Sodium-Glucose Co-transporter-2 Inhibition and ocular outcomes in patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis

Authors

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ABSTRACT

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors are effective for the treatment of macrovascular complications and nephropathy in type 2 diabetes (T2DM) but effects on microvascular eye outcomes are unclear. We conducted a systematic review and meta-analysis of randomized placebo-controlled trials to evaluate the effect of SGLT-2 inhibition on total ocular events and retinopathy in patients with T2DM.

We searched MEDLINE and Embase from database inception date to 11th October 2019. Two reviewers working independently extracted relevant data. Random effects models with inverse variance weighting were selected to estimate summary risk ratios and 95% CIs. We included nine studies, involving 39 982 patients with mean follow-up 2.8 years. There were 1414 total ocular events of which 624 were retinopathy events. SGLT-2 inhibition was not associated with a change in the risk of total ocular events (RR 0.97; 95% CI 0.85, 1.11) or retinopathy (RR 0.98; 95% CI 0.84, 1.16) with consistent effects across studies (P-heterogeneity=0.35 and 0.45, respectively).

The effects of SGLT-2 inhibition on eye disease in individuals with T2DM are likely null, though the available data cannot excluded small-to-moderate benefits or harms.

INTRODUCTION

Diabetic retinopathy (DR) is a common but serious microvascular complication of diabetes that can result in significant loss of vision with resultant impairment of functional capacity and quality of life. One in three patients with diabetes have DR and 1 in 10 have the most severe proliferative form of the condition or macular oedema.[1] In addition, diabetes is associated with glaucoma, cataracts and other eye events which occur earlier and more frequently in this

patient group.[2] Glucose lowering has been demonstrated to delay the development and progression of DR and the effects of novel glucose lowering agents on retinopathy is of significant interest.[3]

Sodium glucose cotransporter 2 (SGLT-2) inhibitors block glucose reabsorption in the proximal tubule of the kidney leading to enhanced glucose excretion. Previous studies have demonstrated the effectiveness of SGLT2 inhibitors in reducing intermediate markers of cardiometabolic health, macrovascular complications and nephropathy in type 2 diabetes.[4-7] Effects on DR, however, are uncertain and were not specified *a priori* in the completed studies. Accordingly, we conducted a systematic review and meta-analysis of all randomised trials of SGLT-2 inhibitors versus placebo that described effects on DR or other ocular events in adult patients with type 2 diabetes.

METHODS

Search strategy

We searched MEDLINE and Embase via Ovid (inception d to 11th October 2019) for relevant trials in English-language publications. The search used text and Medical Subject Headings relating to: SGLT-2 inhibitors, T2DM, randomised, placebo-control trial design, the names of individual SGLT-2 inhibitor medications, retinopathy and other ocular outcomes (Table S1). We also reviewed the references lists of eligible studies, review articles and reports to identify other relevant data (including abstracts) as well as the clinicals.gov website.

Study inclusion criteria

We included randomised, placebo-controlled trials that reported on eye-related adverse events (AEs). Duplicate reports, trials in type 1 diabetes, trials in children and trials that reported no eye outcomes were excluded. Two authors (CL and YH) independently screened the titles and abstracts of all identified articles for eligibility and reviewed full-text articles of

potentially eligible studies. Disagreements related to the eligibility of studies were resolved through discussion with a third author (CA). We used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement to guide conduct and reporting.

Outcomes

The primary outcome was total ocular events comprising; (1) blindness that was not clearly attributable to a non-diabetic cause; (2) retinopathy comprising non-proliferative retinopathy, proliferative retinopathy, retinal oedema， haemorrhage or detachment; (3) macular oedema; (4) vitreous abnormality comprising haemorrhage or detachment; (5) cataract; (6) glaucoma; (7) requirement for retinal photocoagulation therapy, intravitreal treatment, vitrectomy, or other eye-related surgery; (8) other ocular complications comprising anterior ischemic optic neuropathy, papillopathy, iris rubeosis, ocular movement disorders, corneal oedema, nerve alterations, neurotropic ulcers, retinal artery or retinal vein occlusion, retinal arteriolar emboli or, neovascularisation; or (9) other non-specific eye-related adverse events including infection, inflammation and bleeding. The secondary diabetic retinopathy outcome comprised of (1), (2), (3), (4) and (7) as described above.

Data extraction and analysis

Two authors (CL and YH) independently extracted data using a standardised form. We assessed risk of bias at the study level using the Cochrane risk-of-bias tool. Risk of bias graphs were generated using Review Manager 5.3 software, with each domain judged as low risk, high risk or unclear risk. Any discrepancies in data extraction or risk-of-bias assessment were resolved in consultation with a third author (CA). We used Egger's regression test to assess for publication bias in addition to making a visual inspection of funnel plots.

The average characteristics of the included population were estimated by weighting the mean value or proportion for each study by sample size and then dividing through by the total sample. Where only the median value was reported it was imputed as the mean. The numbers of eye outcomes were summarized using the on-treatment approach taken by the included trials. Relative risks (RRs) were used as the common measure of association across studies because hazard ratios (HR) were not always available. HRs were treated as RRs where necessary. We evaluated the constancy of effects across trials using the I^2 statistic and by calculating the P value for heterogeneity. I^2 values more than 50% and a heterogeneity p value of <0.05 were considered to indicate differences beyond chance. We pooled the RRs using random effect models given the underlying methodological heterogeneity such as baseline characteristics of the participants, length of follow-up, and adjustment for confounders.[8] We also did analyses including only studies that reported effect estimates based on HRs and performed meta-regressions to investigate possible modifying effects of: the magnitude of reduction in HbA1C, systolic blood pressure and body weight; the duration of diabetes mellitus; history of retinopathy; history of hypertension; mean/median follow up time; age; concomitant metformin therapy at study baseline; and the selectivity of the SGLT2 inhibitors; on the observed RR for each trial. Statistical analyses were performed using Review Manager 5.3, Stata/IC 15.1 and PASS 15.0.

