

**Supplementary Table 1.** Trials in type 1 diabetes mellitus comparing anti-diabetes agent versus placebo in adjunct to insulin treatment included in this meta-analysis

Study	Study duration	Treatment group	No. of patients	Age, yr	Men, %	BMI, kg/m <sup>2</sup>	DM duration, yr	Baseline HbA1c, %	Baseline weight, kg
<b>Metformin vs. placebo in adjunct to insulin treatment</b>									
Parallel design									
Anderson et al. (2017) [1]	12 mo	MET 1,000 mg bid+ins	45	14±2.5	47	-	5.2±3.6	8.4±0.95	-
		Placebo+ins	45	13.3±2.6	44	-	5.8±4.1	8.8±0.85	-
Codner et al. (2013) [2]	9 mo	MET 850 mg bid+ins	13	17.7±1.6	0	23.7±3	9.3±5.1	10.3±2.3	-
		Placebo+ins	11	16.7±1.7	0	26.2±5.5	5.5±3.1	9.6±1.5	-
Hamilton et al. (2003) [3]	12 wk	MET 500–1,000 mg bid+ins	14	15.9±1.9	43	22.8±4.2	9.9±4.4	9.3±1.4	63.3±13.6
		Placebo+ins	13	16±1.7	54	25.7±2.9	7±3.8	8.6±0.8	71.6±11.7
Jacobsen et al. (2009) [4]	24 wk	MET 2,000 mg qd+ins	12	43.5±13.1	-	29.5±2.7	17.8±10.3	8.85±0.1	87.6±13.2
		Placebo+ins	12	37.3±9.6	-	29.2±2.8	20.3±10.2	9.34±0.94	92±10.2
Lund et al. (2008) [5]; Lund et al. (2009) [6]	52 wk	MET 2,000 mg qd+ins	49	46.1±11.6	67	26.2±3.4	30±23	9.48±0.99	80.5±12.5
		Placebo+ins	51	44.9±10.8	61	25.8±4.3	26±25	9.6±0.86	79±15.3
Libman et al. (2015) [7]	26 wk	MET 2,000 mg qd+ins	71	15.4±1.7	38	-	7.5±3.6	8.8±0.8	77±3
		Placebo+ins	69	15.1±1.8	30	-	6.4±3	8.8±0.7	76±2.5
Meyer et al. (2002) [8]	24 wk	MET 850 mg bid+ins	31	39.9±12.9	55	26.4±4.6	16.9±8.9	7.58±0.84	78.4±18.1
		Placebo+ins	31	41.1±9.8	65	25.8±3.6	21.6±10.2	7.57±0.76	74.5±11.7
Nadeau et al. (2015) [9]	24 wk	MET 500–2,000 mg qd+ins	40	15.9±1.7	-	23.5±3	6.7±3.6	9.5±1.3	65.7±12.3
		Placebo+ins	40	16±1.6	-	24.3±4.1	6.3±3.5	9.4±1.1	67.1±13.2
Nwosu et al. (2015) [10]	36 wk	MET 1,000 mg qd+ins	15	15±2.5	53.3	28.2±6.6	5.7±4.4	9.3±1.5	75.5±25
		Placebo+ins	13	14.5±3.1	38.5	27.5±3.7	5.7±5	8.7±0.4	70.8±17.9
Petrie et al. (2017) [11]; Petrie et al. (2017) [12]	36 mo	MET 2,000 mg qd+ins	219	55.2±8.5	59	28.4±4.5	33.4±11	8.1±0.9	83.9±15.4
		Placebo+ins	209	55.8±8.8	59	28.5±4.1	34.3±10.5	8±0.8	83.5±13.7
Pitocco et al. (2013) [13]	24 wk	MET 850–2,550 mg qd+ins	21	46±8	42.8	28.7±2.1	9.2±0.7	7.24±0.9	83±12
		Placebo+ins	21	41±10	42.8	27.3±2	8.8±0.8	7.73±0.42	77±11
Sarnblad et al. (2003) [14]	12 wk	MET 500–1,000 mg bid+ins	16	17.2±1.7	31	26.2±8.4	9.1±5	9.3±1.1	68.8±17
		Placebo+ins	14	16.9±1.4	29	23.9±6.1	7.1±3	9.3±1.4	66.6±18.3
Ziaee et al. (2017) [15]	24 wk	MET 500–2,000 mg qd+ins	-	-	50	23.21±1.4	-	8.36±0.8	-
		Placebo+ins	-	-	50	-	-	-	-
Cross-over design									
Khan et al. (2006) [16]	16 wk	MET 850 mg tid+ins	15	48	-	31.3	19	8.5±1.4	91±12
		Placebo+ins	15	48	-	31.1	19	8.7±1.1	91±12
<b>AGI vs. placebo in adjunct to insulin treatment</b>									
Parallel design									
Hollander et al. (1997) [17]	36 wk	Acarbose 50–300 mg tid+ins	114	37.7±1.1	66	24.6±0.3	15.8±1	6.58±0.09	73.2±1.2
		Placebo+ins	122	36.8±1.1	65	24.9±0.3	13.4±1	6.59±0.09	73±1.2
Riccardi et al. (1999) [18]	24 wk	Acarbose 50–100 mg tid+ins	57	32.6±11.78	47	24.62±3.53	-	9.1±1.37	66.1±11.58
		Placebo+ins	59	36.3±15.35	42	24.74±3.05	-	9.1±1.34	68.1±10.54
Double blind, cross-over design									
Dimitriadis et al. (1988) [19]	4 wk	Bay-m-1248 40 mg qd+ins	17	25±2	100	23±2	10±2	-	-
		Bay-m-1099 100 mg bid+ins	17	25±2	100	23±2	10±2	-	-
		Placebo+ins	17	25±2	100	23±2	10±2	-	-

