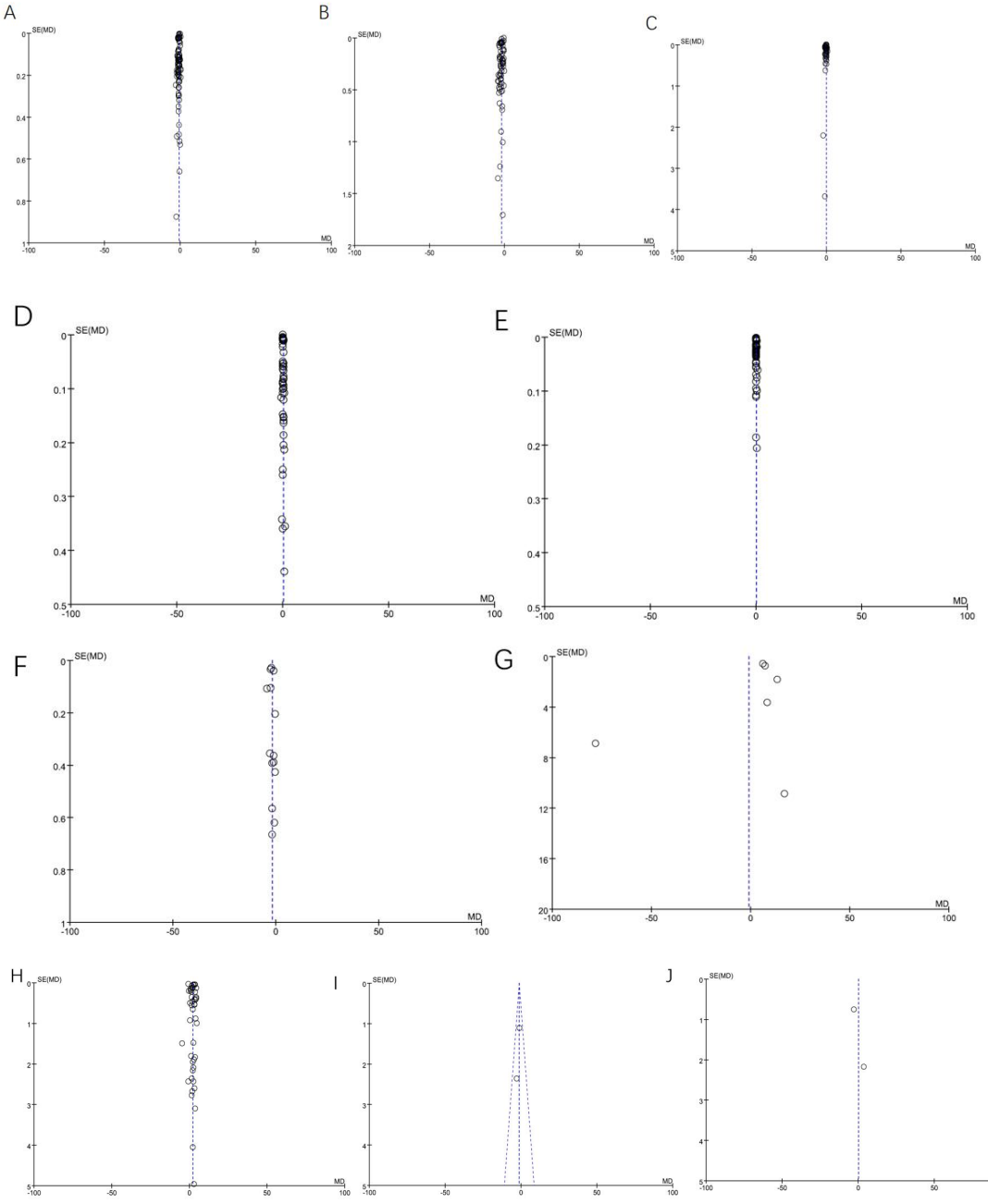
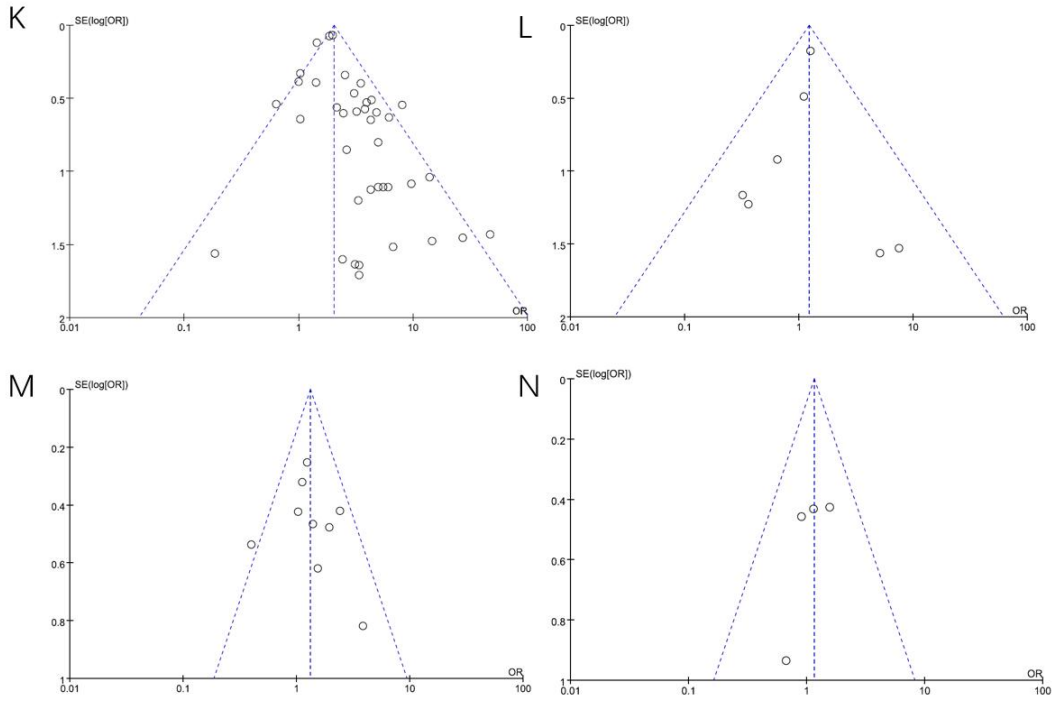
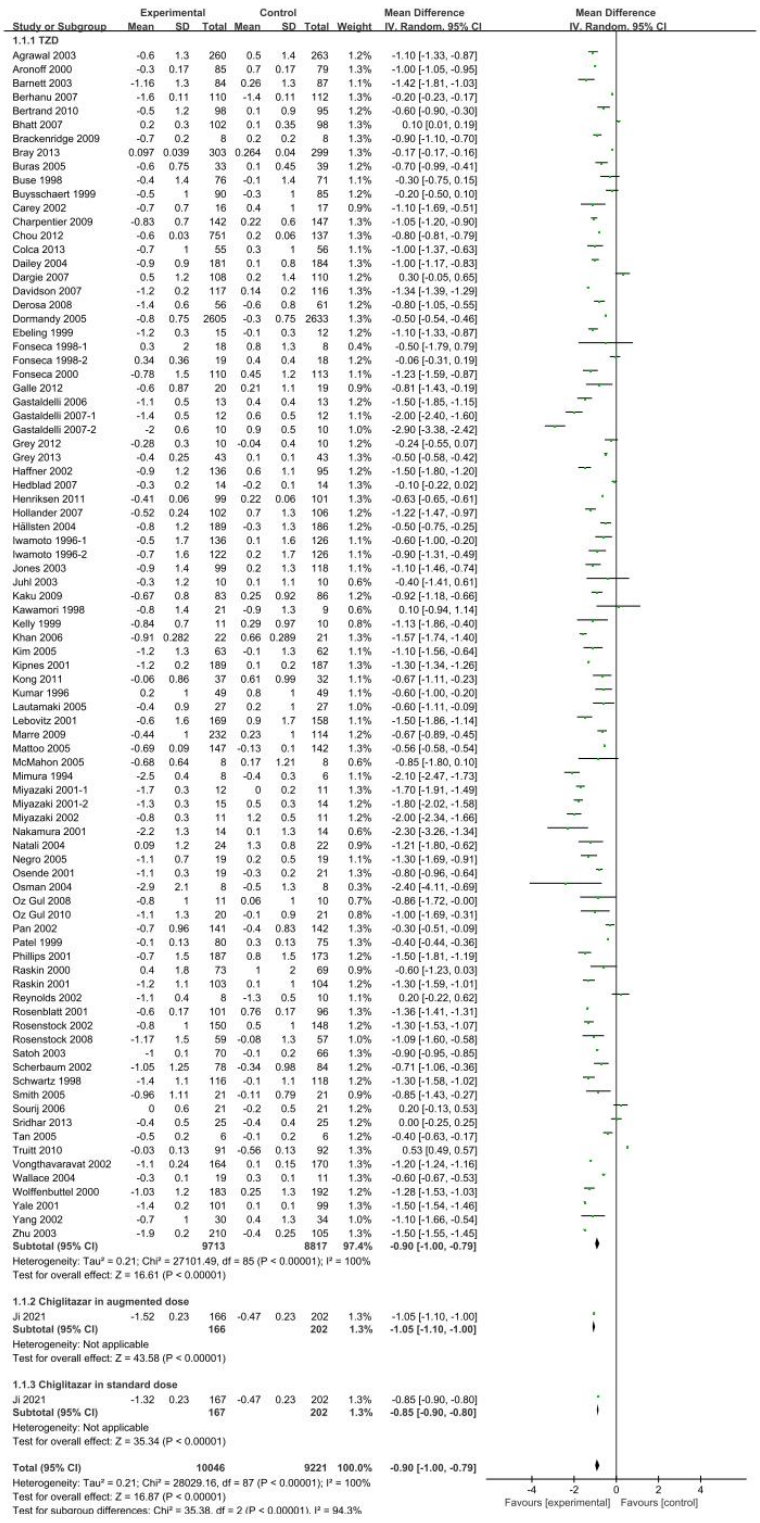
SUPPLEMENTARY MATERIALS

