Supplementary material

Supplement to: Täger et al. Comparative efficacy of sodium-glucose cotransporter-2 inhibitors (SGLT2i) for cardiovascular outcomes in type 2 diabetes: a systematic review and network meta-analysis of randomised controlled trials**.** Heart Failure Reviews 2020.

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Appendix

Search Algorithms

Pubmed and Cochrane Central Register of Controlled Trials search:

("type 2 diabetes mellitus" OR "T2D" OR "diabetes mellitus type 2" OR "type 2 diabetes" OR "diabetes type 2") AND ("SGLT2 inhibitor*" OR "SGLT2i" OR "Empagliflozin" OR "Dapagliflozin" OR "Canagliflozin" OR "Ertugliflozin") AND ("cardiovascular outcome" OR "myocardial infarction" OR "stroke" OR "heart failure" OR "MACE" OR "major adverse cardiac events" OR "major adverse cardiovascular events" OR "death") AND (trial OR random* OR controlled) NOT review

www.clinicaltrials.gov search

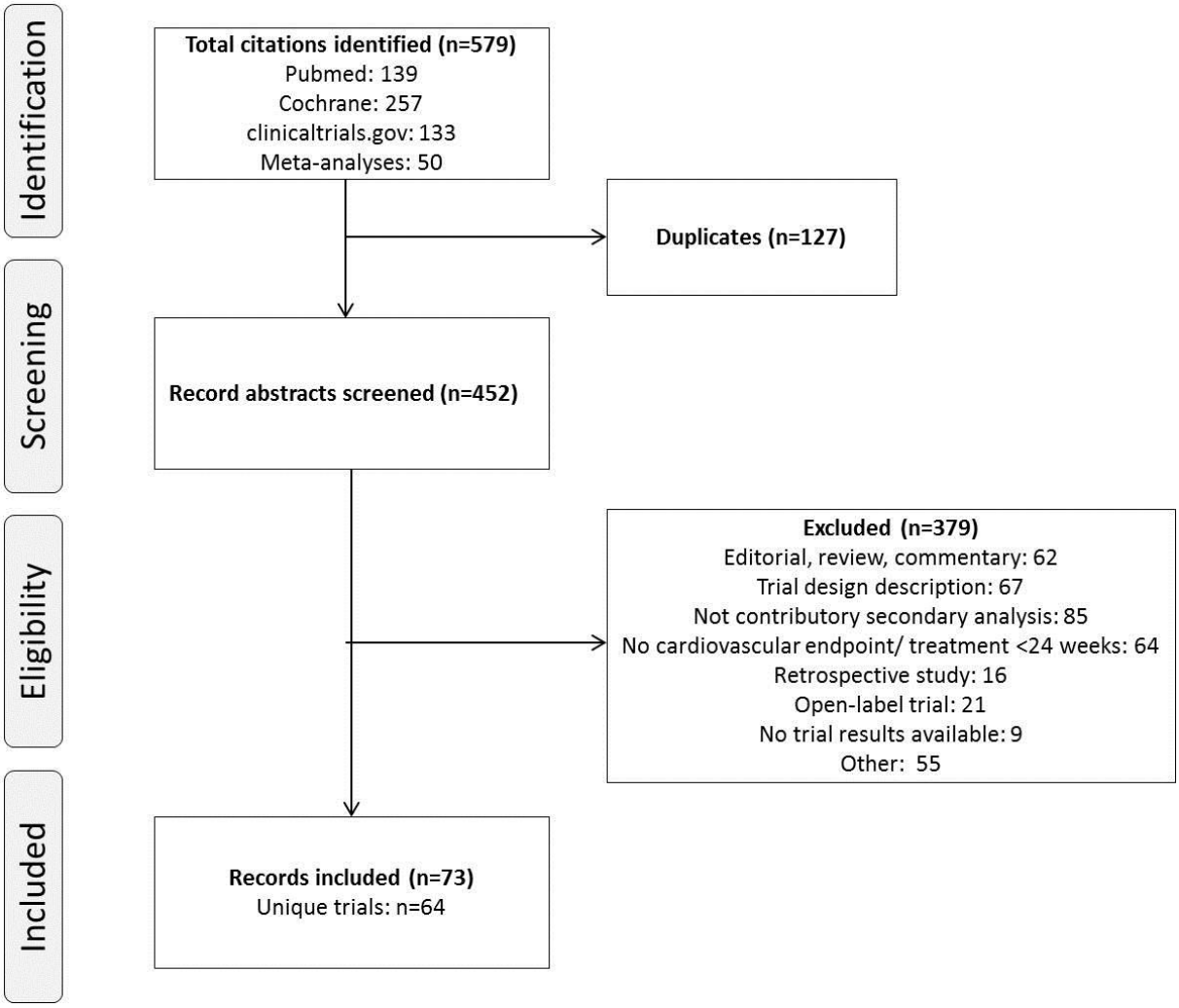
Condition or disease: type 2 diabetes mellitus OR diabetes mellitus type 2 OR type 2 diabetes OR diabetes type 2 OR T2D OR T2DM

Other terms: Empagliflozin OR Canagliflozin OR Dapagliflozin OR Ertugliflozin

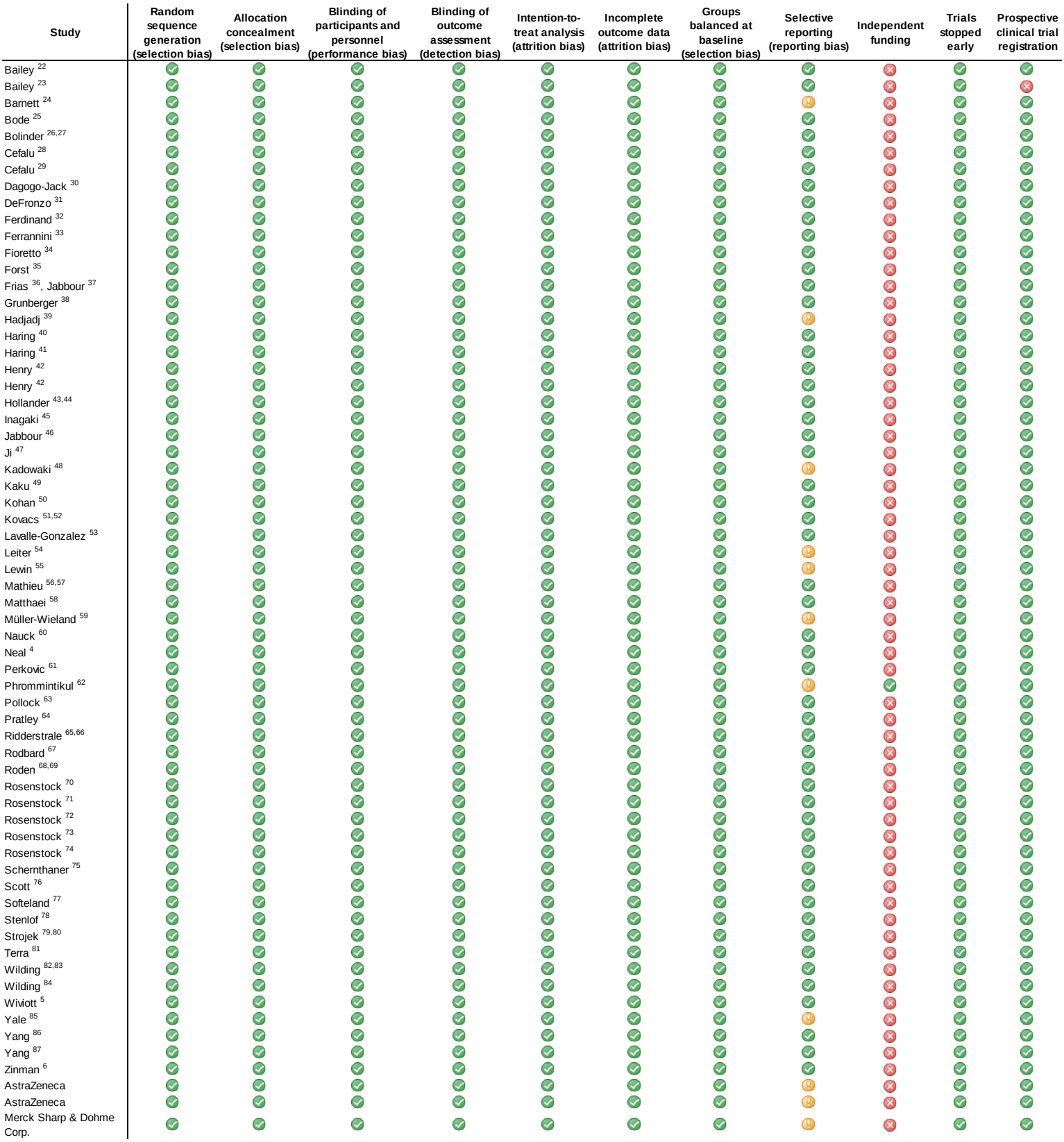
Applied Filters: Completed, adult (18–64), older adult (65+), phase 3, phase 4