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Supplementary Table 1. Continued

Study	Study duration	Treatment group	No. of patients	Age, yr	Men, %	BMI, kg/m <sup>2</sup>	DM duration, yr	Baseline HbA1c, %	Baseline weight, kg
Marena et al. (1991) [20]	6 wk	Acarbose 100 mg tid+ins	14	35.1±13.2	71.4	22.5±2.4	7.9±5.9	9.6±0.2	-
		Placebo+ins	14	35.1±13.2	71.4	22.5±2.4	7.9±5.9	9.6±0.2	-
Mcculloch et al. (1983) [21]	12 wk	Acarbose 100 mg tid+ins	14	40.4	78.5	-	16.42	-	-
		Placebo+ins	14	40.4	78.5	-	16.42	-	-
Serrano-Rios et al. (1988) [22]	3–6 wk	Bay-m-1099 50 mg bid+ins	9	26	77.7	-	-	6.6	-
		Bay-m-1248 10 mg qd+ins	9	26	77.7	-	-	6.6	-
		Placebo+ins	9	26	77.7	-	-	6.6	-
Single-blind, cross-over design									
Kennedy et al. (1987) [23];	4 wk	Bay-m-1099 50 mg tid	9	33	88.8	25	-	9.7±0.7	-
Kennedy et al. (1988) [24]		Placebo+ins	9	33	88.8	25	-	9.7±0.7	-
TZD vs. placebo in adjunct to insulin treatment									
Parallel design									
Bhat et al. (2007) [25]	6 mo	Pioglitazone 30 mg qd+ins	30	22.4±5.8	-	19.7±1.4	7.6±4.4	7.08±0.48	48.7±5.6
		Placebo+ins	30	21.5±5.4	-	19.6±1.7	7.5±4.6	7.3±0.37	50±6.9
Strowig et al. (2005) [26]	8 mo	Rosiglitazone 4 mg bid+ins	25	43.7±13.3	64	32.7±5.4	20.7±13.3	7.9±1.3	92.7±11.8
		Placebo+ins	25	41.1±9.2	72	31.1±3.1	18.1±9.3	7.7±0.8	96.4±12.2
Tafari et al. (2013) [27]	24 wk	Pioglitazone 15–30 mg qd+ins	8	10.2	38	19.6	2.9	6.7	39.5
		Placebo+ins	7	11.7	57	18.8	3.4	7.9	45
Zdravkovi et al. (2006) [28]	6 mo	Pioglitazone 30 mg qd+ins	18	14±1.9	50	23.4±5.9	5.7±3.1	8.8±0.8	-
		Placebo+ins	17	14.7±2	47	26.1±5.1	7±3.9	8.9±1	-
Cross-over design									
Stone et al. (2008) [29]	28 wk	Rosiglitazone 4 mg bid+ins	18	13.6±1.6	56	22.3±3.9	-	8.6±1	-
		Placebo+ins	18	13.6±2	39	23.8±4	-	8.7±1	-
GLP-1RA vs. placebo in adjunct to insulin treatment									
Parallel design									
Ahren et al. (2016) [30]	26 wk	Liraglutide 1.8 mg qd+ins	205	43.2±28.5	45	28.9	21.4	8.04	83.6
		Liraglutide 1.2 mg qd+ins	209	42.8±27.5	49	28.8	21.1	8.07	84.7
		Liraglutide 0.6 mg qd+ins	211	43.9±34	44	28.9	21	8.09	83.1
		Placebo+ins	206	42.7±26	46	28.9	20.7	8.12	84.2
Dejgaard et al. (2016) [31];	24 wk	Liraglutide 1.8 mg qd+ins	50	47±13	60	30.3±3.5	20±12	8.7±0.7	93.4±14.2
		Placebo+ins	50	49±12	70	29.8±3.1	25±12	8.7±0.7	94±12.5
Frandsen et al. (2015) [33];	12 wk	Liraglutide 1.8 mg qd+ins	18	39.5±2.7	61	24.17±0.64	18.33±2	8.8±0.2	75.83±2.89
		Placebo+ins	18	36.1±1.6	72	22.75±0.41	19.56±1.6	8.7±0.1	74.89±1.66
Kuhadiya et al. (2016) [35]	12 wk	Liraglutide 0.6 mg qd+ins	14	45±4	64.3	26±3	19±3	7.46±0.19	80±4
		Liraglutide 1.2 mg qd+ins	16	42±3	50	33±2	21±3	7.84±0.17	96±4
		Liraglutide 1.8 mg qd+ins	16	42±3	25	28±4	20±3	7.41±0.15	83±4
		Placebo+ins	17	50±3	41.2	28±2	19±3	7.69±0.17	80±6

