807
Study duration	−0.001	−0.012–0.010	0.789	0.010	−0.006–0.025	0.201
Baseline HbA1c	0.460	−1.099–2.019	0.515	0.320	−0.535–1.175	0.454
Baseline weight	−0.007	−0.058–0.044	0.762	/	/	/
HbA1c change	/	/	/	0.020	−0.698–0.739	0.954
GLP-1RA						
HbA1c change						
Total group						
Age	0.050	−0.033–0.134	0.197	−0.033	−0.121–0.054	0.442
Sex	0.005	−0.011–0.020	0.492	0.011	−0.003–0.025	0.112
BMI	0.031	−0.065–0.127	0.467	−0.009	−0.094–0.077	0.840
Duration of diabetes	0.012	−0.068–0.092	0.735	−0.001	−0.044–0.041	0.948
Study duration	0.006	−0.039–0.050	0.771	0.004	0.001–0.007	0.023
Baseline HbA1c	0.712	−0.252–1.676	0.124	0.168	−0.129–0.464	0.258
Baseline weight	0.012	−0.018–0.041	0.390	/	/	/
Weight change	0.273	−0.298–0.844	0.295	0.023	−0.089–0.135	0.675
Weight change						
Total group						
Age	−0.003	−0.144–0.137	0.955	0.039	−0.211–0.289	0.753
Sex	−0.005	−0.031–0.020	0.634	0.024	−0.023–0.072	0.302
BMI	0.013	−0.200–0.227	0.886	−0.173	−0.413–0.067	0.152

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Supplementary Table S3: Contd...

Variables	Asian			Caucasian		
	Coefficient	95% *CI*	*P*	Coefficient	95% *CI*	*P*
Duration of diabetes	0.021	−0.144–0.186	0.771	0.091	−0.048–0.231	0.190
Study duration	−0.023	−0.083–0.037	0.395	−0.001	−0.016–0.013	0.866
Baseline HbA1c	1.879	−0.065–3.824	0.056	0.171	−0.975–1.318	0.762
Baseline weight	−0.003	−0.069–0.064	0.925	−0.032	−0.106–0.042	0.381
HbA1c change	0.135	−1.490–1.760	0.850	−0.268	−2.021–1.486	0.757

Data are given as median values with the interquartile range in parentheses. *P* values indicated the significance of the comparisons between Asia and Caucasian. *CI*: Confidence interval; SU: Sulfonylurea; BMI: Body mass index; HbA1c: Glycosylated hemoglobin; MET: Metformin; AGI: Alpha glucosidase inhibitors; TZD: Thiazolidinediones; DPP-4i: Dipeptidyl peptidase-4 inhibitors; SGLT2i: Sodium-glucose cotransporter 2 inhibitors; GLP-1RA: Glucagon-like peptide-1 analogs; /: No reported data.