Supplementary Figures

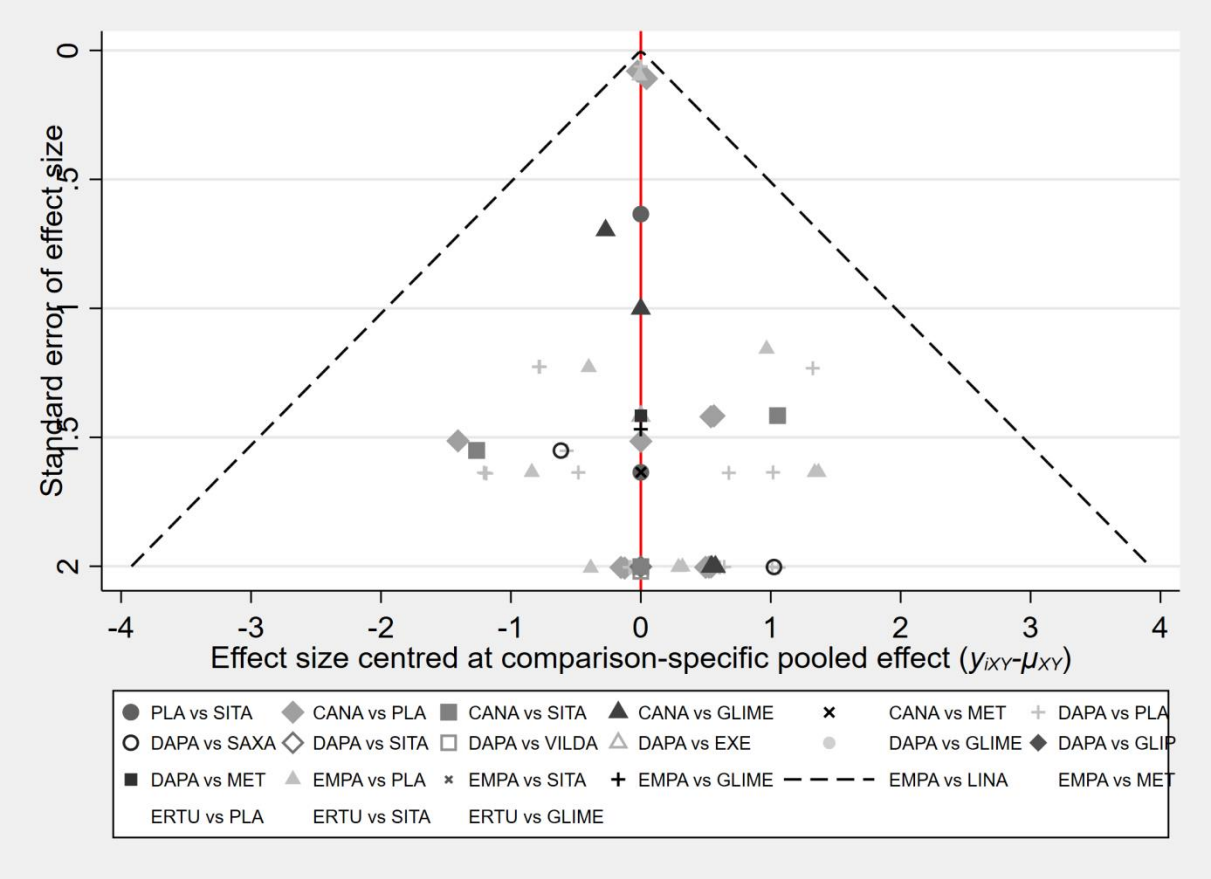
eFig. 1 Flow chart of study identification and selection



eFig. 2 Individual risk of bias assessment

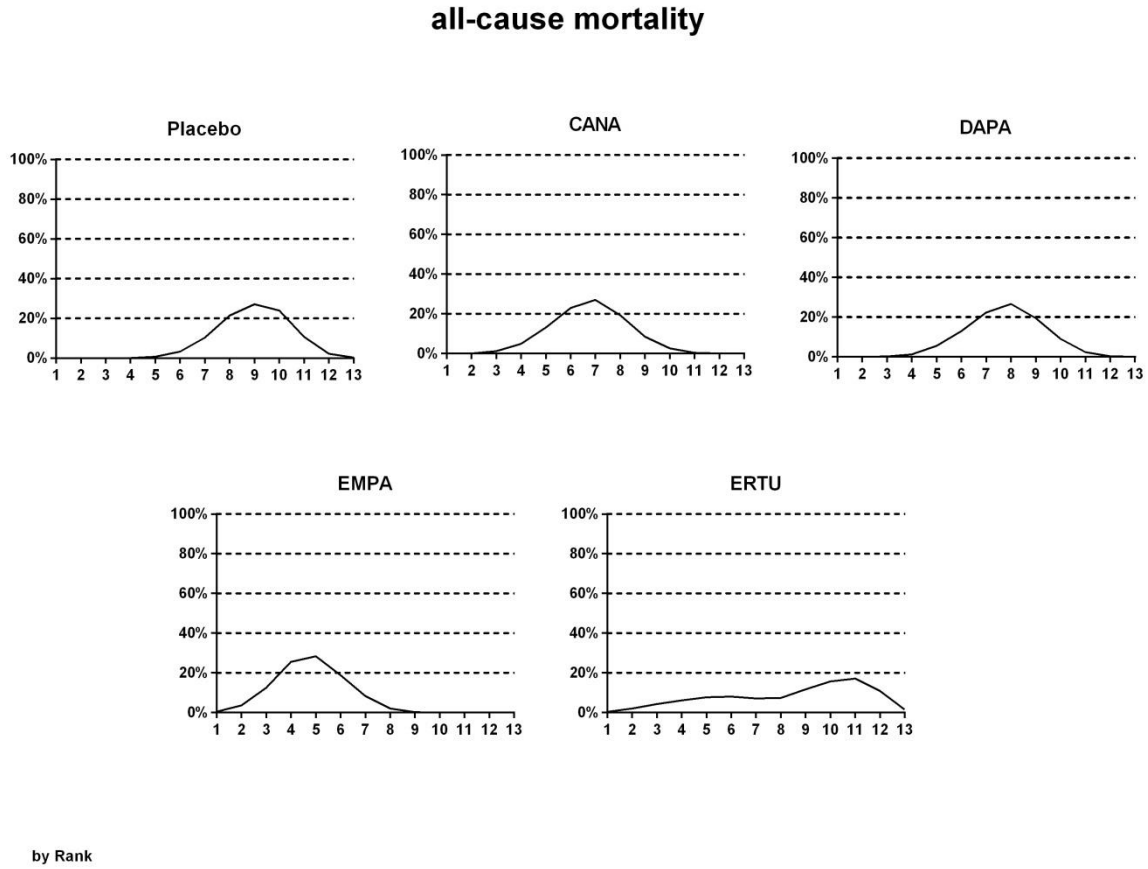


eFig. 3 Comparison funnel plot (all-cause mortality)



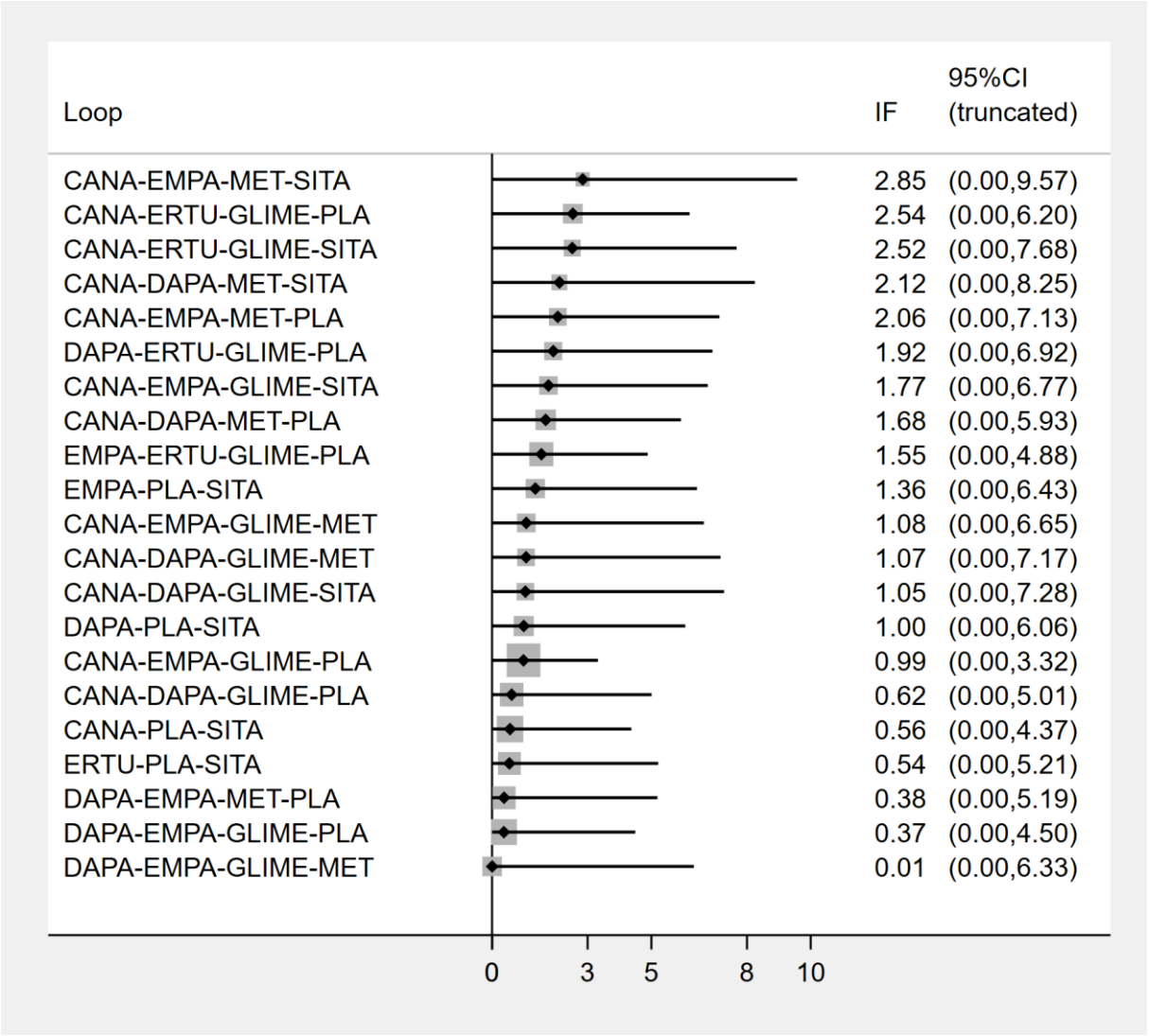
Legend: CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; ERTU, ertugliflozin; EXE, exenatide; GLIME, glimepiride; GLIP, glipizide; LINA, linagliptin; MET, metformin; PLA, placebo; SAXA, saxagliptin; SITA, sitagliptin; VILDA, vildagliptin.