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Supplementary Table 1. Continued

Study	Study duration	Treatment group	No. of patients	Age, yr	Men, %	BMI, kg/m <sup>2</sup>	DM duration, yr	Baseline HbA1c, %	Baseline weight, kg
Mathieu et al. (2016) [36]	52 wk	Liraglutide 1.8 mg qd+ins	346	43.7±13.3	47.7	29.5±5.2	21.5±12.6	8.14±0.74	86.3±17.3
		Liraglutide 1.2 mg qd+ins	346	43.9±13.1	48.3	29.3±5.1	21.6±12.2	8.16±0.779	85.4±17.2
		Liraglutide 0.6 mg qd+ins	350	43.6±12.8	46.9	29.5±5.3	20.9±12.2	8.18±0.738	86.5±17.3
		Placebo+ins	347	43.4±12.6	48.1	29.8±5.6	21.6±11.8	8.15±0.728	86.4±17.8
Cross-over design									
Dube et al. (2018) [37]	24 wk	Liraglutide 1.8 mg qd+ins	7	-	-	-	-	7.4±0.1	89±3.8
		Ins+lira	8	-	-	-	-	7.4±0.1	89±3.8
DPP-4i vs. placebo in adjunct to insulin treatment									
Parallel design									
Garg et al. (2013) [38]	20 wk	Sitagliptin 100 mg qd+ins	63	37±13	51	27.5±4.9	22±11	8.2±0.7	82±16
		placebo	62	39±15	58	27.4±4.2	20±11	8.6±0.7	82±15
Cross-over design									
Ellis et al. (2011) [39]	8 wk	Sitagliptin 100 mg qd+ins	10	33±14	-	27.6±3.7	15±6	9.5±0.7	-
		Placebo	9	32±12	-	26.7±2.6	20±9	9.2±0.7	-
Farngren et al. (2012) [40]	4 wk	Vildagliptin 50 mg bid+ins	14	29.8±4.1	78.6	25.4±1.9	11.6±4.1	7.53±0.6	-
		Placebo	14	30.2±5.1	71.4	24±4.2	10.4±4.6	7.46±0.48	-
Foley et al. (2008) [41]	4 wk	Vidagliptin 100 mg bid+ins	11	39.3	-	24	19.7	7.6±0.9	-
		Ins+placebo	11	39.3	-	24	19.7	7.6±0.9	-
George et al. (2016) [42]	12 wk	Saxagliptin 5 mg qd+ins	14	42.9	-	26	20.5	8.0±2.33	74.1±3
		Placebo+ins	14	42.9	-	26	20.5	8.0±2.33	74.1±3
Schopman et al. (2015) [43]	6 wk	Sitagliptin 100 mg qd+ins	8	30.5	100	24.1	8	8.3±0.9	-
		Placebo+ins	8	33.5	100	24.6	12	12±2.9	-
SGLT-2i vs. placebo in adjunct to insulin treatment									
Parallel design									
Buse et al. (2018) [44]	52 wk	Sotagliflozin 200 mg qd+ins	263	46.6±13.48	47.9	29.81±5.686	25±13.15	7.61±0.735	86.96±18.539
		Sotagliflozin 400 mg qd+ins	262	46.4±13.12	45.8	29.63±5.297	24±12.88	7.56±0.724	86.5±18.004
		Placebo+ins	268	45.2±12.72	51.1	29.55±5.188	24.2±12.38	7.54±0.712	87.3±17.709
Dandona et al. (2017) [45]	24 wk	Dapagliflozin 5 mg qd+ins	259	41.9±14.1	43	28.3±5.8	19.7±12.0	8.53±0.71	80.8±18.2
		Dapagliflozin 10 mg qd+ins	259	42.7±14.1	50	28.1±5.2	19.9±11.1	8.52±0.64	82.0±17.3
		Placebo+ins	260	42.7±13.6	51	28.6±5.2	21.2±12.2	8.53±0.67	84.3±18.3
Danne et al. (2018) [46]	52 wk	Sotagliflozin 200 mg qd+ins	261	42.3±13.59	53.3	27.97±5.275	18.2±10.82	7.74±0.806	81.93±17.386
		Sotagliflozin 400 mg qd+ins	263	41.7±13.23	50.6	27.85±4.921	18.9±11.18	7.71±0.819	81.97±17.963
		Placebo+ins	258	39.7±13.43	51.9	27.5±5.17	18.1±10.72	7.79±0.881	81.08±16.857
Famulla et al. (2017) [47]; Pieber et al. (2015) [48]	4 wk	Empagliflozin 2.5 mg qd+ins	19	41.9±12.4	79	24.7±3.6	-	8.35±0.75	75.9±14.2
		Empagliflozin 10 mg qd+ins	19	39.6±11.6	79	27.4±3.5	-	8.28±0.79	87.1±13.3
		Empagliflozin 25 mg qd+ins	18	41.9±9.7	56	25.4±3.5	-	8.15±0.54	76.9±14.5
		Placebo+ins	19	40.5±10.6	68	25.4±3.7	-	8.18±0.67	79.8±13.8
Garg et al. (2017) [49]	24 wk	Sotagliflozin 400 mg qd+ins	699	43.3±14.2	51.2	28.29±5.13	20.5±12.4	8.26±0.96	82.4±17.13
		Placebo+ins	703	42.4±14.0	48.2	28.10±5.18	19.6±12.1	8.21±0.92	81.55±17.03