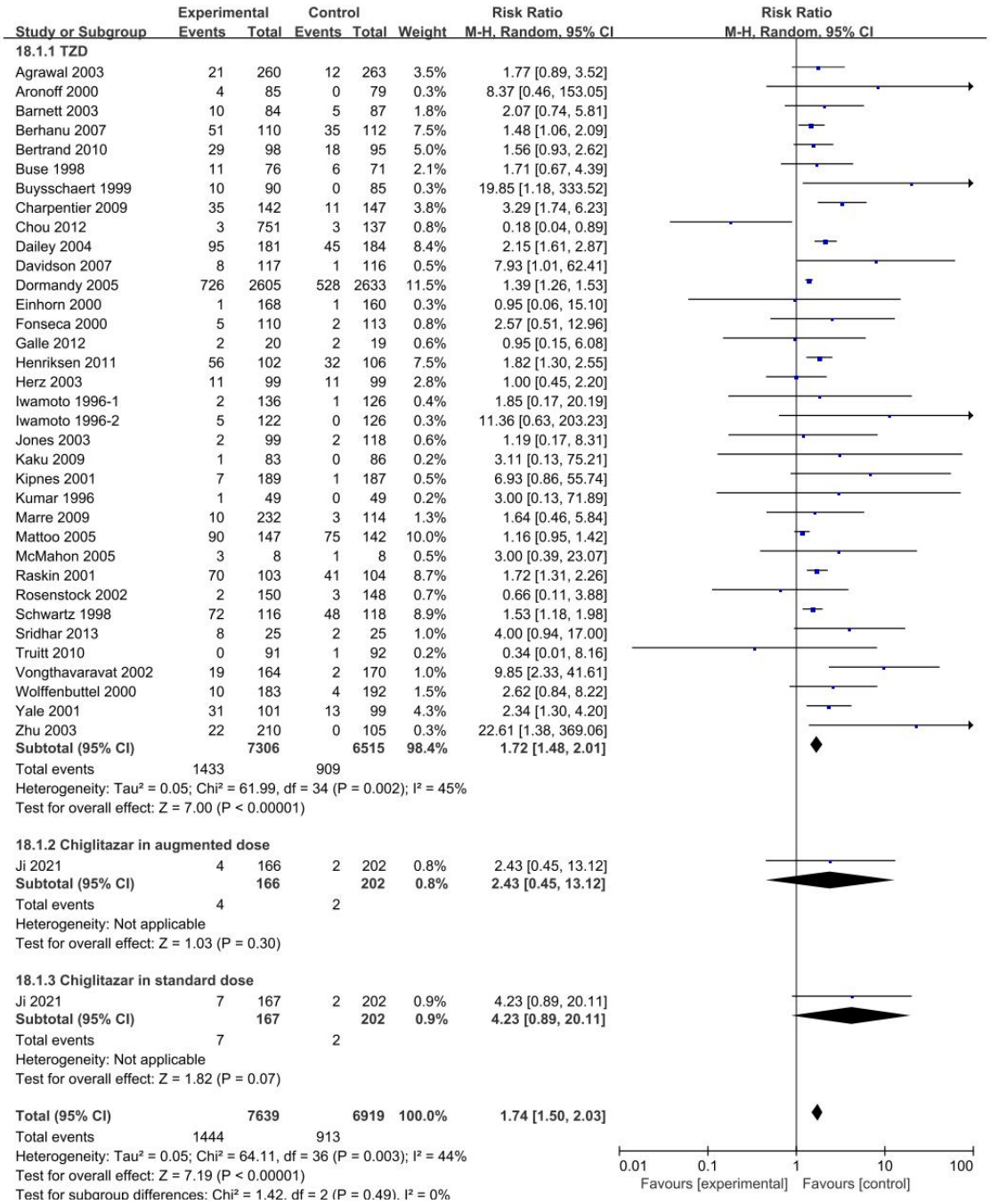




Supplementary Figure 1 Funnel plot of analysis endpoints. A-C: Endpoints of HbA1c, FBG, TG; D-G: Endpoints of LDL-C, HDL-C, HOMA-IR, HOMA-β; H-J: Endpoints of body weight, ALT, AST; K-N: Endpoints of edema, bone fracture, upper respiratory tract infection, urinary tract infection.



Supplementary Figure 2 Forest plot of the HbA1c change outcome.



Supplementary Figure 3 Forest plot of the hypoglycemia outcome.

Pooled treatment effect estimates and indirect comparison - efficacy endpoints (Chiglitazar in standard doses)

Efficacy endpoints	Participants	WMD and 95% CI	I^2
HbA1c (%)			
Chiglitazar versus placebo	167/202	-0.85 (-0.90, -0.80)	Not applicable
TZD versus placebo	9713/8817	-0.90 (-1.00, -0.79)	100%
Chiglitazar versus TZD	167/9713	0.05 (-0.07, 0.16)	
FBG (mmol/L)			
Chiglitazar versus placebo	167/202	-1.49 (-1.94, -1.04)	Not applicable
TZD versus placebo	5381/4585	-2.05 (-2.32, -1.77)	100%
Chiglitazar versus TZD	167/5381	0.56 (0.03, 1.08)	
TG (mmol/L)			
Chiglitazar versus placebo	167/202	-0.23 (-0.25, -0.21)	Not applicable
TZD versus placebo	6681/6026	-0.21 (-0.27, -0.15)	98%
Chiglitazar versus TZD	167/6681	-0.02 (-0.09, 0.05)	
LDL-C (mmol/L)			
Chiglitazar versus placebo	167/202	0.22 (0.21, 0.23)	Not applicable
TZD versus placebo	6717/6076	0.15 (0.11, 0.19)	99%
Chiglitazar versus TZD	167/6717	0.15 (0.11, 0.19)	
HDL-C (mmol/L)			
Chiglitazar versus placebo	167/202	0.070 (0.066, 0.074)	Not applicable
TZD versus placebo	7115/6458	0.10 (0.08, 0.11)	99%
Chiglitazar versus TZD	167/7115	-0.03 (-0.04, -0.01)	

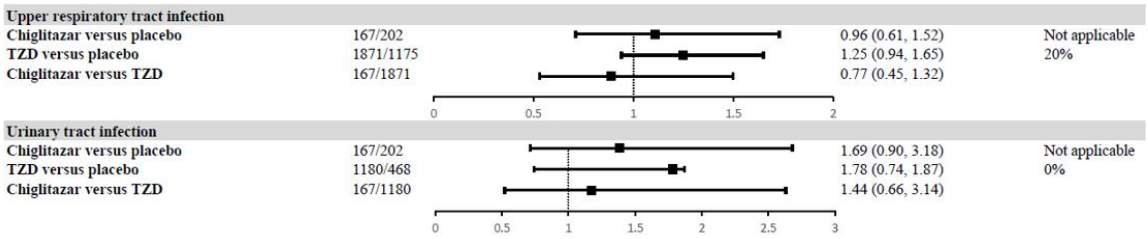
HOMA-IR			
Chiglitazar versus placebo	167/202	-0.96 (-1.01, -0.91)	Not applicable
TZD versus placebo	1434/816	-1.81 (-2.30, -1.33)	99%
Chiglitazar versus TZD	167/1434	0.87 (0.36, 1.35)	
HOMA-β			
Chiglitazar versus placebo	167/202	8.39 (7.98, 8.80)	Not applicable
TZD versus placebo	1257/512	-1.11 (-8.12, 5.90)	97%
Chiglitazar versus TZD	167/1257	9.50 (2.48, 16.52)	
ALT (U/L)			
Chiglitazar versus placebo	167/202	-3.30 (-5.92, -0.68)	Not applicable
TZD versus placebo	67/71	-1.35 (-8.32, -0.62)	0%
Chiglitazar versus TZD	167/67	-1.95 (-5.23, -1.33)	
AST (U/L)			
Chiglitazar versus placebo	167/202	-0.50 (-2.79, -1.79)	Not applicable
TZD versus placebo	67/71	-0.03 (-6.44, 6.40)	88%
Chiglitazar versus TZD	167/67	-0.48 (-7.29, 6.34)	

Pooled treatment effect estimates and indirect comparison - safety endpoints (Chiglitazar in standard doses)

Safety endpoints	Participants	WMD and 95% CI	I^2
Weight gain (kg)			
Chiglitazar versus placebo	167/202	1.70 (1.14, 2.26)	Not applicable
TZD versus placebo	6884/6142	2.15 (1.51, 2.79)	100%
Chiglitazar versus TZD	167/6884	0.05 (-0.07, 0.16)	

Pooled treatment effect estimates and indirect comparison - safety endpoints (Chiglitazar in standard doses)

Safety endpoints	Participants	RR and 95% CI	I^2
Hypoglycemia			
Chiglitazar versus placebo	167/202	4.23 (0.89, 20.11)	Not applicable
TZD versus placebo	7904/7135	1.72 (1.48, 2.01)	45%
Chiglitazar versus TZD	167/7904	2.67 (0.44, 16.11)	
Edema			
Chiglitazar versus placebo	167/202	15.62 (0.90, 271.57)	Not applicable
TZD versus placebo	12578/11860	2.04 (1.72, 2.42)	44%
Chiglitazar versus TZD	167/12578	7.69 (0.44, 134.44)	
Bone fractures			
Chiglitazar versus placebo	167/202	3.63 (0.15, 88.41)	Not applicable
TZD versus placebo	3998/3404	1.18 (0.87, 1.60)	0%
Chiglitazar versus TZD	167/3998	3.08 (0.12, 76.16)	



Supplementary Figure 4 Pooled treatment effect estimates and indirect comparison between chiglitazar in standard doses and TZD of efficacy and safety endpoints. HbA1c: Hemoglobin A1c; FBG: Fasting blood glucose; TG: Triglycerides; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; HOMA-IR: Homeostasis model assessment of insulin resistance; HOMA-β: Homeostasis model assessment of β cell function; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; RR: Risk ratios; 95%CI: 95% confidential intervals.