eFig. 4 Graphical ranking of SGLT2i based on SUCRA values (all-cause mortality)



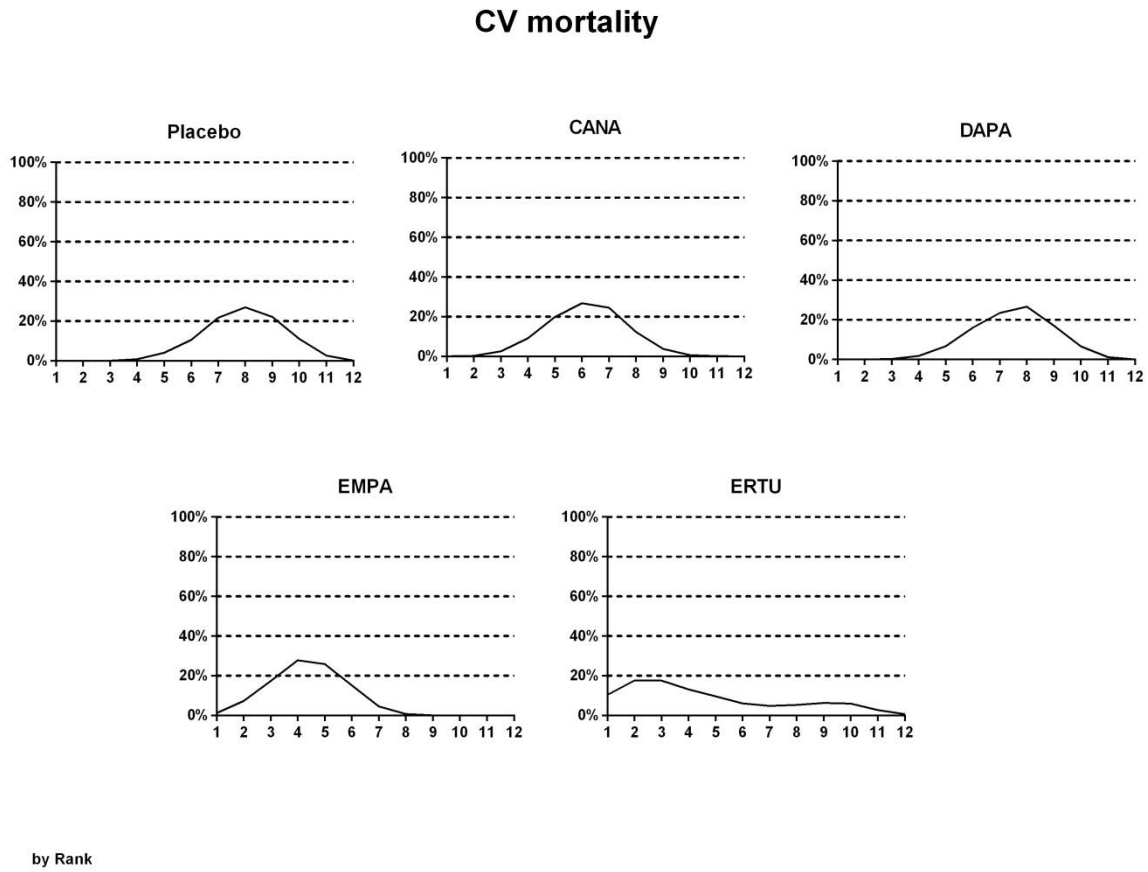
Legend: CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; ERTU, ertugliflozin.

eFig. 5 Plot of inconsistency between direct and various indirect effect for any (same) comparison within closed loops regarding all-cause mortality



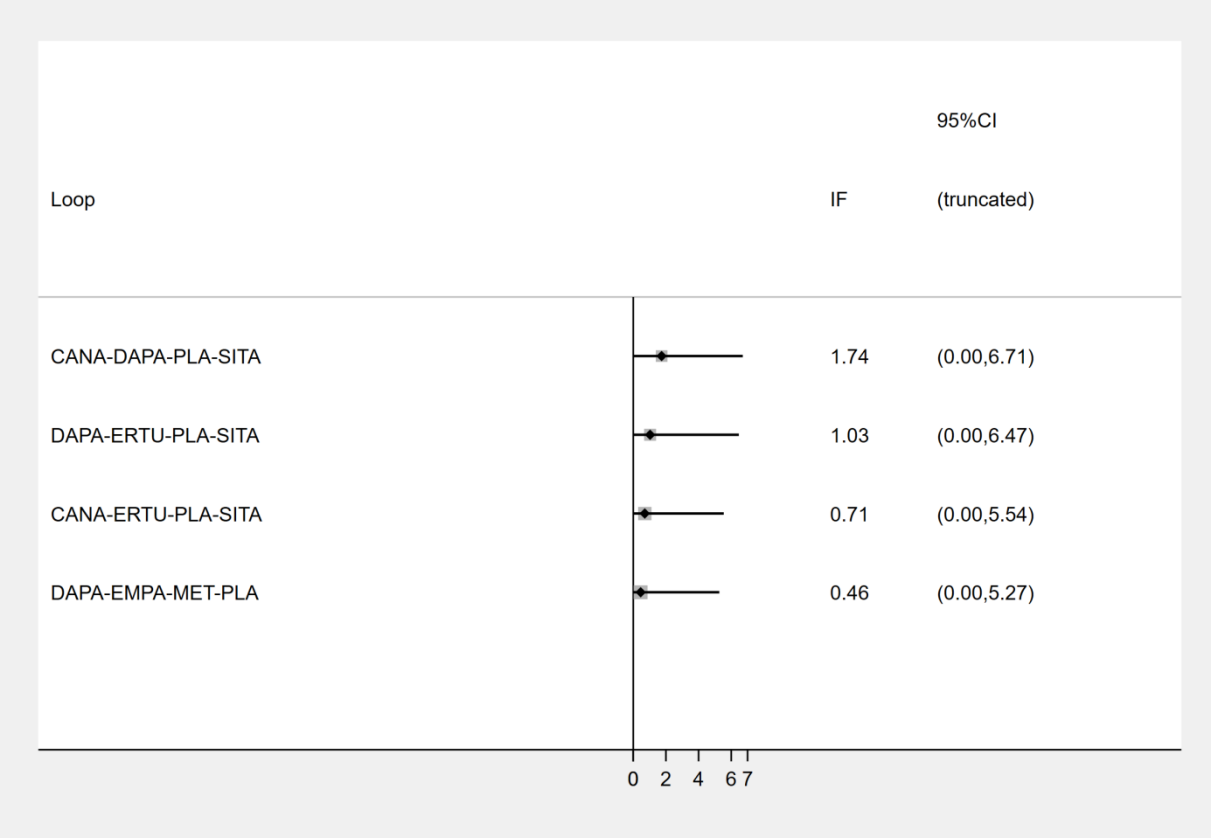
Legend: CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; ERTU, ertugliflozin; EXE, exenatide; GLIME, glimepiride; GLIP, glipizide; IF, inconsistency factor; LINA, linagliptin; MET, metformin; PLA, placebo; SAXA, saxagliptin; SITA, sitagliptin; VILDA, vildagliptin.

eFig. 6 Graphical ranking of SGLT2i based on SUCRA values (cardiovascular mortality)