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Supplementary Table 1. Continued

Study	Study duration	Treatment group	No. of patients	Age, yr	Men, %	BMI, kg/m <sup>2</sup>	DM duration, yr	Baseline HbA1c, %	Baseline weight, kg
Henry et al. (2015) [50]; Rodbard et al. (2017) [51]; Peters et al. (2016) [52]	18 wk	Canagliflozin 100 mg qd+ins	117	42.0±11.6	59	28.0±3.9	22.0±11.5	7.9±0.5	84.1±14.2
		Canagliflozin 300 mg qd+ins	117	42.8±11.0	55.6	28.1±3.9	21.9±10.6	8.0±0.5	82.9±15.0
		Placebo+ins	117	42.0±11.9	53.8	28.0±3.6	23.3±11.0	7.9±0.6	83.0±15.4
Kuhadiya et al. (2016) [53]	12 wk	Dapagliflozin 10 mg qd+ins	17	55±3	70	31±1	25±3	7.8±0.21	85±3.8
		Placebo+ins	9	52±3	50	27±2	31±5	7.4±0.2	79±3.8
Sands et al. (2015) [54]	4 wk	Sotagliflozin 400 mg+ins	16	45.5±17	50	27.1±3.1	16.8±19.7	7.94±0.55	9.45±3.45
		Placebo+ins	17	34.0±13	47	26.2±3.0	18.5±18.05	7.98±0.51	8.89±3.96
Shimada et al. (2018) [55]	4 wk	Empagliflozin 2.5 mg qd+ins	13	44.2±12.6	38.5	24.4±3.93	16.8±1.2	8.02±0.36	63.3±10.5
		Empagliflozin 10 mg qd+ins	12	44.5±11.8	33.3	22.68±3.27	14.3±8.4	8.12±0.37	59.9±10.6
		Empagliflozin 25 mg qd+ins	12	46.6±10.8	66.7	22.6±2.7	20.8±13.5	7.89±0.91	60.5±10.2
		Placebo+ins	11	43.9±11.7	45.5	23.7±2.6	14.8±10.0	8.23±0.47	63.6±7.7
Mathieu et al. (2018) [65]	24 wk	Dapagliflozin 5 mg qd+ins	271	42.7±13.4	43.5	27.3±5.1	19.3±11.8	8.45±0.69	78.8±17.4
		Dapagliflozin 10 mg qd+ins	270	42.4±12.8	44.8	27.8±5.5	19.4±11.9	8.43±0.69	80.1±18.3
		Placebo+ins	272	43.0±13.7	43.8	27.6±5.4	19.0±11.6	8.43±0.65	78.9±18.9
Rosenstock et al. (2018) [66]	52 wk	Empagliflozin 10 mg qd+ins	243	45.7±12.5	48.6	29.5±5.5	22.8±12.6	8.10±0.60	86.2±18.2
		Empagliflozin 25 mg qd+ins	241	45.3±13.9	46.1	29.5±6.0	22.5±13.0	8.06±0.53	86.6±18.3
		Placebo+ins	239	44.5±13.5	45.6	28.5±5.3	22.4±12.4	8.13±0.57	83.4±15.3
	24 wk	Empagliflozin 2.5 mg qd+ins	237	43.4±14.2	49.8	28.0±4.4	20.8±11.9	8.14±0.61	81.6±14.6
		Empagliflozin 10 mg qd+ins	244	42.4±13.3	46.7	28.7±5.1	20.5±11.9	8.19±0.64	83.7±17.0
		Empagliflozin 25 mg qd+ins	242	44.2±13.5	50.8	28.4±5.6	21.2±11.4	8.19±0.65	83.3±18.9
Placebo+ins	238	42.2±13.2	47.9	27.8±5.1	21.7±13.0	8.19±0.58	80.71±16.9		
Cross-over design									