Supplementary Table 1 Baseline characteristics of included studies

Author, year	Follow-up duration (weeks)	Treatment	No. of patients	Age (years)	Male (%)	BMI (kg/m^2)	Diabetes duration (years)	Baseline HbA1c (%)	Predominant ethnicity
Chiglitazar (chiglitazar)									
Ji, 2021 [1]	24	Chiglitazar 48mg	166	51.8±9.9	65.1	26.1	1.4	8.6±0.7	Asian (100%)
		placebo	202	51.2±10.0	61.4	26.1	1.4	8.6±0.7	
Pioglitazone (thiazolidinedione)									
Aronoff, 2000 [2]	26	pioglitazone 30mg	85	NA	NA	NA	NA	10.2±0.21	Caucasian (78%)
		placebo	79	NA	NA	NA	NA	10.4±0.22	
Chou, 2012 [3]	26	pioglitazone 45mg	751	55.0±10.8	53.0	30.0	4.4	7.7±0.58	Caucasian (55%)
		placebo	137	55.4±12.3	48.9	30.1	4.9	7.7±0.54	

Colca, 2013 [4]	12	pioglitazone 45mg	55	55.0±NA	56.0	NA	4.4	8.2±NA	NA
		placebo	56	53.0±NA	48.0	NA	4.9	8.0±NA	
Khan, 2006 [5]	26	pioglitazone 30mg	22	52.7±9.0	68.2	32.3	NA	8.5±0.31	Caucasian (68%)
		placebo	21	54.8±8.7	28.6	32.0	NA	8.6±0.32	
Kong, 2011 [6]	12	pioglitazone 30mg	37	53.6±7.6	56.8	24.9	5.6	7.5±0.82	Asian (100%)
		placebo	32	54.0±8.5	59.4	25.5	5.9	7.4±0.62	
Miyazaki, 2001 [7]	16	pioglitazone 45mg	12	NA	NA	28.7	NA	8.9±0.3	Caucasian
		placebo	11	NA	NA	29.5	NA	7.9±0.3	
Miyazaki, 2002 [8]	26	pioglitazone 30mg	11	51±2	72.7	32.2	NA	8.5±0.5	Caucasian (55%)
		placebo	11	58±3	27.3	32.8	NA	8.6±0.5	
Rosenblatt, 2001 [9]	16	pioglitazone 30mg	101	53.8±10.0	50.5	31.5	NA	10.7±1.8	Caucasian (69%)

		placebo	96	55.2±10.0	56.2	30.7	NA	10.4±1.7	
Scherbaum, 2002 [10]	26	pioglitazone 30mg	78	59.6±NA	41.0	29.3	4.6	9.1±NA	NA
		placebo	84	59.1±NA	56.0	29.2	5.6	8.8±NA	
Sourij, 2006 [11]	12	pioglitazone 30mg	21	60.3±7.5	NA	NA	0.1	6.1±0.6	NA
		placebo	21	60.3±7.5	NA	NA	0.1	6.1±0.5	
Truitt, 2010 [12]	26	pioglitazone 45mg	91	56.6±10.1	58.2	32.9	6.6	8.0±0.8	Caucasian (51%)
		placebo	92	55.3±9.3	51.1	32.2	6.7	8.2±1.0	
Wallace, 2004 [13]	12	pioglitazone 45mg	19	61.4±6.3	73.7	29.8	2.6	6.7±0.9	NA
		placebo	11	62.6±10.0	72.7	28.9	2.5	6.7±0.9	
Berhanu, 2007 [14]	29	pioglitazone 45mg	110	52.9±11.3	43.6	30.7	7.7	8.4±0.1	Caucasian
		placebo	112	52.5±11.1	41.1	31.8	8.5	8.6±0.1	
Brackenridge,	12	pioglitazon	8	61.0±7.9	87.5	30.8	4.0	7.5±0.2	NA

2009 [15]		e 30mg							
		placebo	8	60.8±6.3	87.5	32.0	2.9	6.6±0.1	
Charpentier, 2009 [16]	28	pioglitazone 30mg	142	60.2±9.6	64.6	29.1	12.5	8.1±0.7	Caucasian (87%)
		placebo	147	59.2±9.3	66.2	29.2	12.1	8.2±0.6	
Galle, 2012 [17]	26	pioglitazone 30mg	20	68.9±6.8	70.0	31.5	13.8	7.4±0.9	NA
		placebo	19	69.6±9.4	68.4	30.3	12.4	7.7±0.9	
Gastaldelli, 2007 [18]	18	pioglitazone 45mg	10	55.0±4.0	50.0	28.9	6.0	9.3±0.4	Caucasian (50%)
		placebo	10	55.0±4.0	40.0	29.9	5.0	8.3±0.4	
Grey, 2012 [19]	26	pioglitazone 30mg	10	61.9±10.0	60.0	31.2	NA	7.6±2.1	NA
		placebo	10	57.9±15.2	50.0	33.2	NA	7.1±1.0	
Henriksen, 2011 [20]	26	pioglitazone 45mg	102	60.1±8.6	69.0	33.2	13.8	8.7±1.4	Caucasian (99%)
		placebo	106	60.9±7.8	62.0	33.9	12.6	8.7±1.4	

Kaku, 2009 [21]	28	pioglitazone 30mg	83	52.0±8.6	66.3	25.6	4.5	7.6±1.0	Asian (100%)
		placebo	86	53.0±7.5	57.0	25.4	5.6	7.6±0.9	
Kawamori, 1998 [22]	12	pioglitazone 30mg	21	57.6±8.5	66.7	23.0	12.5	8.4±1.4	Asian (100%)
		placebo	9	60.6±10.0	55.6	22.0	11.9	8.7±1.3	
Kipnes, 2001 [23]	16	pioglitazone 30mg	189	56.6±10.1	60.0	32.4	NA	9.9±0.2	Caucasian (83%)
		placebo	187	56.9±8.9	58.0	32.0	NA	9.9±0.2	
Mattoo, 2005 [24]	26	pioglitazone 30mg	147	58.9±7.4	42.9	31.8	13.4	8.8±0.1	Caucasian (97%)
		placebo	142	58.8±6.9	43.7	32.5	13.6	8.9±0.1	
Nakamura, 2001 [25]	26	pioglitazone 30mg	14	52.5±10.2	64.3	NA	NA	8.4±1.3	NA
		placebo	14	52.5±10.2	NA	NA	NA	8.0±1.1	
Pan, 2002 [26]	12	pioglitazone 30mg	141	NA	NA	NA	NA	8.5±1.3	NA

		placebo	142	NA	NA	NA	NA	8.5±1.1	
Smith, 2005 [27]	24	pioglitazone 45mg	21	56.2±9.7	42.9	32.1	NA	6.9±1.4	Caucasian (71%)
		placebo	21	53.1±9.3	47.6	31.9	NA	6.5±0.7	
Sridhar, 2013 [28]	24	pioglitazone 30mg	25	56.2±5.8	100	25.3	2.2	6.8±0.4	NA
		placebo	25	53.1±7.2	100	25.1	2.9	6.8±0.4	
Grey, 2014 [29]	52	pioglitazone 30mg	43	64.0±15.5	78.0	31.0	NA	7.4±3.5	NA
		placebo	43	63.0±23.0	80.0	31.0	NA	7.5±3.2	
Bray, 2013 [30]	134	pioglitazone 30mg	303	50.7±10.1	NA	34.4	NA	5.0±0.4	NA
		placebo	299	48.1±11.3	NA	34.7	NA	5.0±0.4	
Bone, 2013 [31]	52	pioglitazone 30mg	78	59.0±5.0	0	29.6	NA	NA	Caucasian (90%)
		placebo	78	60.2±6.2	0	30.3	NA	NA	
Dormandy,	138	pioglitazon	2605	61.9±7.6	67.0	30.7	8.0	7.9±0.9	Caucasian

2005 [32]		e 15-45mg							(98%)
		placebo	2633	61.6±7.8	66.0	31.0	8.0	7.8±0.9	
Satoh, 2003 [33]	12	pioglitazone 30mg	70	61.2±1.3	45.7	23.4	NA	8.1±0.1	Asian (100%)
		placebo	66	59.3±1.9	48.5	23.0	NA	8.0±0.2	
McMahon, 2005 [34]	12	pioglitazone 30mg	8	56.5±10.0	25.0	35.1	15.5	7.4±0.6	NA
		placebo	8	52.2±10.0	87.5	32.3	14.0	7.7±0.6	
Herz, 2003 [35]	16	pioglitazone 45mg	99	58.1±11.0	52.5	30.8	20.1	7.5±NA	Caucasian (94%)
		placebo	99	58.0±10.7	49.5	31.7	17.4	7.6±NA	
Einhorn, 2000 [36]	16	pioglitazone 30mg	168	55.5±10.3	54.8	32.1	NA	9.9±1.4	Caucasian (81%)
		placebo	160	55.7±9.9	60.0	32.1	NA	9.8±1.3	
Erdmann, 2007 [37]	NA	pioglitazone	2605	NA	NA	NA	NA	NA	NA
		placebo	2633	NA	NA	NA	NA	NA	

Rosiglitazone (thiazolidinedione)									
Carey, 2002 [38]	16	rosiglitazone 8mg	16	54.2±11.1	87.5	29.8	3.3	7.8±1.3	Caucasian (100%)
		placebo	17	57.9±10.7	76.5	31.3	3.1	7.1±1.4	
Gastaldelli, 2006 [39]	12	rosiglitazone 8mg	13	53.0±2.0	53.8	29.3	4.0	8.6±0.5	Caucasian
		placebo	13	56.0±2.0	61.5	30.2	3.0	8.2±0.4	
Gastaldelli, 2007 [18]	18	rosiglitazone 8mg	12	55.0±3.0	50.0	29.2	4.0	8.7±0.5	Caucasian
		placebo	12	56.0±2.0	66.7	29.8	2.0	8.1±0.4	
Haffner, 2002 [40]	26	rosiglitazone 8mg	136	60.4±9.3	47.8	29.5	4.9	8.6±1.5	NA
		placebo	95	59.8±10.5	61.1	30.1	4.5	8.7±1.5	
Juhl, 2003 [41]	13	rosiglitazone 8mg	10	54.0±9.0	90.0	30.0	NA	7.0±1.4	NA
		placebo	10	54.0±9.0	60.0	31.7	NA	6.8±1.0	
Lautamaki,	16	rosiglitazon	27	64.1±7.8	70.4	29.6	6.7	7.3±0.9	NA

2005 [42]		e 8mg							
		placebo	27	63.2±7.4	70.4	29.6	6.8	7.1±0.9	
Miyazaki, 2001 [43]	12	rosiglitazone 8mg	15	NA	NA	30.0	NA	8.7±0.4	NA
		placebo	14	NA	NA	30.1	NA	8.3±0.4	
Oz Gul, 2008 [44]	12	rosiglitazone 4mg	11	NA	NA	28.3	NA	7.0±1.1	NA
		placebo	10	NA	NA	29.2	NA	6.4±1.1	
Oz Gul, 2010 [45]	12	rosiglitazone 4mg	20	NA	NA	29.6	NA	7.3±1.3	NA
		placebo	21	NA	NA	29.6	NA	7.3±0.9	
Patel, 1999 [46]	12	rosiglitazone 4mg	80	59.7±10.0	68.8	28.4	5.8	9.0±NA	Caucasian (73%)
		placebo	75	56.8±11.5	69.3	28.9	4.2	9.1±NA	
Phillips, 2001 [47]	16	rosiglitazone 8mg	187	56.5±9.7	65.2	29.9	5.9	9.0±1.5	Caucasian (71%)
		placebo	173	57.7±9.2	68.8	29.1	6.6	8.9±1.5	