RESULTS

We identified 995 records after removal of duplicates, assessed 183 full-text articles and identified nine eligible studies.[4-7, 9-13] Included in this analysis are three canagliflozin trials,[5, 6, 11] three dapagliflozin trials,[7, 12, 13] two ipragliflozin trials and one empagliflozin trial.[4, 9, 10] All studies reported eye events as adverse events, excepting the EMPA-REG Outcome trial in which retinopathy was reported as a prespecified microvascular clinical outcome.[4] Six studies

reported retinopathy events.[4-6, 9, 11, 12] Four studies reported on >1000 patients years of follow-up.[4-7] HRs and events rate were presented in three trials [4-6] and RRs were calculated for the other six trials.[7, 9-13]The CANVAS Program reported integrated data from the CANVAS and CANVAS R (CANVAS- Renal) trials and six of the nine studies were multicentre studies.[4-7, 12, 13] Trial sample size ranged from 146 participants to 17 160 participants and median follow-up from 16 weeks to 219 weeks.[7, 11] The mean age of participants in the contributing studies ranged from 54 to 64 years, and the proportion of women from 25.8% to 52.2%, the mean glycosylated haemoglobin from 8.1% to 8.9%, and the mean BMI from 25.3 kg/m^2 to 32.0 kg/m^2.

Trials were generally of high quality (Figure S1)[11] with no evidence of publication bias (Figure S2 and Figure S3). In total, 39 982 patients were included in the meta-analyses with 1414 total ocular events and 624 retinopathy events.

Effects of SGLT-2 inhibitor use on total ocular events and retinopathy

SGLT-2 inhibiton did not affect the risk of total ocular events compared with placebo (RR 0.97; 95% CI 0.85, 1.11) with consistent effects across the included studies (I^2=10%, *P* for heterogeneity=0.35) (Figure 1). Likewise, there was no detectable effect of SGLT-2 inhibitor on the risk of retinopathy (RR 0.98; 95% CI 0.84, 1.16) with consistent effects across all studies (I^2=0%; *P* for heterogeneity=0.45) (Figure 1). Findings were directly comparable if analyses were restricted to the 3 large scale studies that reported HRs (Figure S5 and Figure S6).

Meta regression analyses identified no evidence that the magnitude of effect of randomised treatment on HbA1C, systolic blood pressure or body weight was associated with the impact of SGLT2 inhibition on eye events. Similarly, duration of diabetes mellitus, history of retinopathy, history of hypertension, mean/median follow up time, age, concomitant

metformin therapy at study baseline and the selectivity of the SGLT2 inhibitors did not modify the association between SGLT2 inhibition and ocular events or retinopathy events (all P> 0.10) (Figure S7).

DISCUSSION

In this meta-analysis of randomised placebo control trials including 39 982 patients and 1414 eye events, there was no detectable association between SGLT-2 inhibition and the risk of total ocular events or retinopathy in patients with type 2 diabetes. The absence of any protective effect is somewhat unexpected given SGLT-2 inhibition is associated with improved glycaemic control and lower blood pressure, both of which have been observed to reduce risks of diabetic microvascular disease in prior overviews.[3, 14] Further, SGLT-2 inhibition has large and clearly proven benefits for nephropathy, another frequent and serious microvascular complications of diabetes.[15]

The benefits of glucose control for microvascular diabetic complications have been most clearly demonstrated in a prior meta-analysis that compared more intensive versus less intensive glucose lowering.[3] In that meta analysis, the risk of the composite primary eye outcome of retinopathy was reduced by 13% in those assigned to intense versus standard glycaemic control (HR 0.87; 95% CI 0.76, 1.00; P=0.04). The weighted mean difference in HbA1c between randomised groups in that analysis was almost twice as large (-0.9% versus -0.49%) as that achieved by the SGLT-2 inhibitors included in the present meta-analysis, providing one possible explanation for the absence of an effect of SGLT-2 inhibition on eye outcomes. It is also possible that the shorter mean duration of follow-up in the trials of SGLT-2 inhibition compared to the prior overview ((2.8 years versus 5.0 years) may have mitigated against the detection of effects of SGLT-2 inhibition on microvascular eye outcomes.[3] The

other key difference between the prior overview and the present study is that more intensive glucose lowering was achieved with a range of different therapies, often used in combination, rather than SGLT-2 inhibitors alone. Metformin, specifically, has been shown to be significantly associated with a reduction in the risk of developing non proliferative diabetic retinopathy.[16] In the current study, we did not find an interaction between the risk for diabetic retinopathy and concomitant metformin therapy with SGLT-2 inhibition, though the power of the meta-regression analyses was limited.

Intensive blood pressure control has previously been demonstrated to reduce the risk of incident diabetic retinopathy by 20% (HR,0.80; 0.71 to 0.92) but not progression of estbalished diabetic retinopathy (RR 0.88; 0.73 to 1.05) during a 4 to 5 year follow-up period.[14] In that study, however, angiotensin converting enzyme inhibitors were the only class of anti-hypertensive agent that demonstrated a benefit for ocular outcomes raising uncertainty about the role of blood pressure lowering *per se* versus inhibition of the renin angiotensin aldosterone system. If it is the latter that is important then this would explain why the blood pressure lowering effects of SGLT-2 inhibition were not associated with protection.

A strength of this meta-analysis is the inclusion of new data from the CANVAS Program and CREDENCE trial, which add significantly to previous reports based on a more limited number of studies.[17] With 1414 outcomes, this current analysis provides 80% power at p=0.05 to detect a 0.5% or greater proportional difference in events between randomised groups.The included studies also benefited from rigorous trial designs and high quality trial conduct though none were designed specifically to assess ocular outcomes. The majority of data for eye complications emanate from adverse event reporting and there was no grading of retinopathy. Under-reported of eye events is probable and baseline history of ocular disease

attained via history alone was likely imprecise. There was also likely inconsistency of diagnostic and reporting criteria across studies and countries.

CONCLUSIONS

The use of SGLT-2 inhibitor, as compared to placebo, was not associated with an increase or decrease in the risk of total ocular events or retinopathy in patients with type 2 diabetes.