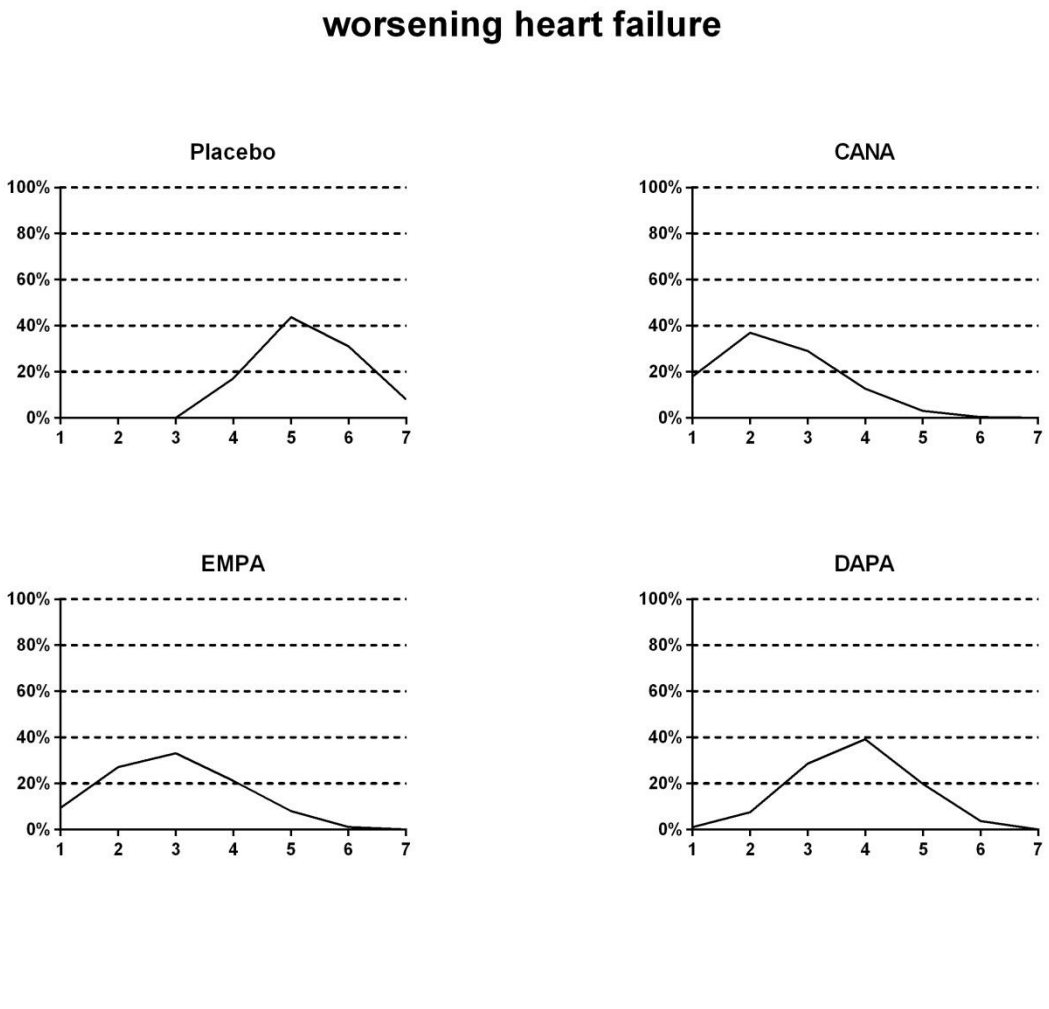
Legend: CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; ERTU, ertugliflozin.

eFig. 7 Plot of inconsistency between direct and various indirect effect for any (same) comparison within closed loops regarding cardiovascular mortality



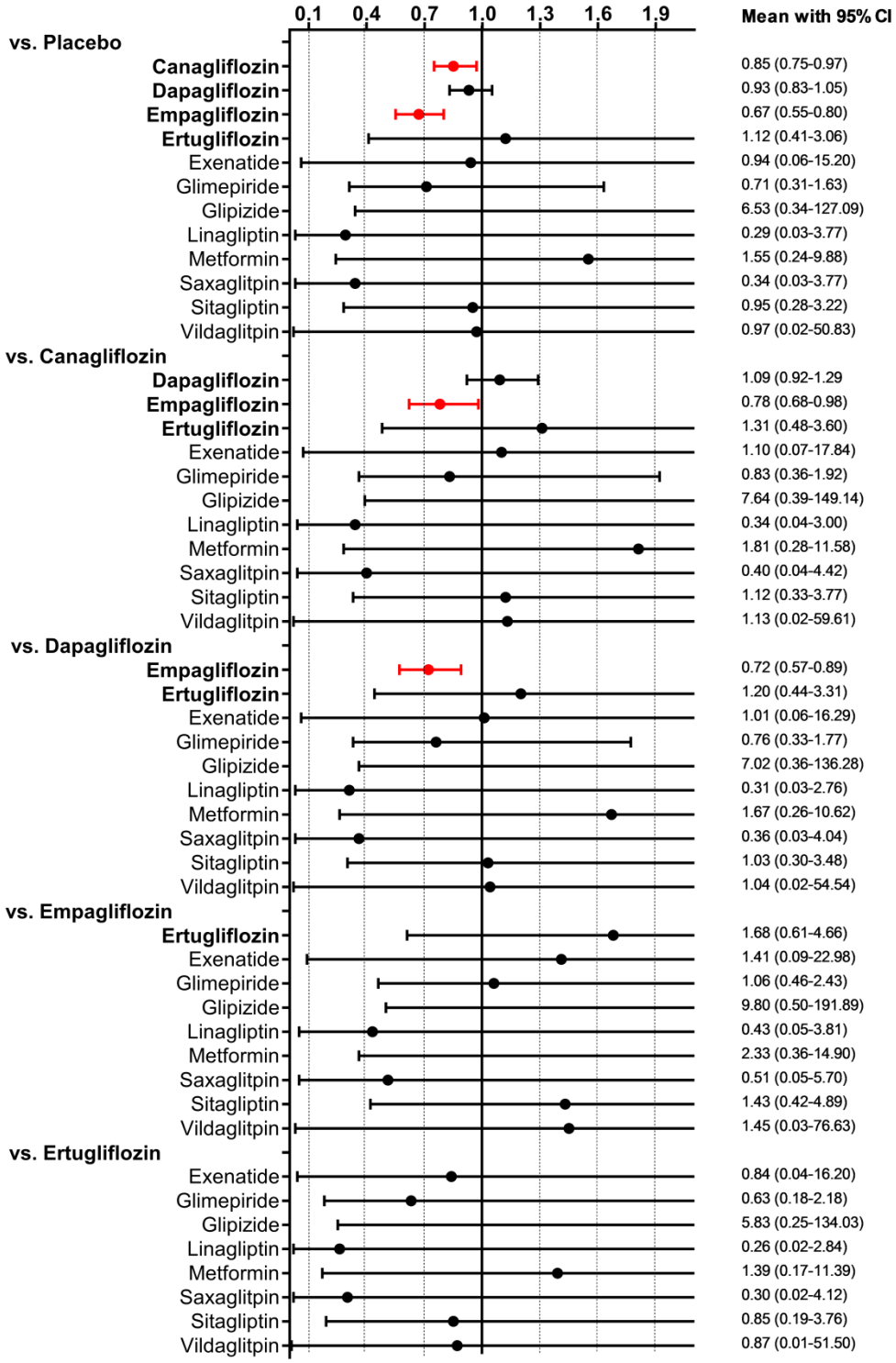
Legend: CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; ERTU, ertugliflozin; IF, inconsistency factor ; MET, metformin; PLA, placebo.

eFig. 8 Graphical ranking of SGLT2i based on SUCRA values (worsening HF)



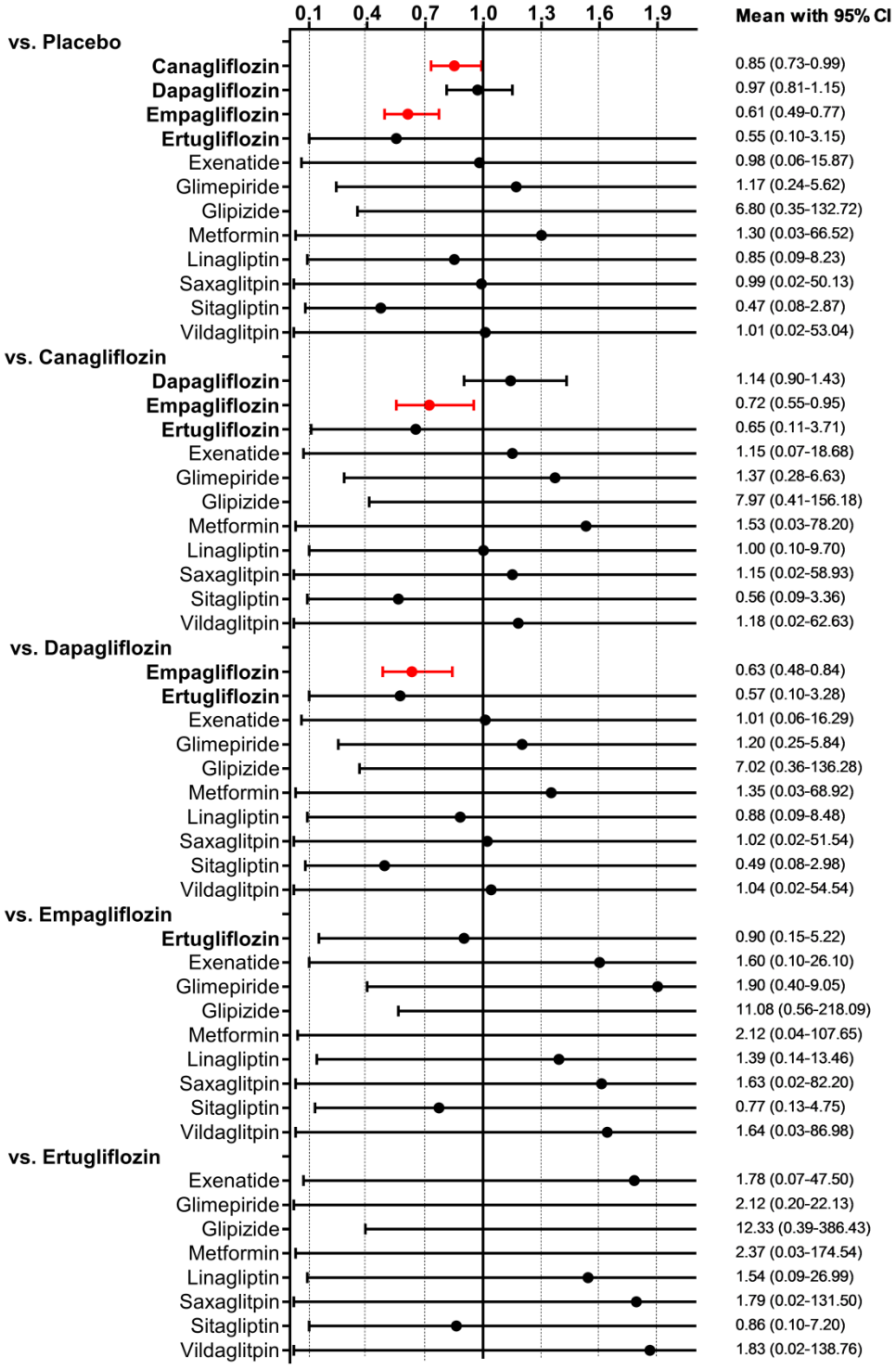
Legend: CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin.