Raskin, 2000 [48]	8	rosiglitazone 4mg	73	58.5±9.8	61.6	30.2	5.6	8.7±1.4	Caucasian (71%)
		placebo	69	60.1±9.4	59.4	30.4	4.0	8.7±1.6	
Tan, 2005 [49]	24	rosiglitazone 8mg	6	NA	NA	30.8	NA	7.2±0.3	NA
		placebo	6	NA	NA	30.8	NA	7.5±0.4	
Barnett, 2003 [50]	26	rosiglitazone 8mg	84	54.3±24.0	80.0	26.8	6.5	9.2±1.3	Asian (100%)
		placebo	87	54.1±23.0	75.0	26.4	6.5	9.1±1.3	
Bertrand, 2010 [51]	52	rosiglitazone 8mg	98	64.2±7.3	92.0	30.2	7.8	6.9±1.3	NA
		placebo	95	65.9±6.9	92.0	29.5	8.4	6.9±0.8	
Dailey, 2004 [52]	24	rosiglitazone 8mg	181	57.0±9.0	58.0	32.0	9.0	8.1±0.9	Caucasian (77%)
		placebo	184	57.0±10.0	61.0	32.0	9.0	8.1±0.8	
Davidson, 2007 [53]	24	rosiglitazone 8mg	117	52.0±11.9	45.3	31.3	6.0	9.2±1.3	NA

		placebo	116	53.0±10.4	48.3	31.9	6.2	9.4±1.4	
Derosa, 2008 [54]	26	rosiglitazone 8mg	56	55.0±4.0	46.4	28.6	3.0	7.8±0.7	Caucasian (100%)
		placebo	61	54.0±3.0	47.5	28.4	4.0	8.0±0.9	
Fonseca, 2000 [55]	26	rosiglitazone 8mg	110	58.3±8.8	68.2	29.8	8.3	8.9±1.5	Caucasian (77%)
		placebo	113	58.8±9.2	74.3	30.3	7.3	8.6±1.3	
Hollander, 2007 [56]	24	rosiglitazone 4mg	189	52.6±10.1	48.1	33.7	13.0	9.0±1.2	Caucasian (57%)
		placebo	186	53.8±10.2	46.2	33.0	12.6	9.1±1.3	
Marre, 2009 [57]	26	rosiglitazone 4mg	232	56.0±9.8	47.0	29.4	6.6	8.4±1.0	NA
		placebo	114	54.7±10.0	47.0	30.3	6.5	8.4±1.0	
Negro, 2005 [58]	52	rosiglitazone 8mg	19	60.3±6.4	52.6	28.3	7.1	8.4±0.6	Asian (100%)
		placebo	19	59.0±8.0	63.2	28.7	6.6	8.1±0.5	
Raskin, 2001 [59]	26	rosiglitazon	103	57.1±10.2	54.4	32.3	12.5	9.0±1.3	Caucasian

		e 8mg							(71%)
		placebo	104	55.6±10.3	55.8	32.7	11.7	8.9±1.1	
Reynolds, 2002 [60]	26	rosiglitazone 4mg	8	NA	NA	36.4	NA	8.0±0.3	NA
		placebo	10	NA	NA	36.3	NA	9.8±0.5	
Rosenstock, 2008 [61]	26	rosiglitazone 8mg	59	63.0±9.0	44.0	29.9	6.4	8.1±1.5	Caucasian (100%)
		placebo	57	65.0±9.0	60.0	29.1	6.6	7.9±1.3	
Wolffenbuttel, 2000 [62]	26	rosiglitazone 4mg	183	60.6±8.7	55.2	28.3	7.0	9.2±1.2	Caucasian (98%)
		placebo	192	61.9±9.1	57.3	28.1	8.0	9.2±1.3	
Yang, 2002 [63]	26	rosiglitazone 4mg	30	58.9±9.4	43.3	25.8	NA	9.5±1.1	NA
		placebo	34	57.8±8.9	38.2	25.8	NA	9.7±1.4	
Zhu, 2003 [64]	24	rosiglitazone 8mg	210	58.9±6.9	48.0	24.9	7.9	9.8±1.5	Asian (100%)
		placebo	105	58.8±7.7	46.0	25.1	7.6	9.8±1.3	

Gruntmanis, 2010 [65]	26	rosiglitazone 4mg	56	56.7±8.8	41.0	33.9	NA	7.6±1.8	Caucasian
		placebo	55	55.8±8.3	40.0	33.5	NA	7.6±1.7	
Gold, 2010 [66]	24	rosiglitazone 2mg	162	71.7±8.6	36.0	24.3	NA	NA	Caucasian (67%)
		placebo	159	72.5±8.6	40.0	25.3	NA	NA	
Hallsten, 2002 [67]	26	rosiglitazone 4mg	14	58.6±2.0	71.4	29.3	NA	6.8±0.2	NA
		placebo	14	57.7±1.9	71.4	30.3	NA	6.3±0.1	
Kim, 2005 [68]	12	rosiglitazone 4mg	63	58.8±8.8	66.7	23.9	12.0	9.7±1.7	Asian (100%)
		placebo	62	58.1±9.5	62.9	24.5	10.1	9.3±1.3	
Lebovitz, 2001 [69]	26	rosiglitazone 8mg	169	61.0±9.5	66.9	29.1	5.4	8.8±1.6	Caucasian (73%)
		placebo	158	59.0±10.9	65.8	29.9	4.6	9.0±1.7	
Natali, 2004 [70]	16	rosiglitazone 8mg	24	59.0±7.0	NA	27.6	6.5	7.7±1.2	NA

		placebo	22	58.0±9.0	NA	30.2	3.4	7.6±0.8	
Osman, 2004 [71]	26	rosiglitazone 4mg	8	53.5±12.0	12.5	NA	7.8	10.3±3.2	NA
		placebo	8	57.3±20.5	62.5	NA	6.8	8.7±1.9	
Jones, 2003 [72]	26	rosiglitazone 8mg + metformin	99	56.6±10.0	57.0	33.7	5.0	8.8±1.4	NA
		Placebo + metformin	118	57.5±9.0	70.0	34.0	5.0	8.7±1.3	
Vongthavaravat, 2008 [73]	26	rosiglitazone 4mg	164	54.6±23.0	45.7	27.1	5.0	9.1±NA	Caucasian
		placebo	170	57.3±20.0	42.4	27.1	6.0	8.9±NA	
Agrawal, 2003 [74]	26	rosiglitazone 4mg	260	56.5±9.0	67.7	31.0	7.7	9.2±1.3	NA
		placebo	263	57.2±8.0	66.5	30.7	7.7	9.2±1.4	
Albertini, 2007 [75]	12	rosiglitazone 8mg	64	55.5±8.0	65.6	31.3	4.3	NA	Caucasian (94%)

		placebo	71	56.4±6.9	63.4	29.8	4.1	NA	
Bhatt, 2007 [76]	52	rosiglitazone 8mg	102	59.4±9.8	80.4	NA	NA	5.8±1.3	Caucasian (99%)
		placebo	98	59.4±9.6	79.6	NA	NA	5.7±0.2	
Dargie, 2007 [77]	52	rosiglitazone 8mg	108	64.3±8.8	84.3	28.8	NA	7.8±1.3	Caucasian (99%)
		placebo	110	63.9±8.6	79.1	28.6	NA	7.8±1.3	
DREAM, 2006 [78]	156	rosiglitazone 8mg	2635	54.6±10.9	41.7	30.8	NA	NA	NA
		placebo	2634	54.8±10.9	39.9	31.0	NA	NA	
Hedblad, 2007 [79]	52	rosiglitazone 8mg	99	67.0±6.0	51.0	30.0	3.7	6.9±0.8	NA
		placebo	101	66.0±8.0	59.0	29.0	4.5	6.9±0.8	
Troglitazone (thiazolidinedione)									
Ebeling, 1999 [80]	16	troglitazone 400mg	15	62.6±2.2	33.3	32.2	15.9	8.7±0.3	NA
		placebo	12	63.5±2.8	50.0	33.1	14.3	8.8±0.3	

Fonseca, 1998-1 [81]	26	troglitazone 600mg	18	60.4±5.9	44.4	37.3	NA	9.5±2.0	NA
		placebo	8	52.6±7.5	37.5	39.6	NA	10.1±1.4	
Fonseca, 1998-2 [82]	26	troglitazone 400mg	19	54.0±11.0	59.2	32.4	5.3	8.5±2.1	Caucasian (74%)
		placebo	18	54.0±11.0	59.2	32.4	5.3	8.7±1.9	
Iwamoto, 1996-1 [83]	12	troglitazone 400mg	136	54.6±10.1	50.7	24.1	6.3	8.6±1.5	NA
		placebo	126	57.4±9.3	53.2	24.7	7.5	8.5±1.5	
Iwamoto, 1996-2 [84]	12	troglitazone 400mg	122	57.8±9.0	50.8	23.7	NA	9.2±1.4	NA
		placebo	126	58.7±8.0	42.9	23.3	NA	9.0±1.5	
Kumar, 1996 [85]	12	troglitazone 800mg	49	56.0±15.5	57.1	27.7	6.0	6.9±NA	NA
		placebo	49	57.0±15.5	73.5	28.9	7.0	7.0±NA	
Rosenstock, 2002 [86]	16	troglitazone 600mg	150	58.0±26.5	59.0	29.5	NA	8.4±1.1	Caucasian (79%)

		placebo	148	58.0±25.5	59.0	29.0	NA	8.2±1.2	
Buras, 2005 [87]	12	troglitazone 600mg	33	58.0±9.0	60.6	30.9	8.0	7.6±1.4	NA
		placebo	39	57.0±9.0	66.7	32.6	8.0	7.9±1.4	
Buse, 1998 [88]	26	troglitazone 400mg	76	58.0±10.0	50.0	34.8	NA	9.0±1.4	Caucasian (80%)
		placebo	71	57.0±11.0	49.0	34.5	NA	9.0±1.4	
Buysschaert, 1999 [89]	16	troglitazone 200mg	90	60.0±25.5	66.7	NA	6.4	7.9±NA	Caucasian (91%)
		placebo	85	60.0±21.5	51.8	NA	7.8	8.5±NA	
Kelly, 1999 [90]	12	troglitazone 600mg	11	58.0±8.6	72.7	28.7	NA	7.5±1.4	NA
		placebo	10	58.6±7.5	80.0	28.6	NA	8.4±1.5	
Mimura, 1994 [91]	12	troglitazone 400mg	8	53.0±NA	50.0	22.4	NA	9.3±0.4	NA
		placebo	6	58.0±NA	50.0	21.3	NA	9.7±0.3	
Osende, 2001	12	troglitazone	19	57.2±1.8	68.4	30.4	NA	9.1±0.3	NA

[92]		600mg							
		placebo	21	57.0±1.7	52.4	31.5	NA	9.2±0.2	
Schwartz, 1998 [93]	26	troglitazone 600mg	116	56.0±9.0	46.0	35.1	10.0	9.3±1.1	Caucasian (67%)
		placebo	118	56.0±10.0	51.0	35.0	10.0	9.4±1.1	
Yale, 2001 [94]	24	troglitazone 400mg	101	58.0	55.0	30.1	11.9	9.6±0.1	NA
		placebo	99	60.0	58.0	30.0	10.8	9.7±0.1	

NA: Not available; BMI: Body mass index; HbA1c: Hemoglobin A1c.