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DISCLOSURES

J. Yu, B. Neal and C. Arnott are employees of the George Institute. Z. Zhou reports receiving a Scientia PhD Scholarship from the University of New South Wales, Sydney.is a full-time employee of the George Institute for Global Health. K.W. BLN is supported by an Australian National Health and Medical Research Council Postgraduate Scholarship and a University Postgraduate Award from the University of New South Wales; he has received travel support from Janssen. H.J.L. Heerspink has served as a consultant for Abbvie, Astellas, AstraZeneca, Boehringer Ingelheim, Fresenius, Gilead, Janssen, Merck, and Mitsubishi-Tanabe and has received grant support from Abbvie, AstraZeneca, Boehringer Ingelheim, and Janssen.M. V. Perkovic has received fees for Advisory Boards, Steering Committee roles, or Scientific Presentations from Abbvie, Astellas, Astra Zeneca, Bayer, Baxter, BMS, Boehringer Ingelheim, Dimerix, Durect, Eli Lilly, Gilead, GSK, Janssen, Merck, Mitsubishi Tanabe, Mundipharma,

Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Retrophin, Sanofi, Servier, Vifor, and Tricida. MJJ is responsible for research projects that have received unrestricted funding from Gambro, Baxter, CSL, Amgen, Eli Lilly, and Merck; has served on advisory boards sponsored by Akebia, Baxter, and Boehringer Ingelheim; and has spoken at scientific meetings sponsored by Janssen, Amgen, and Roche, with any consultancy, honoraria, or travel support paid to her institution. BN reports grants from Janssen, Advisory Board and Honoraria from Janssen, Mitsubishi Tanabe Pharma Corporation, during the conduct of the study; other support from Merck Sharpe Dohme, and Servier, outside the submitted work . All fees are paid to his institution. CA is supported by a NSW Health Early Mid Career Grant and an NHMRC/MRFF Investigator grant.

AUTHOR CONTRIBUTIONS

CL, ZZ, BLN, CA and BN designed the study and planned the analysis. CL and YH identified trials for inclusion and extracted data. CL, YH and ZZ performed data analyses and checked for statistical inconsistency. CL and CA wrote the first draft of the manuscript. All other authors contributed to the interpretation of data and subsequent draft and approved the final version.

REFERENCES

1. Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012;35(3):556-64.

2. Radda S, Bolz M, Egger S, et al. [Diagnosis, treatment and monitoring of diabetic eye disease (Update 2019)]. Wiener klinische Wochenschrift. 2019;131(Suppl 1):164-168. Diagnose, Therapie und Verlaufskontrolle der diabetischen Augenerkrankung (Update 2019).

3. Zoungas S, Arima H, Gerstein HC, et al. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual

247 participant data from randomised controlled trials. Lancet Diabetes Endocrinol.
248 2017;5(6):431-437.
249 4. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and
250 Mortality in Type 2 Diabetes. The New England journal of medicine. 2015;373(22):2117-28.
251 5. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal
252 Events in Type 2 Diabetes. New England Journal of Medicine. 2017;377(7):644-657.
253 6. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2
254 Diabetes and Nephropathy. The New England journal of medicine. 2019;380(24):2295-2306.
255 7. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type
256 2 Diabetes. The New England journal of medicine. Jan 24 2019;380(4):347-357.
257 8. Cai X, Zhang Y, Li M, et al. Association between prediabetes and risk of all cause
258 mortality and cardiovascular disease: updated meta-analysis. BMJ (Clinical research ed).
259 2020;370:m2297.
260 9. Kashiwagi A, Akiyama N, Shiga T, et al. Efficacy and safety of ipragliflozin as an add-on
261 to a sulfonylurea in Japanese patients with inadequately controlled type 2 diabetes: results of
262 the randomized, placebo-controlled, double-blind, phase III EMIT study. Journal: Article.
263 Diabetology international. 2015;6(2):125-138.
264 10. Kashiwagi A, Shiga T, Akiyama N, et al. Efficacy and safety of ipragliflozin as an add-on
265 to pioglitazone in Japanese patients with inadequately controlled type 2 diabetes: a
266 randomized, double-blind, placebo-controlled study (the SPOTLIGHT study). Diabetology
267 International. 2014;6(2):104-116.
268 11. Inagaki N, Harashima S, Maruyama N, Kawaguchi Y, Goda M, Iijima H. Efficacy and
269 safety of canagliflozin in combination with insulin: a double-blind, randomized, placebo-
270 controlled study in Japanese patients with type 2 diabetes mellitus. Cardiovasc Diabetol.
271 2016;15:89.

12. Yang W, Han P, Min KW, et al. Efficacy and safety of dapagliflozin in Asian patients with type 2 diabetes after metformin failure: A randomized controlled trial. J Diabetes. 2016;8(6):796-808.

13. Yang W, Ma J, Li Y, et al. Dapagliflozin as add-on therapy in Asian patients with type 2 diabetes inadequately controlled on insulin with or without oral antihyperglycemic drugs: A randomized controlled trial. J Diabetes. 2018;10(7):589-599.

14. Do DV, Wang X, Vedula SS, et al. Blood pressure control for diabetic retinopathy. Sao Paulo Med J. 2015;133(3):278-9.

15. Arnott C, Li Q, Kang A, et al. Sodium‐Glucose Cotransporter 2 Inhibition for the Prevention of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus: A Systematic Review and Meta‐Analysis. Journal of the American Heart Association. 2020;9(3)

16. Fan YP, Wu CT, Lin JL, et al. Metformin Treatment Is Associated with a Decreased Risk of Nonproliferative Diabetic Retinopathy in Patients with Type 2 Diabetes Mellitus: A Population-Based Cohort Study. J Diabetes Res. 2020;2020:9161039.

17. Tang H, Li G, Zhao Y, et al. Comparisons of diabetic retinopathy events associated with glucose-lowering drugs in patients with type 2 diabetes mellitus: A network meta-analysis. Diabetes, Obesity and Metabolism. 2018;20(5):1262-1279.