eFig. 9 Predictive interval plot for all-cause mortality in sensitivity analyses including extension periods of trials



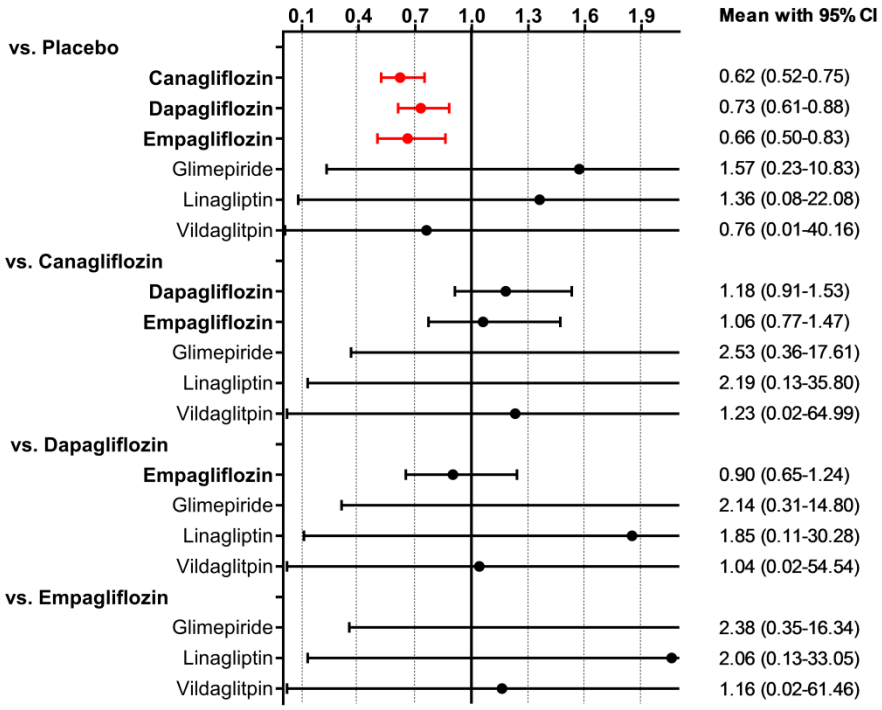
Legend: The predictive interval plot represents a forest plot of the joint estimated summary effects from both direct and indirect comparisons along with their confidence intervals. Significant estimated summary effects are shown in red colour.

eFig. 10 Predictive interval plot for cardiovascular mortality in sensitivity analyses including extension periods of trials



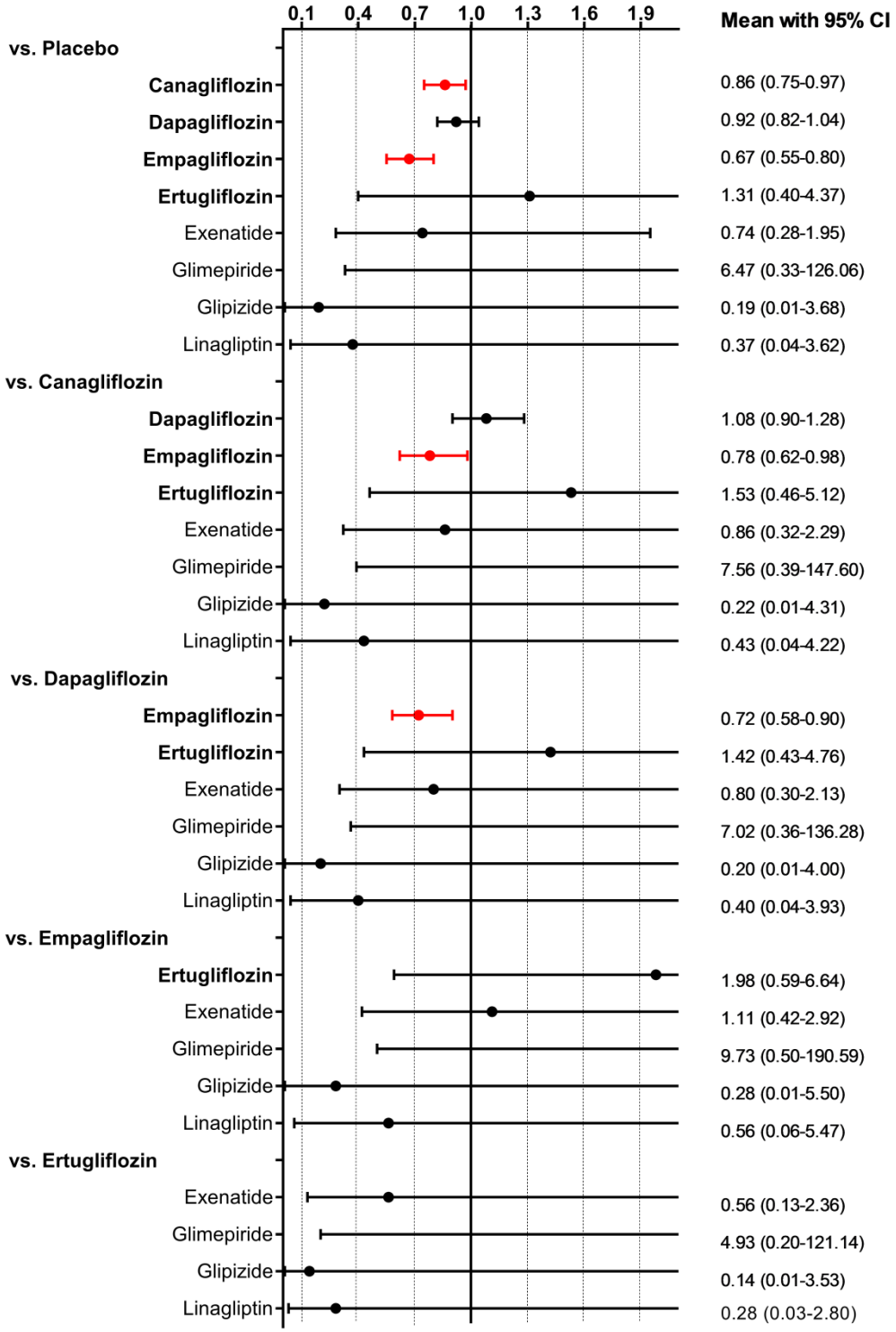
Legend: The predictive interval plot represents a forest plot of the joint estimated summary effects from both direct and indirect comparisons along with their confidence intervals. Significant estimated summary effects are shown in red colour.

eFig. 11 Predictive interval plot for worsening HF in sensitivity analyses including extension periods of trials