DREAM: Diabetes REduction Assessment with ramipril and rosiglitazone Medication.

Supplementary Table 2 Risk of bias in included studies (by Cochrane collaboration's tool)

Author, year	Adequate randomization sequence generation	Adequate allocation concealment	Blinding of participants and caregivers	Binding of outcome assessors and adjudicators	Free of frequent missing outcome data	Free of selective outcome reporting	Free of other bias
Chiglitazar (chiglitazar)							
Ji, 2021 [1]	**Definitely yes** Randomization was achieved via a web response system with a computer-generated random sequence	**Definitely yes** Sponsors and investigators did not have access to the randomization sequence	**Definitely yes**	**Definitely yes**	**Probably no** Data of 22/166 (13.3%) participants from experimental group and 40/202 (19.8%) from control group missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced

Pioglitazone (thiazolidinedione)							
Aronoff, 2000 [2]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 37/85 (44%) participants from experimental group and 26/79 (33%) from control group missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Chou, 2012 [3]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 172/751 (22.9%) participants from experimental	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced

					group and 41/137 (29.9%) from control group missed		
Colca, 2013 [4]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Khan, 2006 [5]	**Probably yes** Randomized, multicentered, double-blinded trials	**Probably yes** Randomized, multicentered, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Kong, 2011 [6]	**Definitely yes**	**Probably yes**	**Definitely**	**Definitely**	**Probably no**	**Definitely**	**Probably yes**

		Eligible patients were randomized in a double blinded fashion	Randomized, double-blinded trials	**yes**	**yes**	Data of 3/37 (8.1%) participants from experimental group and 7/32 (21.9%) from control group missed	**yes**	Baseline characteristics were generally balanced
Miyazaki, [7]	**2001**	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Miyazaki, [8]	**2002**	**Probably yes** Randomized,	**Probably yes** Randomized,	**Definitely yes**	**Definitely yes**	**Probably no** No information	**Definitely yes**	**Probably yes** Baseline

	double-blinded trials	double-blinded trials			of missed data was reported		characteristics were generally balanced
Rosenblatt, 2001 [9]	**Definitely yes** Patients were given a unique double-blind number in accordance with a randomization schedule	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 54/197 (27.4%) participants in overall study missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Scherbaum, 2002 [10]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally

							balanced
Sourij, 2006 [11]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Truitt, 2010 [12]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Definitely no** Data of 51/91 (56.0%) participants from experimental group and 66/92 (71.7%) from control group missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced

Wallace, 2004 [13]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Berhanu, 2007 [14]	**Definitely yes** Patients were randomized according to a computergenerated schedule	**Definitely yes** The tablets were indistinguishable from one another in all observable characteristics	**Definitely yes**	**Definitely yes**	**Probably no** Data of 14/110 (12.7%) participants from experimental group and 10/112 (8.9%) from control group missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Brackenridge,	**Definitely yes**	**Definitely yes**	**Definitely**	**Definitely**	**Probably no**	**Definitely**	**Probably yes**

2009 [15]	Patients were randomized according to a computergenerated schedule	The tablets were indistinguishable from one another in all observable characteristics	**yes**	**yes**	Data of 13/98 (13.3%) participants from experimental group and 8/95 (8.4%) from control group missed	**yes**	Baseline characteristics were generally balanced
Charpentier, 2009 [16]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 11/145 (7.6%) participants from experimental group and 21/154 (13.6%)	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced

					from control group missed		
Galle, 2012 [17]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 4/19 (21.1%) participants from experimental group and 6/17 (35.3%) from control group missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Gastaldelli, 2007 [18]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally

							balanced
Grey, 2012 [19]	**Definitely yes** Randomization with a variable block size schedule based on computer generated random numbers	**Definitely yes** Only the statistician had access to treatment allocation and he had no contact with participants.	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Henriksen, 2011 [20]	**Definitely yes** Randomization by a contract service provider	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 17/102 (16.7%) participants from experimental group and	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced

					32/109 (29.4%) from control group missed		
Kaku, 2009 [21]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 9/83 (10.8%) participants from experimental group and 7/86 (8.1%) from control group missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Kawamori, 1998 [22]	**Definitely yes** Randomized allocation was performed for	**Definitely yes** Randomized allocation was performed for	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were

	blocks of three patients	blocks of three patients					generally balanced
Kipnes, 2001 [23]	**Probably yes** Randomized, double-blinded trials	**Definitely yes** Randomized allocation was performed for blocks of three patients	**Definitely yes**	**Definitely yes**	**Probably no** Data of 82/560 (14.6%) participants in overall study missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Mattoo, 2005 [24]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 14/142 (9.9%) participants from experimental group and 12/147 (8.2%) from control	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced

					group missed		
Nakamura, 2001 [25]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Pan, 2002 [26]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Smith, 2005 [27]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 6/48 (12.5%) participants in	**Definitely yes**	**Probably yes** Baseline characteristics were

					overall study missed		generally balanced
Sridhar, 2013 [28]	**Probably yes** Randomized, double-blinded trials	**Definitely yes** Both patients and physicians were blinded to the treatment	**Definitely yes**	**Definitely yes**	**Probably no** Data of 4/44 (9.1%) participants in overall study missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Grey, 2014 [29]	**Definitely yes** Randomization using a variable block size schedule based on computer-generated random numbers	**Definitely yes** All the other study personnel and sssubjects were blinded to treatment allocation throughout	**Definitely yes**	**Definitely yes**	**Probably no** Data of 3/43 (7.0%) participants from experimental group and 2/43 (4.7%) from control group	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced

					missed		
Bray, 2013 [30]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Bone, 2013 [31]	**Definitely yes** Computer-generated randomization schedule with no stratification	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 21/78 (26.9%) participants from experimental group and 18/78 (23.1%) from control group missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced

Dormandy, 2005 [32]	**Definitely yes** Randomization via a central interactive voice response system	**Definitely yes** Allocation was done by the method of randomized permuted blocks within centre	**Definitely yes**	**Definitely yes**	**Probably no** Data of 178/2605 (6.8%) participants from experimental group and 187/2633 (7.1%) from control group missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Satoh, 2003 [33]	**Definitely yes** Randomization via a central interactive voice response system	**Definitely yes** Allocation was done by the method of randomized permuted blocks within centre	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced

McMahon, 2005 [34]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 2/10 (20.0%) participants from experimental group and 2/10 (20.0%) from control group missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Herz, 2003 [35]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 7/99 (7.1%) participants from experimental group and	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced

						11/99 (11.1%) from control group missed		
Einhorn, [36]	**2000**	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 21/168 (12.5%) participants from experimental group and 37/160 (23.1%) from control group missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Erdmann, [37]	**2007**	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were

							generally balanced
Rosiglitazone (thiazolidinedione)							
Carey, 2002 [38]	**Definitely yes** Patients were then randomized in equal numbers	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Gastaldelli, 2006 [39]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Gastaldelli, 2007 [18]	**Probably yes** Randomized,	**Probably yes** Randomized,	**Definitely yes**	**Definitely yes**	**Probably no** No information	**Definitely yes**	**Probably yes** Baseline

	double-blinded trials	double-blinded trials			of missed data was reported		characteristics were generally balanced
Haffner, 2002 [40]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Juhl, 2003 [41]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Lautamaki, 2005	**Probably yes**	**Probably yes**	**Definitely**	**Definitely**	**Probably no**	**Definitely**	**Probably yes**

[42]	Randomized, double-blinded trials	Randomized, double-blinded trials	**yes**	**yes**	Data of 4/62 (6.5%) participants in overall study missed	**yes**	Baseline characteristics were generally balanced
Miyazaki, 2001 [43]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Oz Gul, 2008 [44]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced

Oz Gul, 2010 [45]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Patel, 1999 [46]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 69/380 (18.2%) participants in overall study missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Phillips, 2001 [47]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 39/187 (20.7%) participants from	**Definitely yes**	**Probably yes** Baseline characteristics were generally

					experimental group and 66/173 (38.4%) from control group missed		balanced
Raskin, 2000 [48]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 10/73 (13%) participants from experimental group and 17/69 (24%) from control group missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Tan, 2005 [49]	**Probably yes** Randomized,	**Probably yes** Randomized,	**Definitely yes**	**Definitely yes**	**Probably no** No information	**Definitely yes**	**Probably yes** Baseline

	double-blinded trials	double-blinded trials			of missed data was reported		characteristics were generally balanced
Barnett, 2003 [50]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 4/84 (4.8%) participants from experimental group and 9/87 (10.3%) from control group missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Bertrand, 2010 [51]	**Definitely yes** Treatment assignment	**Definitely yes** Allocation of blinded study	**Definitely yes**	**Definitely yes**	**Probably no** Data of 13/98 (13.3%)	**Definitely yes**	**Probably yes** Baseline characteristics

	remained blinded throughout the study	medication were provided to each patient			participants from experimental group and 8/95 (8.4%) from control group missed		were generally balanced
Dailey, 2004 [52]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 101/365 (27.7%) participants in overall study missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Davidson, 2007 [53]	**Definitely yes** Randomized centrally and used an interactive voice	**Definitely yes** Randomized centrally and used an	**Definitely yes**	**Definitely yes**	**Probably no** Data of 23/117 (19.7%) participants	**Definitely yes**	**Probably yes** Baseline characteristics were

	response system	interactive voice response system			from experimental group and 22/116 (19.0%) from control group missed		generally balanced
Derosa, 2008 [54]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Fonseca, 2000 [55]	**Definitely yes** Randomization was computer generated	**Definitely yes** No participants knew the allocation until completion	**Definitely yes**	**Definitely yes**	**Probably no** Data of 18/110 (16.4%) participants from	**Definitely yes**	**Probably yes** Baseline characteristics were generally

					experimental group and 22/113 (19.5%) from control group missed		balanced
Hollander, 2007 [56]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 62/209 (29.7%) participants from experimental group and 63/212 (29.7%) from control group missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Marre, 2009 [57]	**Probably yes** Randomized,	**Probably yes** Randomized,	**Definitely yes**	**Definitely yes**	**Probably no** Data of 37/231	**Definitely yes**	**Probably yes** Baseline

	double-blinded trials	double-blinded trials			(16.0%) participants from experimental group and 31/114 (27.1%) from control group missed		characteristics were generally balanced
Negro, 2005 [58]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Definitely yes** No data of participants were missed in this trial	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Raskin, 2001 [59]	**Definitely yes** Randomization codes were	**Definitely yes** No personnel in this study knew	**Definitely yes**	**Definitely yes**	**Probably no** Data of 24/103 (23.0%)	**Definitely yes**	**Probably yes** Baseline characteristics

	generated with an internal software system	details about the allocation			participants from experimental group and 22/104 (21.0%) from control group missed		were generally balanced
Reynolds, 2002 [60]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Rosenstock, 2008 [61]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 2/59 (3.4%) participants	**Definitely yes**	**Probably yes** Baseline characteristics were

					from experimental group and 5/57 (8.8%) from control group missed		generally balanced
Wolffenbuttel, 2000 [62]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 44/183 (24%) participants from experimental group and 69/192 (36%) from control group missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Yang, 2002 [63]	**Probably yes**	**Probably yes**	**Definitely**	**Definitely**	**Probably no**	**Definitely**	**Probably yes**