290 **Table 1 Baseline characteristics of included randomized placebo-controlled trials and trial participants**

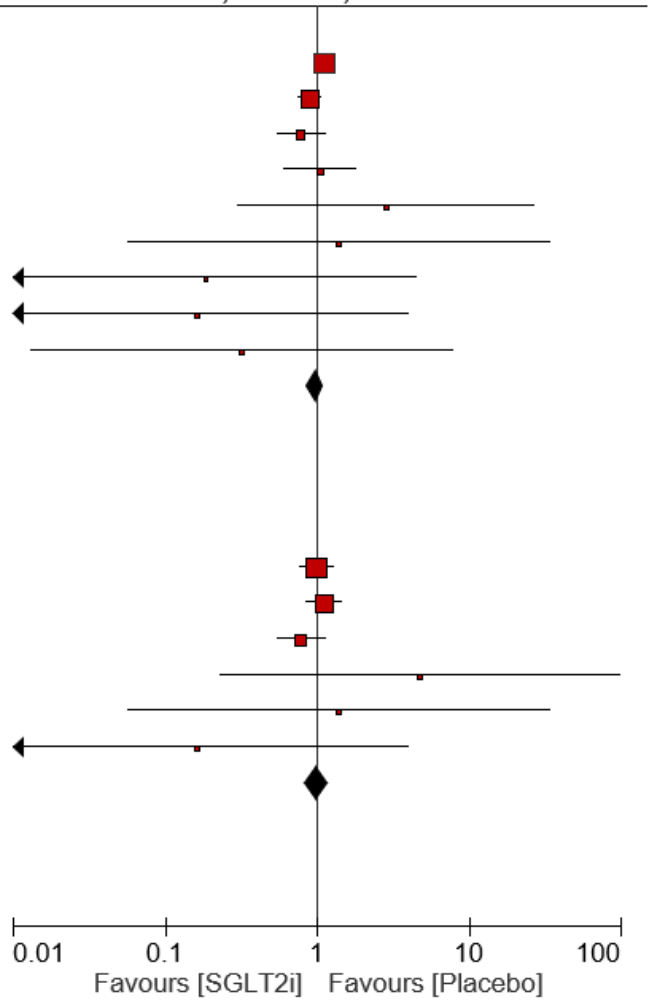
First author (year)	Name	Intervention, (mg)	Background treatments (%)	No	Age (y)	Male (%)	Median follow-up (w)	HbA1C (%)	Duration of diabetes (y)	History of retinopathy (%)
Zinman[4] (2015)	EMPA-REG OUTCOME	Empagliflozin, 10/25	Insulin(48.2);Sulphonylurea(42.8);Metformin(74.0);TZD(4.3);GLP-1(2.8);DPP-4 (11.3);RAAS(80.7);Beta blocker(64.9); statin (77.0)	7020	63	71.5	161.8	8.1	≤5 y 18.0%; >5 to 10 y 24.9%; >10 y 57.1%	22.0
Neal[5] (2017)	CANVAS Program	Canagliflozin, 100/ 300	Insulin(50.2);Sulphonylurea (43.0); Metformin (77.2); TZD (4.9); GLP-1 (4.0); DPP-4 (12.4); Antithrombotic (73.6); RAAS (80.0);Beta blocker(53.5);statin (74.9)	10142	63	64.2	126.1	8.2	13.5	21.0
Perkovic[6] (2019)	CREDENCE	Canagliflozin, 100	Insulin (65.5); Sulfonylurea (28.8); Metformin (57.8); GLP-1 (4.2); DPP-4 (17.1); TZD (3.1); Antithrombotic (59.6); RAAS (99.9); Beta blocker (40.2); statin (69.0)	4401	63	66.1	136.7	8.3	15.8	42.8
Wiviott[7] (2019)	DECLARE-TIMI 58	Dapagliflozin, 10	Insulin (40.9); Sulphonylurea (42.7); Metformin (82.0); TZD (0); GLP-1 (4.4); DPP-4 (16.8); Antiplatelet agents (61.1); RAAS (81.3); Beta blocker (52.6%) ; statin/ezetimibe (75.0)	17160	64	62.6	219.2	8.3	11.0	NR
Kashiwagi[8] (2015-1)	EMIT	Ipragliflozin, 50	Sulphonylurea (100);RAAS(NR);Beta blocker (NR); statin/ezetimibe (NR)	245	60	65.8	24.0	8.4	10.5	NR
Kashiwagi[9] (2015-2)	SPOTLIGHT	Ipragliflozin, 50	Pioglitazone (100); RAAS (NR); Beta blocker (NR); statin/ezetimibe (NR)	152	56	74.2	24.0	8.3	6.8	NR
Inagaki[10] (2016)	NR	Canagliflozin, 100	Insulin (100); RAAS (NR); Beta blocker (NR); statin/ezetimibe (NR)	146	58	63.7	16.0	8.9	13.8	41.8
Yang[11] (2016)	NR	Dapagliflozin, 5/10	Metformin (100); RAAS (NR); Beta comblocker(NR);statin/ezetimibe(NR)	444	54	54.3	24.0	8.1	4.9	NR
Yang[12] (2018)	NR	Dapagliflozin, 10	Insulin (100); Sulfonylurea (11.0); Metformin (45.2); TZD (4.0); GLP-1 (NR);	272	58	47.8	24.0	8.5	12.5	NR

								DPP-4 (5.5); RAAS (NR); Beta blocker (13.6); statin/ezetimibe (NR);	

Abbreviations: w, week; y, year; NR, not reported; TZD, Thiazolidinedione ; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4 ; RAAS, renin angiotensin aldosterone system; CANVAS and CANVAS-R indicates CANagliflozin cardioVascular Assessment Program; CREDENCE, The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation Trial; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events Trial; EMPA-REG Outcome, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 diabetes Mellitus; EMIT study, A Study to Assess the Efficacy and Safety of ASP1941 in Combination With Sulfonylurea in Type 2 Diabetic Patients; SPOTLIGHT, A Study to Assess the Efficacy and Safety of ASP1941 in Combination With Pioglitazone in Type 2 Diabetic Patients; a Participants are included in the intention-to-treat analysis

Figure 1. Effects of SGLT-2 inhibitors on eye-related adverse events and retinopathy for patients with type 2 diabetes.