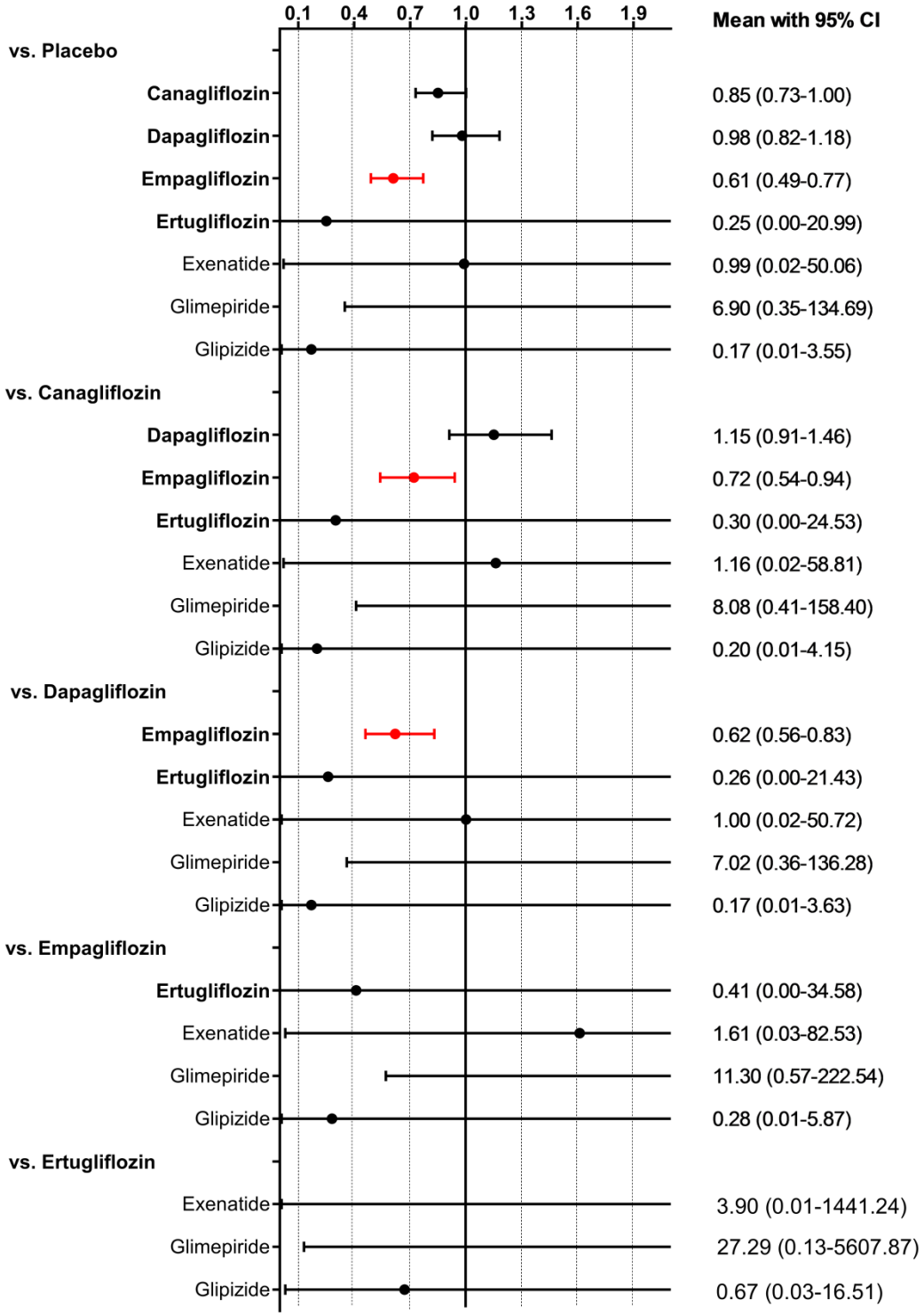
Legend: The predictive interval plot represents a forest plot of the joint estimated summary effects from both direct and indirect comparisons along with their confidence intervals. Significant estimated summary effects are shown in red colour. HF, heart failure.

eFig. 12 Predictive interval plot for all-cause mortality in sensitivity analyses excluding trials with a follow-up duration <52 weeks



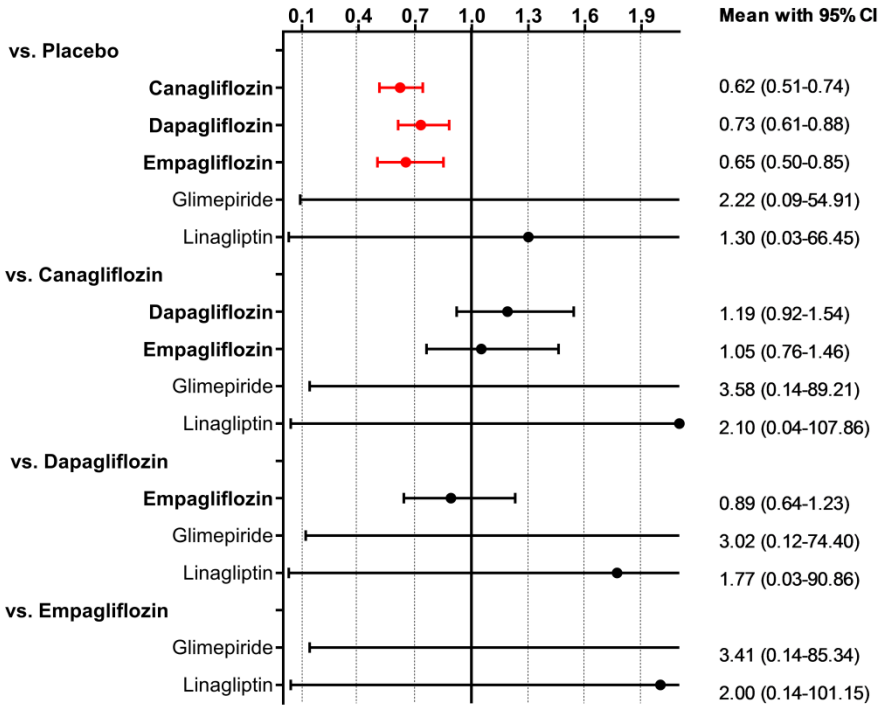
Legend: The predictive interval plot represents a forest plot of the joint estimated summary effects from both direct and indirect comparisons along with their confidence intervals.

eFig. 13 Predictive interval plot for cardiovascular mortality in sensitivity analyses excluding trials with a follow-up duration <52 weeks



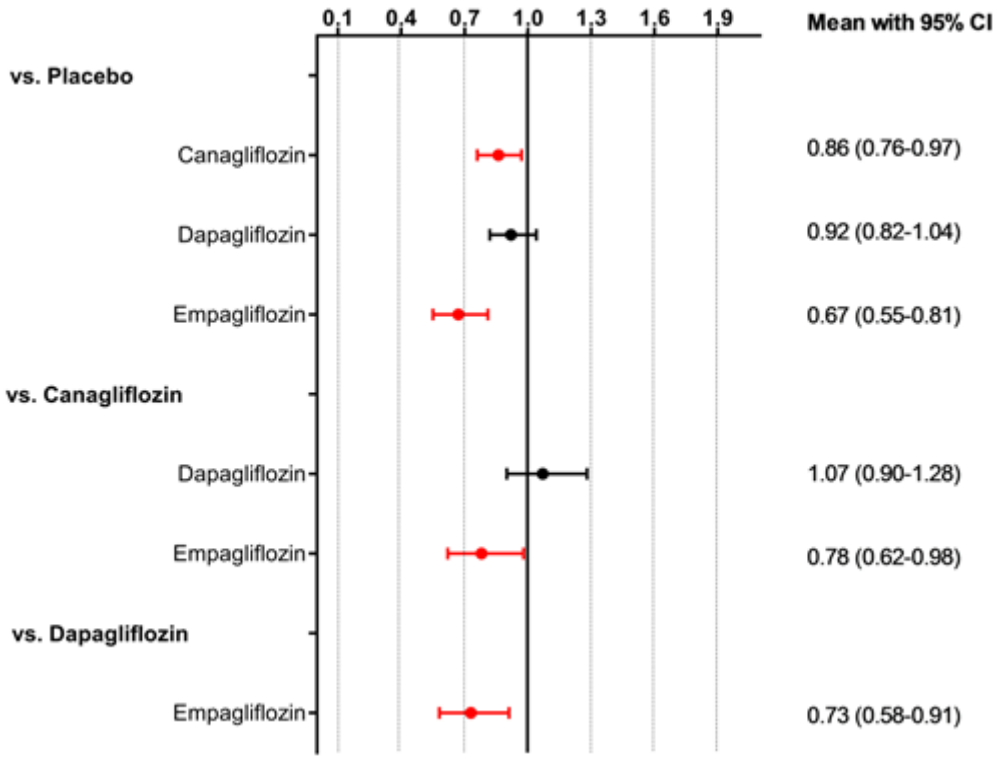
Legend: The predictive interval plot represents a forest plot of the joint estimated summary effects from both direct and indirect comparisons along with their confidence intervals.

eFig. 14 Predictive interval plot for worsening HF in sensitivity analyses excluding trials with a follow-up duration <52 weeks



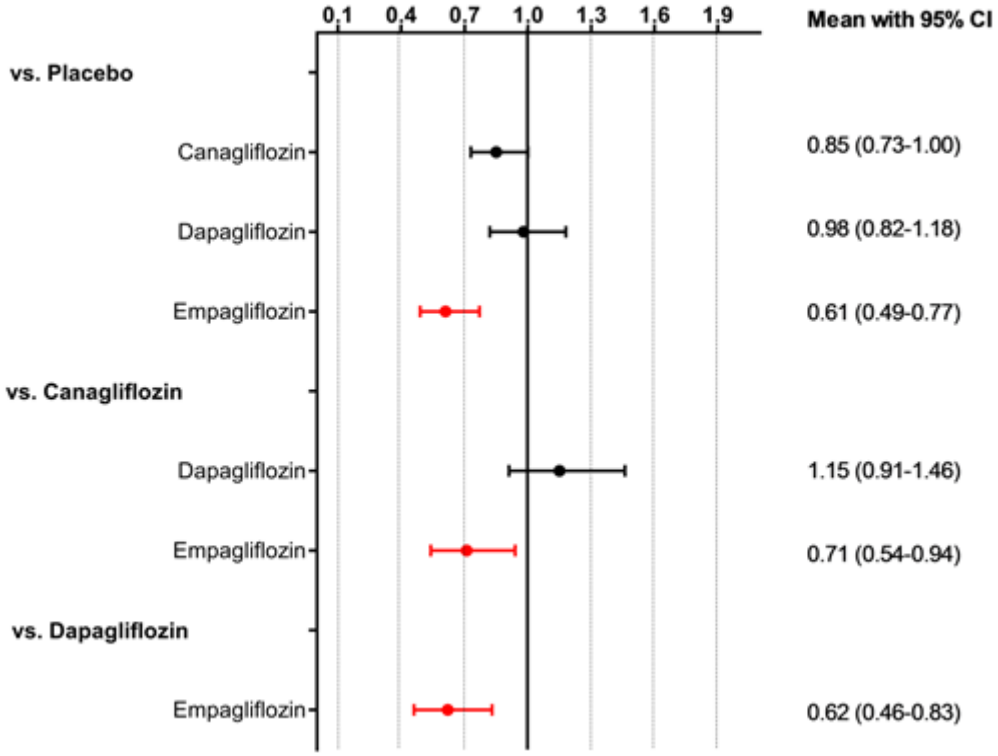
Legend: The predictive interval plot represents a forest plot of the joint estimated summary effects from both direct and indirect comparisons along with their confidence intervals. HF, heart failure.