	Randomized, double-blinded trials	Randomized, double-blinded trials	**yes**	**yes**	No information of missed data was reported	**yes**	Baseline characteristics were generally balanced
Zhu, 2003 [64]	**Definitely yes** Randomization was achieved using computer-generated codes	**Definitely yes** Allocation code was obtained from an opaque envelope	**Definitely yes**	**Definitely yes**	**Probably no** Data of 24/210 (11.3%) participants from experimental group and 37/105 (34.8%) from control group missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Gruntmanis, 2010 [65]	**Probably yes** Randomized,	**Probably yes** Randomized,	**Definitely yes**	**Definitely yes**	**Probably no** Data of 18/74	**Definitely yes**	**Probably yes** Baseline

	double-blinded trials	double-blinded trials			(24.3%) participants from experimental group and 21/76 (27.6%) from control group missed		characteristics were generally balanced
Gold, 2010 [66]	**Definitely yes** Randomization was conducted by software	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 29/156 (18.6%) participants from experimental group and 28/159 (17.6%) from control	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced

					group missed		
Hallsten, 2002 [67]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Kim, 2005 [68]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 6/63 (9.5%) participants from experimental group and 2/62 (3.2%) from control group missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced

Lebovitz, 2001 [69]		**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 45/169 (26.6%) participants from experimental group and 77/158 (48.7%) from control group missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Natali, 2004 [70]		**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 4/24 (17%) participants from experimental group and 6/22	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced

					(29%) from control group missed		
Osman, 2004 [71]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Definitely yes** No data of participants were missed in this trial	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Jones, 2003 [72]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Vongthavaravat, 2008 [73]	**Definitely yes** Randomization	**Definitely yes** Treatment	**Definitely yes**	**Definitely yes**	**Probably no** Data of 36/164	**Definitely yes**	**Probably yes** Baseline

		list was computer generated	allocation codes were concealed in opaque envelopes			(22.0%) participants from experimental group and 60/170 (35.3%) from control group missed		characteristics were generally balanced
Agrawal, [74]	**2003**	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Albertini, [75]	**2007**	**Probably yes** Randomized, double-blinded	**Probably yes** Randomized, double-blinded	**Definitely yes**	**Definitely yes**	**Probably no** Data of 2/64 (22.0%)	**Definitely yes**	**Probably yes** Baseline characteristics

	trials	trials			participants from experimental group and 9/71 (35.3%) from control group missed		were generally balanced
Bhatt, 2007 [76]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Dargie, 2007 [77]	**Definitely yes** Randomization list was computer generated	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 30/108 (27.8%) participants	**Definitely yes**	**Probably yes** Baseline characteristics were

						from experimental group and 32/110 (29.1%) from control group missed		generally balanced
DREAM, [78]	**2006**	**Definitely yes** Randomization by a concealed and computerized telephone system	**Definitely yes** Randomization by a concealed and computerized telephone system	**Definitely yes**	**Definitely yes**	**Probably no** Data of 772/2635 (29.3%) participants from experimental group and 658/2634 (25.0%) from control group	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced

					missed		
Hedblad, 2007 [79]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 108/442 (24.4%) participants in overall study missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Troglitazone (thiazolidinedione)							
Ebeling, 1999 [80]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Fonseca, 1998-1 [81]	**Probably yes** Randomized, double-blinded	**Probably yes** Randomized, double-blinded	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data	**Definitely yes**	**Probably yes** Baseline characteristics

	trials	trials			was reported		were generally balanced
Fonseca, 1998-2 [82]	**Definitely yes** Randomization through a double-blinded schedule	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 13% participants from experimental group and 26% from control group missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Iwamoto, 1996-1 [83]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 9/136 (6.6%) participants from experimental	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced

					group and 13/126 (10.3%) from control group missed		
Iwamoto, 1996-2 [84]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 23/145 (15.9%) participants from experimental group and 20/146 (13.7%) from control group missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Iwamoto, 1996-2 [84]	**Probably yes** Randomized, double-blinded	**Probably yes** Randomized, double-blinded	**Definitely yes**	**Definitely yes**	**Probably no** Data of 23/145 (15.9%)	**Definitely yes**	**Probably yes** Baseline characteristics

	trials	trials			participants from experimental group and 20/146 (13.7%) from control group missed		were generally balanced
Kumar, 1996 [85]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 17% participants from experimental group and 33% from control group missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Rosenstock, 2002 [86]	**Definitely yes** Randomization	**Probably yes** Randomized,	**Definitely yes**	**Definitely yes**	**Probably no** Data of 45/151	**Definitely yes**	**Probably yes** Baseline

	through the use of double-dummy blinding of the study medications	double-blinded trials			(29.8%) participants from experimental group and 55/148 (37.2%) from control group missed		characteristics were generally balanced
Buras, 2005 [87]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Definitely yes** No data of participants were missed in this trial	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Buse, 1998 [88]	**Probably yes** Randomized, double-blinded	**Probably yes** Randomized, double-blinded	**Definitely yes**	**Definitely yes**	**Probably no** Data of 28/222 (12.6%)	**Definitely yes**	**Probably yes** Baseline characteristics

	trials	trials			participants in overall study missed		were generally balanced
Buysschaert, 1999 [89]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 13/259 (5.0%) participants in overall study missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Kelly, 1999 [90]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** No information of missed data was reported	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Mimura, 1994 [91]	**Probably yes** Randomized,	**Probably yes** Randomized,	**Definitely yes**	**Definitely yes**	**Probably no** No information	**Definitely yes**	**Probably yes** Baseline

	double-blinded trials	double-blinded trials			of missed data was reported		characteristics were generally balanced
Osende, 2001 [92]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Definitely yes** No data of participants were missed in this trial	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Schwartz, 1998 [93]	**Probably yes** Randomized, double-blinded trials	**Probably yes** Randomized, double-blinded trials	**Definitely yes**	**Definitely yes**	**Probably no** Data of 46/350 (13.1%) participants in overall study missed	**Definitely yes**	**Probably yes** Baseline characteristics were generally balanced
Yale, 2001 [94]	**Definitely yes**	**Definitely yes**	**Definitely**	**Definitely**	**Probably no**	**Definitely**	**Probably yes**

	Computer-generated randomization schedule for the entire study	Participants involved in work were blinded to treatment	**yes**	**yes**	Data of 9/101 (8.9%) participants from experimental group and 13/99 (13.1%) from control group missed	**yes**	Baseline characteristics were generally balanced

DREAM: Diabetes REduction Assessment with ramipril and rosiglitazone Medication.

Supplementary Table 3 Subgroup analyses for indirect comparison of efficacy and safety between chiglitazar in augmented doses and TZD

Efficacy endpoints & Subgroups	Weighted mean difference (WMD)	95% Confidential intervals (CIs)
HbA1c (%)		
Age ≥ 60 years old	**-0.295**	**-0.407, -0.184**
Age < 60 years old	-0.090	-0.239, 0.060
Baseline HbA1c ≥ 8.5%	**-0.439**	**-0.577, -0.300**
Baseline HbA1c < 8.5%	0.143	-0.015, 0.301
BMI ≥ 30kg/m^2	**-0.244**	**-0.404, -0.084**
BMI < 30kg/m^2	-0.003	-0.173, 0.166
Diabetes duration ≥ 10 years	-0.076	-0.444, 0.293
Diabetes duration < 10 years	**-0.162**	**-0.306, -0.018**
Male percentage ≥ 50%	**-0.141**	**-0.274, -0.008**
Male percentage < 50%	-0.087	-0.331, 0.157
Asian predominant	0.024	-0.205, 0.253
Caucasian predominant	-0.127	-0.299, 0.045

Follow-up duration ≥ 24 weeks	**-0.232**	**-0.372, -0.092**
Follow-up duration < 24 weeks	-0.370	-0.212, 0.138
Monotherapy	**-0.197**	**-0.342, -0.051**
Combined therapy	-0.100	-0.289, 0.088
TZD subtypes		
Pioglitazone 30mg	-0.199	-0.429, 0.032
Pioglitazone 45mg	-0.110	-0.537, 0.318
Rosiglitazone 4mg	**-0.389**	**-0.667, -0.111**
Rosiglitazone 8mg	**0.164**	**0.009, 0.319**
Troglitazone 400mg	-0.297	-0.862, 0.268
Troglitazone 600mg	-0.038	-0.314, 0.238
FBG (mmol/L)		
Age ≥ 60 years old	0.141	-0.405, 0.687
Age < 60 years old	0.558	-0.024, 1.139
Baseline HbA1c ≥ 8.5%	-0.067	-0.656, 0.521
Baseline HbA1c < 8.5%	**1.048**	**0.439, 1.658**
BMI ≥ 30kg/m^2	0.505	-0.111, 1.121