Study or Subgroup	Number of events (events per 1000 pt-yrs) SGLT2i	Placebo	Weight	Risk Ratio IV, Random, 95% CI
Eye AEs				
CANVAS Program	509(30.5)	229(21.6)	43.3%	1.11 (0.95, 1.30)
CREDENCE	236(50.0)	257(56.4)	38.3%	0.89 (0.75, 1.06)
EMPA-REG OUTCOME	76(5.6)	48(7.3)	12.1%	
DECLARE-TIMI 58	26(0.9)	25(0.8)	5.6%	1.04 (0.60, 1.80)
Inagaki 2016	3(130.4)	1(45.9)	0.4%	2.84 (0.30, 26.67)
Kashiwagi 2015 (1)	0(0)	1(40.3)	0.2%	1.37 (0.06, 33.33)
Kashiwagi 2015 (2)	1(13.2)	0(0)	0.2%	0.19 (0.01, 4.51)
Yang 2016	0(0)	1(16.3)	0.2%	0.16 (0.01, 3.96)
Yang 2018	0(0)	1(15.0)	0.2%	0.32 (0.01, 7.76)
Overall (95% CI)			**100.0%**	**0.97 (0.85, 1.11)**
I^2 = 10% ; $P_{heterogeneity}$ = 0.35				
P = 0.65				
Retinopathy				
CREDENCE	116(23.7)	14(24.0)	40.7%	0.99 (0.77, 1.28)
CANVAS Program	185(10.4)	81(7.3)	37.7%	1.11 (0.85, 1.45)
EMPA-REG OUTCOME	76(5.6)	48(7.3)	20.8%	0.78 (0.54, 1.12)
Inagaki 2016	3(130.4)	1(45.9)	0.3%	4.74 (0.23, 96.98)
Kashiwagi 2015 (1)	1(13.2)	0(0)	0.3%	1.37 (0.06, 33.33)
Yang 2016	0(0)	1(15.0)	0.3%	0.16 (0.01, 3.96)
Overall (95% CI)			**100.0%**	**0.98 (0.84, 1.16)**
I^2 = 0% ; $P_{heterogeneity}$ = 0.45				
P = 0.85				



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297 SGLT-2i, sodium-glucose co-transporter 2 inhibitor; CI, confidence interval; AEs, adverse events; EMPA-REG Outcome, Empagliflozin Cardiovascular Outcome Event Trial in
298 Type 2 diabetes Mellitus Patient; CANVAS Program, Canagliflozin Cardiovascular Assessment Program ; CREDENCE, The Canagliflozin and Renal Endpoints in Diabetes with
299 Established Nephropathy Clinical Evaluation; DECLARE-TIMI 58, Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes; †Eye-related AEs/retinopathy are based on
300 on-treatment analysis. ‡ Hazard ratios were available in CANVAS Program, CREDENCE and EMPA-REG Outcome, with Hazard ratios treated as Risk ratios for the meta-analysis.
301 Risk Ratios of other included studies are calculated.
302

SUPPLEMENTARY APPENDIX

Figure S1. Identification of eligible studies: flow diagram.