eFig. 15 Predictive interval plot for all-cause mortality in sensitivity analyses restricted to patients included in cardiovascular outcome trials



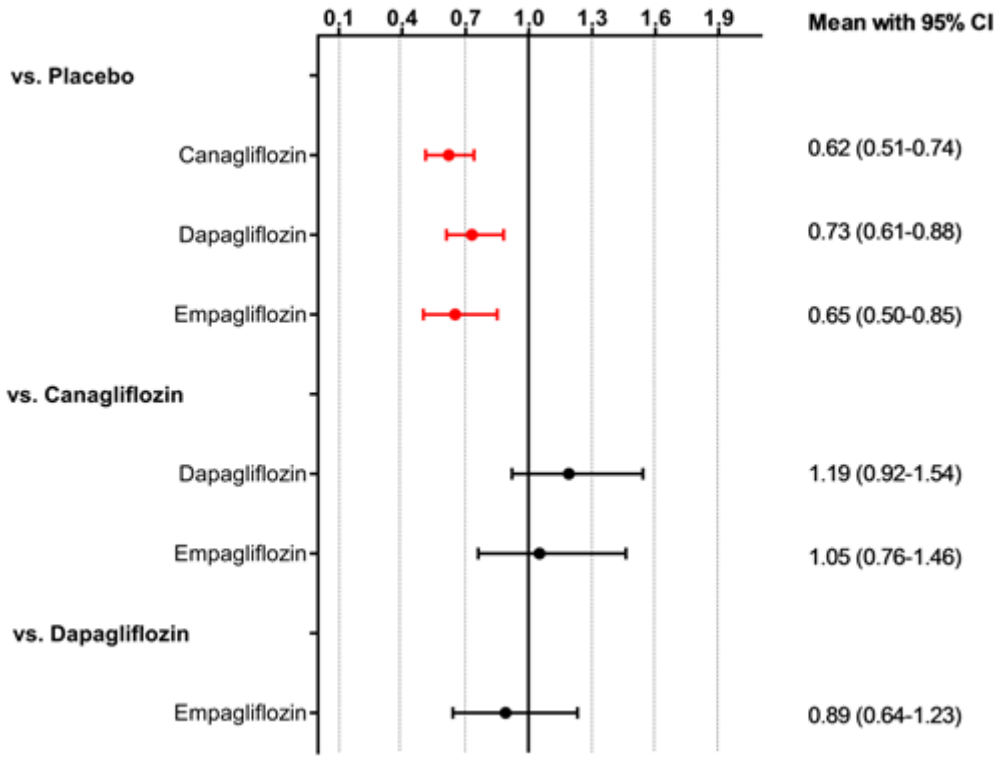
Legend: The predictive interval plot represents a forest plot of the joint estimated summary effects from both direct and indirect comparisons along with their confidence intervals.

eFig. 16 Predictive interval plot for cardiovascular mortality in sensitivity analyses restricted to patients included in cardiovascular outcome trials



Legend: The predictive interval plot represents a forest plot of the joint estimated summary effects from both direct and indirect comparisons along with their confidence intervals.

eFig. 17 Predictive interval plot for worsening HF in sensitivity analyses restricted to patients included in cardiovascular outcome trials



Legend: The predictive interval plot represents a forest plot of the joint estimated summary effects from both direct and indirect comparisons along with their confidence intervals. HF, heart failure.

Supplementary Tables

eTable 1 Patient characteristics

Study	**Age** ***(years)***	**Male** ***(n/%)***	**Cardiovascular disease** ***(n/%)***	**HbA1c** ***(%)***	**eGFR** ***(ml/min/1.73m²)***	**Background diabetes treatment**
Bailey [1]	52.7	292 (53.5)	n.a.	7.87	n.a.	metformin
Bailey [2]	53.0	141 (50.0)	n.a.	7.9	n.a.	none
Barnett [3] [a]	63.9	430 (58.3)	n.a.	8.00	54.4	any
Bode [4]	63.6	396 (55.3)	n.a.	n.a.	n.a.	any
Bolinder [5,6]	60.7	101 (55.6)	47 (26.1)	7.2	n.a.	metformin
Cefalu [7]	56.2	756 (52.1)	n.a.	7.8	n.a.	metformin
Cefalu [8]	62.9	624 (68.3)	922 (100)	8.13	n.a.	any
Dagogo-Jack [9]	59.1	263 (56.9)	n.a.	8.0	87.9	metformin and sitagliptin
DeFronzo [10]	57.4	362 (53.7)	n.a.	7.98	89.6	metformin
Ferdinand [11]	56.8	79 (52.7)	n.a.	8.59	91.3	none or metformin only, or sulfonylurea only, or DPP-4 inhibitor only, or metformin plus sulfonylurea, or metformin plus DPP-4 inhibitor
Ferrannini [12] [a]	52.0	276 (49.5)	n.a.	8.29	n.a.	none

Fioretto [13]	66.3	182 (56.7)	n.a.	8.18	53.5	any
Forst [14]	57.4	216 (63.2)	n.a.	7.9	86.4	metformin and pioglitazone
Frias [15], Jabbour [16]	54.2	328 (47.3)	n.a.	9.3	96.9	metformin
Grunberger [17]	67.3	231 (49.5)	232 (49.7)	8.2	46.6	any except metformin, roseglitazone and SGLT2i
Hadjadj [18]	52.6	747 (54.8)	n.a.	8.46	90.4	none
Haring [19]	57.7	361 (56.7)	n.a.	7.9	89.0	metformin
Haring [20]	57.1	339 (50.7)	n.a.	8.1	87.2	metformin and sulfonylurea
Henry [21]	51.9	265 (44.3)	n.a.	9.2	n.a.	none
Henry [21]	51.6	298 (46.7)	n.a.	9.1	n.a.	none
Hollander [22,23]	58.2	642 (48.5)	n.a.	7.8	87.2	metformin
Inagaki [24]	58.0	192 (70.6)	n.a.	n.a.	n.a.	none
Jabbour [25]	55.0	248 (55.0)	n.a.	7.9	n.a.	metformin and/or sitagliptin
Ji [26]	51.3	237 (65.4)	n.a.	8.26	92.6	none
Kadowaki [27]	57.2	107 (77.5)	n.a.	8.03	84.3	tenegliptin
Kaku [28]	58.9	155 (59.4)	119 (45.6)	7.49	n.a.	none
Kohan [29]	67.0	164 (65.1)	n.a.	8.35	44.6	any
Kovacs [30,31]	54.5	241 (48.4)	n.a.	8.1	85.7	pioglitazone and/or metformin

Lavalle-Gonzalez [32]	55.4	605 (47.1)	n.a.	7.9	n.a.	metformin
Leiter [33]	63.9	644 (66.9)	965 (100)	8.05	n.a.	any
Lewin [34]	54.6	359 (53.9)	n.a.	8.02	87.5	none
Mathieu [35,36]	55.1	146 (45.6)	n.a.	8.2	92.5	metformin and sixagliptin
Matthaei [37]	61.0	118 (54.1)	186 (86.1)	8.16	n.a.	metformin and sulfonylurea
Müller-Wieland [38]	58.4	600 (63.9)	n.a.	8.3	87.1	metformin
Nauck [39]	58.5	441 (55.1)	150 (18.7)	7.7	n.a.	metformin and/or one other OAD
Neal [40]	63.3	6 509 (64.2)	6 656 (65.6)	8.2	76.5	insulin, sulfonylurea, metformin, GLP-1 receptor agonist, and/or DPP-4 inhibitor
Perkovic [41]	63.0	2 907 (66.1)	2 220 (50.4)	8.3	56.2	any
Phrommintikul [42]	63.2	26 (53.1)	49 (100)	8.2	70	any except insulin, GLP-1 receptor agonists, DPP-4 inhibitors or SGLT2i
Pollock [43]	64.4	317 (70.8)	221 (49.3)	8.5	48.9	any except GLP-1 receptor agonists, DPP-4 inhibitors or SGLT2i
Pratley [44]	55.1	664 (53.9)	n.a.	8.6	92.4	metformin
Ridderstrale [45,46]	55.9	853 (55.2)	n.a.	7.92	88.2	metformin
Rodbard [47]	57.4	121 (56.8)	n.a.	8.5	90.5	metformin and sitagliptin
Roden [48,49]	55.0	551 (61.3)	n.a.	7.88	87.4	none