BMI < 30kg/m^2	0.542	-0.025, 1.109
Diabetes duration ≥ 10 years	**0.666**	**0.030, 1.301**
Diabetes duration < 10 years	0.439	-0.060, 0.937
Male percentage ≥ 50%	0.664	-0.052, 1.380
Male percentage < 50%	0.490	-0.178, 1.158
Asian predominant	0.460	-0.240, 1.161
Caucasian predominant	**0.745**	**-0.166, 1.323**
Follow-up duration ≥ 24 weeks	0.533	-0.059, 1.125
Follow-up duration < 24 weeks	0.449	-0.130, 1.029
Monotherapy	0.536	-0.048, 1.120
Combined therapy	0.433	-0.205, 1.071
TG (mmol/L)		
Age ≥ 60 years old	**-0.160**	**-0.286, -0.035**
Age < 60 years old	**-0.151**	**-0.233, -0.069**
Baseline HbA1c ≥ 8.5%	**-0.269**	**-0.356, -0.182**
Baseline HbA1c < 8.5%	-0.036	-0.138, 0.065
BMI ≥ 30kg/m^2	**-0.109**	**-0.213, -0.006**

BMI < 30kg/m^2	**-0.222**	**-0.307, -0.136**
Diabetes duration ≥ 10 years	-0.004	-0.385, 0.376
Diabetes duration < 10 years	**-0.243**	**-0.341, -0.145**
Male percentage ≥ 50%	**-0.146**	**-0.231, -0.061**
Male percentage < 50%	-0.043	-0.364, 0.277
Asian predominant	**-0.299**	**-0.326, -0.273**
Caucasian predominant	**-0.172**	**-0.246, -0.098**
Follow-up duration ≥ 24 weeks	**-0.167**	**-0.260, -0.074**
Follow-up duration < 24 weeks	**-0.176**	**-0.277, -0.075**
Monotherapy	**-0.174**	**-0.250, -0.098**
Combined therapy	**-0.172**	**-0.283, -0.062**
TZD subtypes		
Pioglitazone 30mg	-0.055	-0.182, 0.073
Pioglitazone 45mg	0.106	-0.110, 0.321
Rosiglitazone 4mg	**-0.580**	**-0.861, -0.299**
Rosiglitazone 8mg	**-0.221**	**-0.363, -0.079**
Troglitazone 400mg	0.082	-0.355, 0.519

Troglitazone 600mg	**-0.518**	**-1.031, -0.004**
HDL-C (mmol/L)		
Age ≥ 60 years old	-0.020	-0.054, 0.015
Age < 60 years old	-0.005	-0.030, 0.019
Baseline HbA1c ≥ 8.5%	-0.001	-0.280, 0.025
Baseline HbA1c < 8.5%	-0.007	-0.035, 0.022
BMI ≥ 30kg/m^2	-0.023	-0.052, 0.006
BMI < 30kg/m^2	0.014	-0.002, 0.029
Diabetes duration ≥ 10 years	**-0.054**	**-0.105, -0.004**
Diabetes duration < 10 years	0.004	-0.011, 0.019
Male percentage ≥ 50%	-0.011	-0.034, 0.012
Male percentage < 50%	-0.017	-0.056, 0.021
Asian predominant	0.006	-0.034, 0.046
Caucasian predominant	-0.010	-0.035, 0.015
Follow-up duration ≥ 24 weeks	-0.002	-0.026, 0.022
Follow-up duration < 24 weeks	-0.006	-0.047, 0.034
Monotherapy	0.013	-0.007, 0.033

Combined therapy	-0.027	-0.059, 0.004
LDL-C (mmol/L)		
Age ≥ 60 years old	0.156	-0.011, 0.324
Age < 60 years old	**0.095**	**0.045, 0.146**
Baseline HbA1c ≥ 8.5%	**0.156**	**0.084, 0.229**
Baseline HbA1c < 8.5%	**0.090**	**0.021, 0.159**
BMI ≥ 30kg/m^2	**0.129**	**0.066, 0.192**
BMI < 30kg/m^2	**0.121**	**0.015, 0.227**
Diabetes duration ≥ 10 years	0.032	-0.102, 0.165
Diabetes duration < 10 years	**0.114**	**0.049, 0.178**
Male percentage ≥ 50%	**0.108**	**0.049, 0.166**
Male percentage < 50%	**0.131**	**0.027, 0.235**
Asian predominant	0.195	-0.059, 0.449
Caucasian predominant	**0.142**	**0.092, 0.193**
Follow-up duration ≥ 24 weeks	**0.102**	**0.038, 0.165**
Follow-up duration < 24 weeks	**0.149**	**0.063, 0.235**
Monotherapy	**0.109**	**0.050, 0.167**

Combined therapy	**0.156**	**0.092, 0.219**
HOMA-IR		
Age ≥ 60 years old	0.608	-0.177, 1.392
Age < 60 years old	**1.014**	**0.329, 1.699**
Baseline HbA1c ≥ 8.5%	**0.697**	**0.226, 1.167**
Baseline HbA1c < 8.5%	1.810	-1.229, 4.848
BMI ≥ 30kg/m^2	**1.450**	**0.852, 2.048**
BMI < 30kg/m^2	0.479	-0.160, 0.973
Diabetes duration ≥ 10 years	0.240	-0.477, 0.957
Diabetes duration < 10 years	**0.818**	**0.446, 1.190**
Male percentage ≥ 50%	**1.071**	**0.609, 1.533**
Male percentage < 50%	0.059	-0.036, 0.154
Asian predominant	0.096	-0.073, 0.265
Caucasian predominant	**1.804**	**1.023, 2.585**
Follow-up duration ≥ 24 weeks	**1.080**	**0.722, 1.437**
Follow-up duration < 24 weeks	0.825	-0.622, 2.272
Monotherapy	**1.231**	**0.636, 1.825**

Combined therapy	0.180	-0.835, 1.196
HOMA-β		
Age ≥ 60 years old	NA	NA
Age < 60 years old	**21.709**	**13.581, 29.826**
Baseline HbA1c ≥ 8.5%	**26.360**	**8.795, 43.925**
Baseline HbA1c < 8.5%	**10.577**	**9.323, 11.830**
BMI ≥ 30kg/m^2	**29.421**	**19.341, 39.502**
BMI < 30kg/m^2	**4.157**	**0.977, 7.338**
Diabetes duration ≥ 10 years	**8.340**	**1.192, 15.488**
Diabetes duration < 10 years	**26.360**	**8.795, 43.925**
Male percentage ≥ 50%	**19.175**	**11.873, 26.477**
Male percentage < 50%	-0.036	-21.679, 20.959
Asian predominant	**8.340**	**1.192, 15.488**
Caucasian predominant	**29.421**	**19.341, 39.502**
Follow-up duration ≥ 24 weeks	34.761	-23.207, 92.730
Follow-up duration < 24 weeks	**7.476**	**1.937, 13.015**
Monotherapy	**19.175**	**11.873, 26.477**

Combined therapy	-0.360	-21.679, 20.959
ALT (U/L)		
Age ≥ 60 years old	NA	NA
Age < 60 years old	**-5.249**	**-8.504, -1.994**
Baseline HbA1c ≥ 8.5%	**-5.249**	**-8.504, -1.994**
Baseline HbA1c < 8.5%	NA	NA
BMI ≥ 30kg/m^2	NA	NA
BMI < 30kg/m^2	**-5.249**	**-8.504, -1.994**
Diabetes duration ≥ 10 years	NA	NA
Diabetes duration < 10 years	**-5.600**	**-8.984, -2.216**
Male percentage ≥ 50%	-3.660	-8.965, 1.645
Male percentage < 50%	**-5.600**	**-8.984, -2.216**
Asian predominant	NA	NA
Caucasian predominant	**-5.600**	**-8.984, -2.216**
Follow-up duration ≥ 24 weeks	**-5.600**	**-8.984, -2.216**
Follow-up duration < 24 weeks	-3.660	-8.965, 1.645
Monotherapy	NA	NA

Combined therapy	**-5.249**	**-8.504, -1.994**
AST (U/L)		
Age ≥ 60 years old	NA	NA
Age < 60 years old	-2.976	-9.606, 3.653
Baseline HbA1c ≥ 8.5%	-2.976	-9.606, 3.653
Baseline HbA1c < 8.5%	NA	NA
BMI ≥ 30kg/m^2	NA	NA
BMI < 30kg/m^2	-2.976	-9.606, 3.653
Diabetes duration ≥ 10 years	NA	NA
Diabetes duration < 10 years	0	-2.223, 2.223
Male percentage ≥ 50%	**-6.580**	**-11.140, -2.020**
Male percentage < 50%	0	-2.223, 2.223
Asian predominant	NA	NA
Caucasian predominant	0	-2.223, 2.223
Follow-up duration ≥ 24 weeks	NA	NA
Follow-up duration < 24 weeks	**-6.580**	**-11.140, -2.020**
Monotherapy	NA	NA

Combined therapy	-2.976	-9.606, 3.653
Safety endpoints & Subgroups	**Weighted mean difference (WMD)**	**95% Confidential intervals (CIs)**
Weight gain (kg)		
Age ≥ 60 years old	0.019	-1.039, 1.077
Age < 60 years old	-0.607	-0.607, 1.479
Baseline HbA1c ≥ 8.5%	0.726	-0.074, 1.526
Baseline HbA1c < 8.5%	-0.401	-1.174, 0.372
BMI ≥ 30kg/m^2	-0.241	-0.979, 0.497
BMI < 30kg/m^2	0.990	-0.006, 1.985
Diabetes duration ≥ 10 years	-0.347	-1.437, 0.743
Diabetes duration < 10 years	0.277	-0.685, 1.239
Male percentage ≥ 50%	0.505	-0.248, 1.257
Male percentage < 50%	-0.783	-1.985, 0.420
Asian predominant	0.176	-2.207, 4.559
Caucasian predominant	-0.092	-1.246, 1.061
Follow-up duration ≥ 24 weeks	0.006	-0.979, 0.991

Follow-up duration < 24 weeks	**1.058**	**0.129, 1.987**
Monotherapy	0.417	-0.745, 1.579
Combined therapy	0.180	-0.605, 0.965
Safety endpoints & Subgroups	**Risk Ratio (RR)**	**95% Confidential intervals (CIs)**
Hypoglycemia		
Age ≥ 60 years old	1.346	0.243, 7.455
Age < 60 years old	1.421	0.260, 7.755
Baseline HbA1c ≥ 8.5%	1.326	0.395, 4.451
Baseline HbA1c < 8.5%	1.495	0.272, 8.213
BMI ≥ 30kg/m^2	1.568	0.289, 8.502
BMI < 30kg/m^2	0.822	0.146, 4.618
Diabetes duration ≥ 10 years	1.486	0.272, 8.131
Diabetes duration < 10 years	1.323	0.241, 7.271
Male percentage ≥ 50%	1.369	0.251, 7.450
Male percentage < 50%	1.441	0.258, 8.039
Asian predominant	0.501	0.067, 3.744