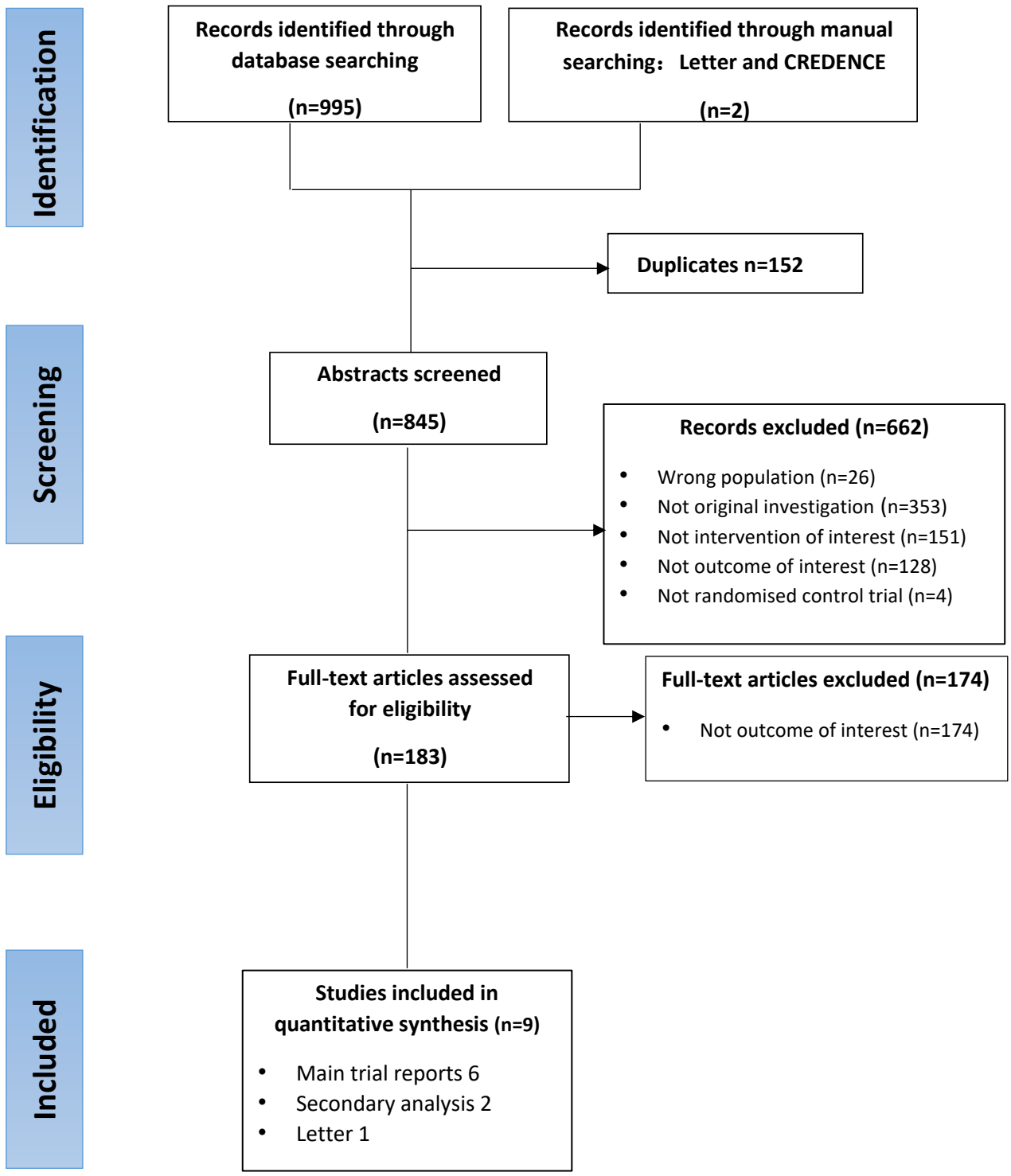


Table S1.Search strategy

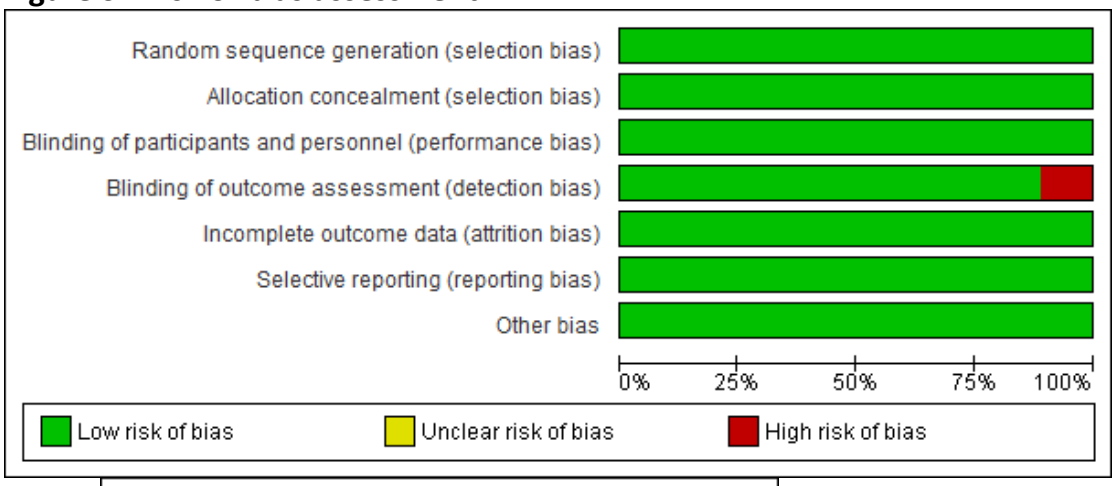
Embase via Ovid

1. exp sodium glucose cotransporter 2 inhibitor/
2. Sodium-Glucose Transporter$.tw.
3. Sodium-Glucose Co-Transporter$.tw.
4. SGLT2.tw.
5. SGLT-2.tw.
6. Sodium-dependent glucose cotransporter$.tw.
7. (dapagliflozin$ or canagliflozin$ or ipragliflozin$ or tofogliflozin$ or empagliflozin$ or sergliflozin$ or remogliflozin$ or ertugliflozin$ or luseogliflozin$ or sotagliflozin).tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp non-insulin dependent diabetes mellitus/
10. 8 and 9
11. exp clinical trial/
12. exp randomization/
13. exp single blind procedure/
14. exp double blind procedure/
15. (random$ adj5 trial$).tw.
16. (random$ adj5 allocation$).tw.
17. (blind$ adj5 method$).tw.
18. 11 or 12 or 13 or 14 or 15 or 16 or 17 (1743115)
19. 10 and 18
20. limit 19 to (human and English language)
21. exp placebo/
22. 20 and 21

Medline via Ovid

1. exp Sodium-Glucose Transporter 2 Inhibitors/
2. Sodium-Glucose Transporter$.tw.
3. Sodium-Glucose Co-Transporter$.tw.
4. SGLT2.tw.
5. SGLT-2.tw.
6. Sodium-dependent glucose cotransporter$.tw.
7. (dapagliflozin$ or canagliflozin$ or ipragliflozin$ or tofogliflozin$ or empagliflozin$ or sergliflozin$ or remogliflozin$ or ertugliflozin$ or luseogliflozin$ or sotagliflozin).tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Diabetes Mellitus, Type 2/
10. 8 and 9
11. exp Clinical Trial/
12. exp Random Allocation/
13. exp Single-Blind Method/
14. exp Double-Blind Method/
15. (random$ adj5 trial$).tw.
16. (random$ adj5 allocation$).tw.
17. (blind$ adj5 method$).tw.
18. 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 10 and 18
20. limit 19 to (English language and humans)
21. exp Placebos/
22. 20 and 21