Biester et al. (2017) [56]	2–10 wk	Sotagliflozin 400 mg qd+ins	17	16±4.5	42	27.3±2.63	8±7	8.22±1.25	69.1±10.7
		Placebo+ins	16	16±4.5	42	27.3±2.63	8±7	8.22±1.25	69.1±10.7
Pramlintide vs. placebo in adjunct to insulin treatment									
Parallel design									
Edelman et al. (2006) [57]; Marrero et al. (2007) [58]; Kovatchev et al. (2008) [59]	29 wk	Pramlintide 15–60 µg tid+ins	148	41±14	48.6	27.7±4.6	19±12	8.1±0.8	81±17
		Placebo+ins	147	41±12	40.8	27.8±4.8	21±12	8.1±0.8	81±17
Herrmann et al. (2013) [60]	29 wk	Pramlintide 30–60 µg tid+ins	82	42±14	39	27±4	20±12	8.1±0.7	79±16
		Placebo+ins	73	41±12	29	28±5	24±12	8±0.8	80±17
Ratner et al. (2004) [61]	52 wk	Pramlintide 60 µg tid+ins	164	39.2±13.1	52	26.4±4.5	18.6±10.7	8.9±1.1	77.3±14.6
		Pramlintide 60 µg qid+ins	161	41.9±13.1	52	26.8±4.4	19.2±10.7	8.9±1	78.3±14.5
		Pramlintide 90 µg tid+ins	172	41±12.8	47	26.3±4.1	18.6±11.4	8.9±0.9	75.8±14.7
		Placebo+ins	154	41.3±13.6	53	26.5±4.9	18.2±10.5	9±1.1	76.9±15.8
Ratner et al. (2005) [62]	26 wk	Pramlintide 30/60 tid/qid+ins	281	41±12	50	25.7±3.6	18±10	7.9±0.4	75.4±13.1
		Placebo+ins	196	42±13	55	25.8±4.0	19±11	7.9±0.4	76.0±14.3
Whitehouse et al. (2002) [63]	52 wk	Pramlintide 30 µg qid+ins	243	40.3±11.6	55	25.2±3.3	16.5±10	8.7±1.3	75±13.8
		Placebo+ins	237	40.4±12.1	55	25.8±3.5	17.1±10.5	8.9±1.5	75.6±13.3

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Supplementary Table 1. Continued

Study	Study duration	Treatment group	No. of patients	Age, yr	Men, %	BMI, kg/m <sup>2</sup>	DM duration, yr	Baseline HbA1c, %	Baseline weight, kg
Single-blinded, cross-over design									
Riddle et al. (2015) [64]	4 wk	Pramlintide 6/9/12 µg/unit ins+ins	19	46±16	63.1	26.4±2.6	-	7.75±0.58	81.5±11.1
		Placebo+ins	19	46±16	63.1	26.4±2.6	-	7.75±0.58	81.5±11.1

Values are presented as mean ± standard deviation.

BMI, body mass index; DM, diabetes mellitus; HbA1c, glycosylated hemoglobin; MET, metformin; bid, twice a day; ins, insulin; qd, once a day; tid, three times a day; AGI, alpha glucosidase inhibitor; TZD, thiazolidinedione; GLP-1RA, glucagon-like peptide-1 receptor agonist; DPP-4i, dipeptidyl peptide 4 inhibitor; SGLT-2i, sodium glucose cotransporter 2 inhibitor.