Caucasian predominant	1.502	0.276, 8.179
Follow-up duration ≥ 24 weeks	1.415	0.261, 7.683
Follow-up duration < 24 weeks	NA	NA
Monotherapy	1.719	0.303, 9.758
Combined therapy	1.326	0.244, 7.214
Edema		
Age ≥ 60 years old	10.685	0.608, 187.901
Age < 60 years old	8.092	0.463, 141.328
Baseline HbA1c ≥ 8.5%	11.959	0.694, 206.214
Baseline HbA1c < 8.5%	5.567	0.314, 98.751
BMI ≥ 30kg/m^2	10.444	0.602, 181.049
BMI < 30kg/m^2	7.224	0.400, 130.426
Diabetes duration ≥ 10 years	11.751	0.658, 209.812
Diabetes duration < 10 years	7.083	0.403, 124.504
Male percentage ≥ 50%	7.617	0.437, 132.781
Male percentage < 50%	13.371	0.762, 234.762
Asian predominant	3.101	0.150, 64.158

Caucasian predominant	8.832	0.506, 154.191
Follow-up duration ≥ 24 weeks	10.624	0.615, 183.682
Follow-up duration < 24 weeks	2.085	0.062, 70.037
Monotherapy	11.508	0.665, 199.043
Combined therapy	7.988	0.454, 140.549
Bone fracture		
Age ≥ 60 years old	6.829	0.349, 133.681
Age < 60 years old	10.219	0.476, 219.314
Baseline HbA1c ≥ 8.5%	6.923	0.354, 135.293
Baseline HbA1c < 8.5%	NA	NA
BMI ≥ 30kg/m^2	6.923	0.354, 135.293
BMI < 30kg/m^2	16.867	0.643, 442.671
Diabetes duration ≥ 10 years	NA	NA
Diabetes duration < 10 years	12.172	0.621, 238.412
Male percentage ≥ 50%	6.853	0.323, 145.575
Male percentage < 50%	13.004	0.413, 409.037
Asian predominant	NA	NA

Caucasian predominant	7.331	0.375, 143.448
Follow-up duration ≥ 24 weeks	12.082	0.618, 236.357
Follow-up duration < 24 weeks	NA	NA
Monotherapy	7.224	0.370, 141.070
Combined therapy	NA	NA
Upper respiratory tract infection		
Age ≥ 60 years old	NA	NA
Age < 60 years old	0.891	0.518, 1.532
Baseline HbA1c ≥ 8.5%	1.155	0.561, 2.381
Baseline HbA1c < 8.5%	0.768	0.446, 1.323
BMI ≥ 30kg/m^2	0.856	0.506, 1.448
BMI < 30kg/m^2	0.937	0.405, 2.168
Diabetes duration ≥ 10 years	NA	NA
Diabetes duration < 10 years	0.891	0.518, 1.532
Male percentage ≥ 50%	0.899	0.494, 1.636
Male percentage < 50%	0.833	-0.909, 0.545
Asian predominant	0.937	0.405, 2.168

Caucasian predominant	0.900	0.517, 1.565
Follow-up duration ≥ 24 weeks	0.828	0.501, 1.369
Follow-up duration < 24 weeks	2.085	0.879, 4.946
Monotherapy	0.936	0.538, 1.725
Combined therapy	0.769	0.404, 1.464
Urinary tract infection		
Age ≥ 60 years old	NA	NA
Age < 60 years old	1.171	0.522, 2.629
Baseline HbA1c ≥ 8.5%	1.512	0.511, 4.470
Baseline HbA1c < 8.5%	1.504	0.446, 2.494
BMI ≥ 30kg/m^2	1.512	0.511, 4.470
BMI < 30kg/m^2	1.504	0.446, 2.494
Diabetes duration ≥ 10 years	NA	NA
Diabetes duration < 10 years	1.171	0.522, 2.629
Male percentage ≥ 50%	1.512	0.511, 4.470
Male percentage < 50%	1.504	0.446, 2.494
Asian predominant	1.504	0.446, 2.494

Caucasian predominant	1.512	0.511, 4.470
Follow-up duration ≥ 24 weeks	1.171	0.522, 2.629
Follow-up duration < 24 weeks	NA	NA
Monotherapy	0.297	0.584, 1.179
Combined therapy	0.919	0.334, 2.531

The results of significance were emphasized in bold and red text.

Abbreviations: NA, not available; BMI, body mass index; HbA1c, hemoglobin A1c; FBG, fasting blood glucose; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β cell function; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Supplementary Table 4 Meta-regression analyses for potential associated baseline characteristics

Parameter	β	95%CI	P value	Parameter	β	95%CI	P value
HbA1c change (%)							
Age (year old)	0.032	-0.002, 0.068	0.065	Diabetes duration (years)	-0.018	-0.063, 0.027	0.421
Male percentage (%)	**0.011**	**0.002, 0.021**	**0.019**	Study duration (year)	0.007	0.000, 0.013	0.038
BMI (kg/m^2)	0.035	-0.010, 0.080	0.124	**Baseline HbA1c (%)**	**-0.320**	**-0.427, -0.212**	**0.0001**
Weight change (kg)							
Age (year old)	-0.049	-0.183, 0.085	0.465	Diabetes duration (years)	0.084	-0.081, 0.250	0.303
Male percentage (%)	0.004	-0.026, 0.035	0.772	Study duration (year)	0.013	-0.005, 0.032	0.157
BMI (kg/m^2)	0.081	-0.116, 0.279	0.410	Baseline HbA1c (%)	0.239	-0.244, 0.722	0.323
FBG (mmol/L)							
Age (year old)	0.051	-0.023, 0.125	0.172	Diabetes duration (years)	-0.027	-0.121, 0.067	0.565
Male percentage (%)	0.009	-0.012, 0.029	0.395	Study duration (year)	0.012	-0.003, 0.026	0.106
BMI (kg/m^2)	-0.026	-0.119, 0.067	0.576	**Baseline HbA1c (%)**	**-0.578**	**-0.768, -0.388**	**0.0001**

TG (mmol/L)							
Age (year old)	0.021	-0.009, 0.050	0.163	Diabetes duration (years)	-0.185	-0.061, 0.024	0.376
Male percentage (%)	0.006	-0.003, 0.015	0.201	Study duration (year)	-0.000	-0.004, 0.004	0.845
BMI (kg/m^2)	**-0.249**	**-0.442, -0.055**	**0.013**	Baseline HbA1c (%)	-0.060	-0.150, 0.031	0.189
HDL-c (mmol/L)							
Age (year old)	0.005	-0.003, 0.014	0.239	Diabetes duration (years)	0.008	-0.003, 0.018	0.157
Male percentage (%)	-0.000	-0.003, 0.002	0.828	Study duration (year)	-0.002	-0.005, 0.001	0.127
BMI (kg/m^2)	0.003	-0.007, 0.014	0.522	Baseline HbA1c (%)	0.009	-0.018, 0.037	0.498
LDL-c (mmol/L)							
Age (year old)	0.015	-0.005, 0.036	0.142	Diabetes duration (years)	0.010	-0.013, 0.032	0.389
Male percentage (%)	**-0.006**	**-0.012, -0.0001**	**0.046**	Study duration (year)	0.000	-0.002, 0.001	0.460
BMI (kg/m^2)	0.005	-0.021, 0.031	0.708	Baseline HbA1c (%)	0.059	-0.005, 0.123	0.071
HOMA-IR							
Age (year old)	-0.009	-0.175, 0.156	0.902	Diabetes duration	-0.092	-0.366, 0.182	0.462

				(years)			
Male percentage (%)	0.041	-0.000, 0.083	0.052	Study duration (year)	-0.020	-0.069, 0.029	0.390
BMI (kg/m^2)	-0.189	-0.389, 0.010	0.061	**Baseline HbA1c (%)**	**-0.573**	**-1.112, -0.034**	**0.039**
HOMA-β							
Age (year old)	1.408	-16.541, 19.358	0.838	Diabetes duration (years)	-0.602	-21.302, 20.098	0.932
Male percentage (%)	0.038	-4.859, 4.935	0.984	Study duration (year)	-2.129	-8.544, 4.285	0.409
BMI (kg/m^2)	-6.049	-19.920, 7.823	0.293	Baseline HbA1c (%)	3.085	-31.440, 37.609	0.816
Upper respiratory tract infection							
Age (year old)	1.159	0.910, 1.476	0.187	Diabetes duration (years)	1.000	0.759, 1.318	1.000
Male percentage (%)	1.010	0.957, 1.067	0.656	Study duration (year)	1.072	0.999, 1.150	0.051
BMI (kg/m^2)	1.051	0.925, 1.195	0.378	Baseline HbA1c (%)	1.256	0.863, 1.828	0.194
Urinary tract infection							
Age (year old)	1.107	0.828, 1.480	0.426	Diabetes duration (years)	1.112	0.766, 1.615	0.512
Male percentage (%)	1.041	0.855, 1.266	0.638	Study duration (year)	0.821	0.460, 1.465	0.447

BMI (kg/m^2)	0.965	0.729, 1.279	0.770	Baseline HbA1c (%)	1.054	0.543, 2.044	0.857
Edema							
Age (year old)	1.049	0.587, 1.878	0.846	Diabetes duration (years)	0.979	0.653, 1.468	0.904
Male percentage (%)	1.014	0.909, 1.133	0.763	Study duration (year)	1.077	0.888, 1.305	0.395
BMI (kg/m^2)	1.020	0.740, 1.407	0.884	Baseline HbA1c (%)	1.173	0.448, 3.068	0.707
Heart failure							
Age (year old)	0.937	0.826, 1.062	0.275	Diabetes duration (years)	0.967	0.774, 1.210	0.719
Male percentage (%)	0.981	0.953, 1.011	0.185	Study duration (year)	0.999	0.989, 1.009	0.832
BMI (kg/m^2)	1.061	0.768, 1.465	0.691	Baseline HbA1c (%)	0.798	0.341, 1.866	0.557
Bone fractures							
Age (year old)	1.005	0.910, 1.110	0.904	Diabetes duration (years)	1.004	0.990, 1.017	0.540
Male percentage (%)	1.020	0.980, 1.061	0.249	Study duration (year)	1.027	0.845, 1.232	0.500
BMI (kg/m^2)	1.066	0.838, 1.357	0.524	Baseline HbA1c (%)	1.034	0.583, 1.833	0.866

HbA1c: Hemoglobin A1c; FBG: Fasting blood glucose; TG: Triglycerides; LDL-C: Low-density lipoprotein cholesterol; HDL-C:

High-density lipoprotein cholesterol; HOMA-IR: Homeostasis model assessment of insulin resistance; HOMA-β: Homeostasis model assessment of β cell function; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; RR: Risk ratios; 95%CI: 95% confidential intervals.

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