Figure S2 Risk of bias assessment



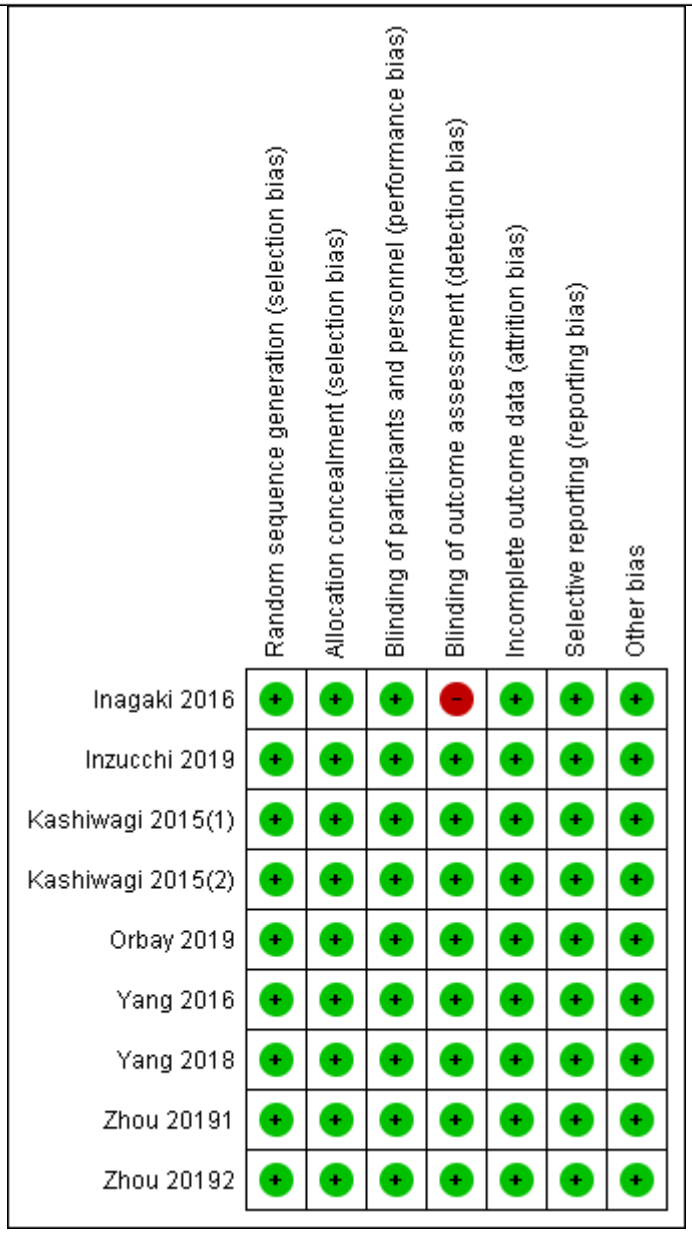
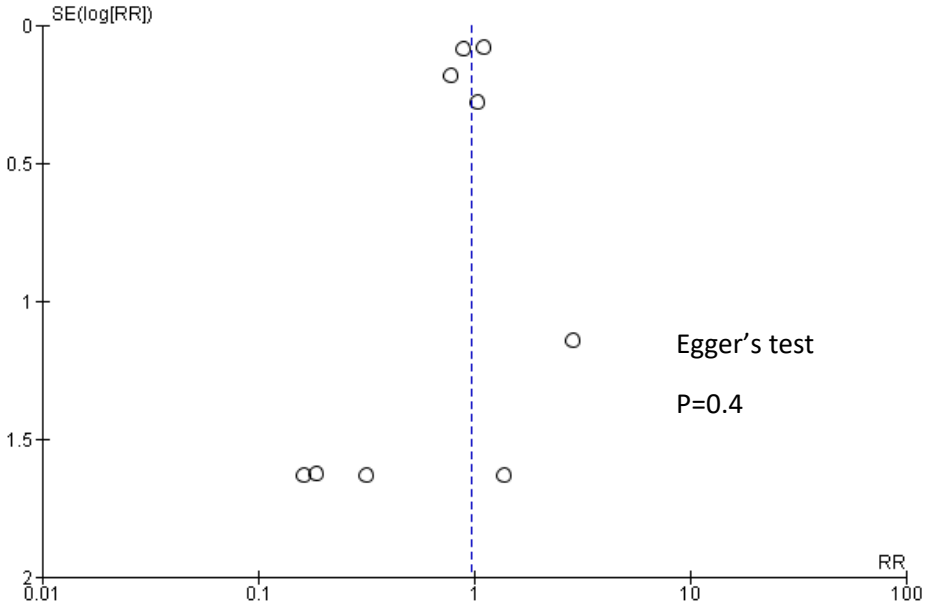


Figure S3 Assessment of publication bias on eye-related adverse events and retinopathy events by funnel plot.

A. Eye-related adverse events



B Retinopathy events

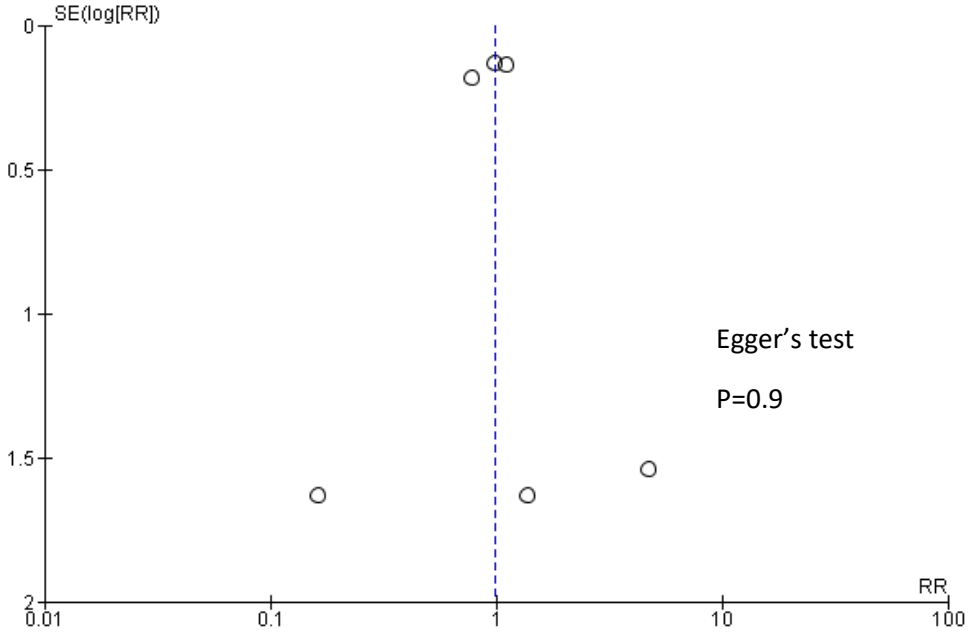
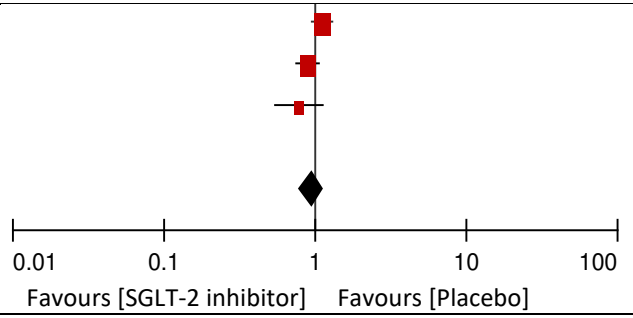


Figure S5. Sensitivity analysis for eye-related AEs due to those studies reporting HRs