Rosenstock [50]	53.5	208 (49.5)	n.a.	8.37	n.a.	pioglitazone
Rosenstock [51]	54	268 (50.2)	n.a.	8.94	94.4	metformin
Rosenstock [52]	58.8	276 (55.9)	n.a.	8.2	84	basal glargine or detemir insulin or NPH insulin, with or without metformin and/or sulphonylurea
Rosenstock [53]	54.9	569 (48.0)	n.a.	8.8	88	none
Rosenstock [54]	56.6	288 (46.4)	n.a.	8.1	90.5	metformin
Schernthaner [55]	56.7	422 (55.9)	n.a.	8.1	n.a.	metformin and sulfonylurea
Scott [56]	67.1	357 (58.1)	n.a.	7.7	n.a.	metformin and sulfonylurea
Softeland [57]	55.2	197 (60.2)	n.a.	7.97	92.3	metformin and linaglitpin
Stenlof [58]	55.4	258 (44.2)	n.a.	8.0	n.a.	none
Strojek [59,60]	58.9	285 (46.8)	212 (34.8)	7.89	n.a.	glimepiride
Terra [61]	56.4	261 (56.6)	n.a.	8.2	87.7	none
Wilding [62,63]	59.3	382 (47.8)	296 (37.0)	8.53	n.a.	insuilin and/or a maximum of two OADs
Wilding [64]	56.8	239 (51.0)	n.a.	8.1	n.a.	metformin and sulfonylurea
Wiviott [65]	63.4	10 738 (62.6)	6 974 (40.6)	8.3	85.2	any
Yale [66]	68.5	163 (60.6)	147 (54.6)	8.0	39.4	any OAD
Yang [67]	53.8	241 (54.3)	n.a.	8.13	n.a.	metformin
Yang [68]	57.5	130 (47.8)	n.a.	8.54	n.a.	≥ 20 IE insulin/day, a maximum of two OADs

Zinman [69]	63.1	5 016 (71.5)	6 964 (99.2)	8.07	74.0	any (insulin, sulfonylurea, metformin, GLP-1 receptor agonist, and/or DPP-4 inhibitor)
AstraZeneca (NCT00736879)	53.0	141 (50.0)	n.a.	7.92	n.a.	none
AstraZeneca (NCT02681094)	56.7	451 (51.1)	n.a.	n.a.	n.a.	metformin
Merck Sharp & Dohme Corp. (NCT02630706)	56.5	281 (55.5)	n.a.	8.12	99.3	metformin

[a] pooled data. DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like protein-1; NPH, Neutral Protamin Hagedorn; OAD, oral antidiabetic drug; SGLT2i, sodium-glucose cotransporter-2 inhibitor

eTable 2 Endpoint characteristics of included trials

Study	All-cause mortality		Cardiovascular mortality		Worsening HF	
	Tx (n)	Ctrl (n)	Tx (n)	Ctrl (n)	Tx (n)	Ctrl (n)
Bailey [1]	0/400	0/134	0/400	0/134	n.a.	n.a.
Bailey [2]	0/214	0/68	0/214	0/68	n.a.	n.a.
Barnett [3]	1/419	3/319	n.a.	n.a.	n.a.	n.a.
Bode [4]	3/477	0/237	n.a.	n.a.	1/477	0/237
Bolinder [5,6]	1/91 [1/91]	0/91 [0/91]	0/91 [0/91]	0/91 [0/91]	n.a. [n.a.]	n.a. [n.a.]
Cefalu [7]	2/968	2/482	n.a.	n.a.	n.a.	n.a.
Cefalu [8]	2/455 [7/455]	1/459 [2/459]	n.a. [n.a.]	n.a. [n.a.]	n.a. [n.a.]	n.a. [n.a.]
Dagogo-Jack [9]	0/309 [0/309]	0/153 [0/153]	0/309 [0/309]	0/153 [0/153]	n.a. [n.a.]	n.a. [n.a.]
DeFronzo [10]	n.a. [1/281]	n.a. [0/132]	n.a. [0/281]	n.a. [0/132]	n.a. [0/281]	n.a. [0/132]
Ferdinand [11]	0/82	0/80	0/82	0/80	1/82	0/80
Ferrannini [12]	1/483	0/75	0/483	0/75	n.a.	n.a.
Fioretto [13]	n.a.	n.a.	0/160	0/161	n.a.	n.a.

Forst [14]	0/227	0/115	0/227	0/115	n.a.	n.a.
Frias [15], Jabbour [16]	1/233 [1/233]	1/230 [1/230]	1/233 [1/233]	1/230 [1/230]	n.a. [n.a.]	n.a. [n.a.]
Grunberger [17]	7/313	3/154	n.a.	n.a.	n.a.	n.a.
Hadjadj [18]	0/333	0/332	0/333	0/332	n.a.	n.a.
Haring [19]	1/441	0/225	1/441	0/225	n.a.	n.a.
Haring [20]	0/430	0/207	0/430	0/207	n.a.	n.a.
Henry [21]	1/203	0/201	1/203	0/201	n.a.	n.a.
Henry [21]	0/219	1/208	0/219	1/208	n.a.	n.a.
Hollander [22,23]	6/888 [9/880]	0/437 [1/435]	n.a. [n.a.]	n.a. [n.a.]	n.a. [n.a.]	n.a. [n.a.]
Inagaki [24]	0/179	0/93	0/179	0/93	n.a.	n.a.
Jabbour [25]	0/225 [0/225]	1/226 [1/226]	0/225 [0/225]	0/226 [0/226]	n.a. [n.a.]	n.a. [n.a.]
Ji [26]	0/261	0/132	0/261	0/132	n.a.	n.a.
Kadowaki [27]	0/70	0/68	0/70	0/68	n.a.	n.a.
Kaku [28]	0/174	0/87	0/174	0/87	n.a.	n.a.
Kohan [29]	1/168 [5/168]	2/84 [5/84]	n.a. [4/168]	n.a. [3/168]	n.a. [n.a.]	n.a. [n.a.]

Kovacs [30,31]	2/333 [4/233]	1/165 [1/165]	n.a. [3/233]	n.a. [1/165]	n.a. [n.a.]	n.a. [n.a.]
Lavalle-Gonzalez [32]	1/735	1/366 and 1/183 [a]	n.a.	n.a.	n.a.	n.a.
Leiter [33]	2/482 [5/482]	1/483 [4/483]	n.a. [n.a.]	n.a. [n.a.]	n.a. [n.a.]	n.a. [n.a.]
Lewin [34]	3/270	0/135	n.a.	n.a.	0/270	0/135
Mathieu [35,36]	0/160 [1/160]	0/160 [0/160]	0/160 [n.a.]	0/160 [n.a.]	2/160 [3/160]	0/160 [2/160]
Matthaei [37]	0/108	0/108	0/108	0/108	n.a.	n.a.
Müller-Wieland [38]	0/314	0/313	0/314	0/313	0/314	1/313
Nauck [39]	0/406	3/408	0/406	3/408	n.a.	n.a.
Neal [40]	362/5 795	306/4 347	243/5 795	201/4 347	115/5 795	137/4 347
Perkovic [41]	168/2 202	201/2 199	110/2 202	140/2 199	89/2 202	141/2 199
Phrommintikul [42]	0/25	0/24	0/25	0/24	n.a.	n.a.
Pollock [43]	1/144	0/148	n.a.	n.a.	1/144	0/148
Pratley [44]	1/498	0/247	1/498	0/247	n.a.	n.a.
Ridderstrale [45,46]	5/765 [8/765]	5/780 [8/780]	n.a. [2/765]	n.a. [4/780]	n.a. [1/765]	n.a. [2/780]
Rodbard [47]	0/108	0/108	0/108	0/108	n.a.	n.a.

Roden [48,49]	0/448 [0/448]	0/223 and 1/228 [a] [1/223 and 1/228] [a]	n.a. [n.a.]	n.a. [n.a.]	n.a. [n.a.]	n.a. [n.a.]
Rosenstock [50]	1/281	0/139	0/281	0/139	0/281	1/139
Rosenstock [51]	0/179	0/176	0/179	0/176	n.a.	n.a.
Rosenstock [52]	0/324	1/170	n.a.	n.a.	n.a.	n.a.
Rosenstock [53]	0/475	1/237	n.a.	n.a.	n.a.	n.a.
Rosenstock [54]	0/412	0/209	0/412	0/209	n.a.	n.a.
Schernthaner [55]	2/377	0/378	2/377	0/378	n.a.	n.a.
Scott [56]	0/306	0/307	0/306	0/307	n.a.	n.a.
Softeland [57]	0/222	0/110	0/222	0/110	n.a.	n.a.
Stenlof [58]	1/392	1/192	0/392	0/192	n.a.	n.a.
Strojek [59,60]	2/450 [3/450]	0/146 [0/146]	2/450 [3/450]	0/146 [0/146]	n.a. [n.a.]	n.a. [n.a.]
Terra [61]	0/305	0/156	0/305	0/156	n.a.	n.a.
Wilding [62,63]	1/607 [3/610]	0/197 [0/197]	n.a. [3/610]	n.a. [0/197]	n.a. [n.a.]	n.a. [n.a.]
Wilding [64]	0/313	0/156	0/313	0/156	n.a.	n.a.
Wiviott [65]	529/8 582	570/8 578	245/8 582	249/ 8578	212/8 582	286/ 8578
Yale [66]	1/179	1/90	n.a.	n.a.	n.a.	n.a.

Yang [67]	0/299	0/145	0/299	0/145	n.a.	n.a.
Yang [68]	0/139	0/133	0/139	0/133	n.a.	n.a.
Zinman [69]	269/4 687	194/2 333	172/4 687	137/2 333	126/4 687	95/2 333
AstraZeneca (NCT00736879)	0/214	0/68	0/214	0/68	n.a.	n.a.
AstraZeneca (NCT02681094)	2/294	0/296	n.a.	n.a.	n.a.	n.a.
Merck Sharp & Dohme Corp. (NCT02630706)	0/339	0/167	0/339	0/167	n.a.	n.a.

Ctrl, control; HF, heart failure; n.a., not available; Tx, treatment. [a] This study comprised two comparators. Numbers in brackets represent results of the extension periods of the respective trials.

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