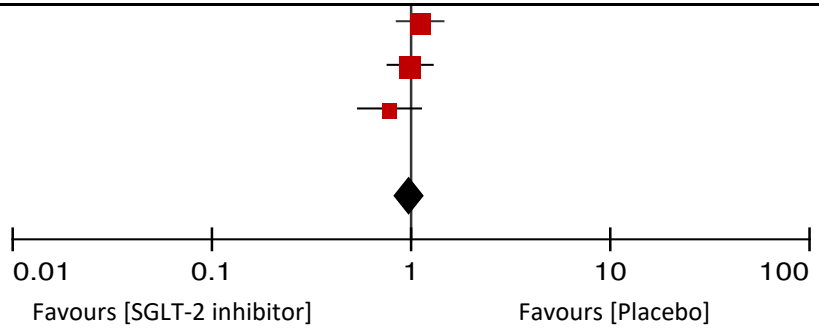
Study or Subgroup	Number of events (event per 1000 pt-yrs) SGLT-2i	Placebo	weight	Hazard Ratio IV,Random, 95% CI
CANVAS Program	509(30.5)	229(21.6)	41.50%	1.11[0.95, 1.30]
CREDENCE	236(50)	257(56.4)	39.30%	0.89[0.75, 1.06]
EMPA-REG OUTCOME	76(5.6)	48(7.3)	19.10%	0.78[0.54, 1.12]
Overall	**821**	**534**	**100.00%**	**0.95[0.78, 1.16]**
I^2 = 62%; $P_{heterogeneity}$=0.07;				P = 0.61



Random effect with inverse variance weighing. Hazard ratios are shown for Empagliflozin Cardiovascular Outcome Event Trial in Type 2 diabetes Mellitus Patient (EMPA-REG Outcome), Canagliflozin Cardiovascular Assessment Program(CANVAS Program) and The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) Total eye adverse events are shown for other included studies. SGLT-2i, sodium-glucose co-transporter 2 inhibitor; CI, confidence interval.

Figure S6 Sensitivity analysis retinopathy events due to those studies reporting HRs

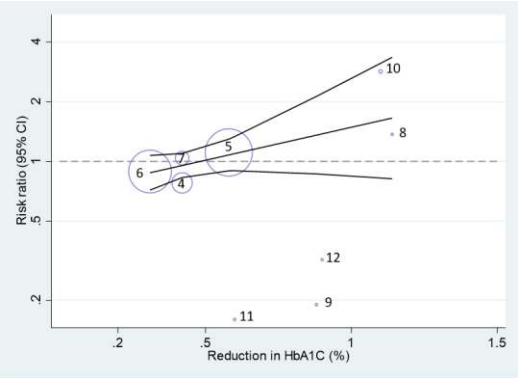
Study or Subgroup	Number of events (event per 1000 pt-yrs) SGLT2i	Placebo	weight	Hazard Ratio IV,Fixed, 95% CI
CANVAS Program	185(10.4)	81(7.3)	37.6%	1.11(0.85, 1.45)
CREDENCE	116(23.7)	114(24)	39.8%	0.99(0.77, 1.29)
EMPA-REG OUTCOME	76(5.6)	48(7.3)	22.5%	0.78(0.54-1.12)
Overall	**377**	**243**	**100.0%**	**0.98[0.82, 1.17]**
I^2 = 16%; $P_{heterogeneity}$=0.30;				*P*=0.86



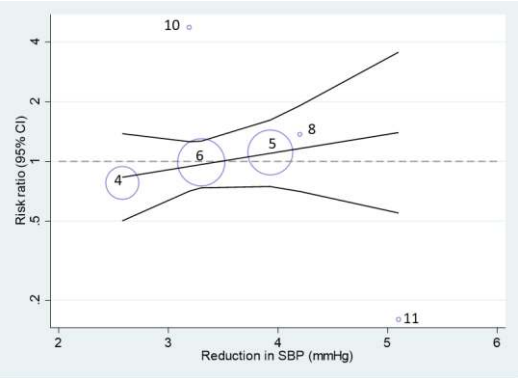
Hazard ratios are shown for Empagliflozin Cardiovascular Outcome Event Trial in Type 2 diabetes Mellitus Patient (EMPA-REG Outcome), Canagliflozin Cardiovascular Assessment Program(CANVAS Program) and The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE). Diabetic retinopathy adverse events are shown for other included studies. SGLT-2i, sodium-glucose co-transporter 2 inhibitor; CI, confidence interval.

Figure S7. Meta-Regression of Selected Trial Characteristics and Individual Trial Risk Ratios for Eye-related Adverse Events (AEs) and Retinopathy Events

A. Eye-related AEs and reduction in HbA1C

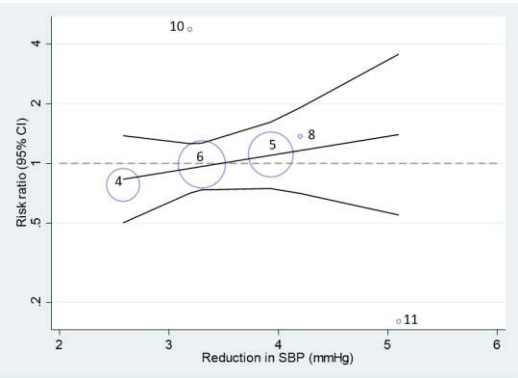


B. Retinopathy events and reduction in HbA1C

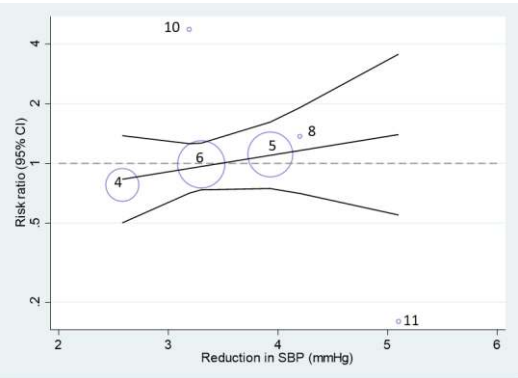


A. Meta-regression of risk ratio (RR) for eye-related AEs according to reduction in Haemoglobin A1C(HbA1C) with regression coefficient of 0.65 [95% CI, -0.65 to 1.94];*P* = .28[4-12].B. Meta-regression of RR for retinopathy events according to reduction in HbA1C with regression coefficient of 0.36 [95% CI, -2.55 to 3.27];*P* = .75.[4,5,6,8,10,11] Effects of SGLT-2 inhibitor on reduction in HbA1C were assessed with the use of mixed models in sdudies;[4-6] fixed model in sdudies;[8,10,11] least-squares in study;[7,10] unknown in study.[12]

C. Eye-related AEs and reduction in SBP

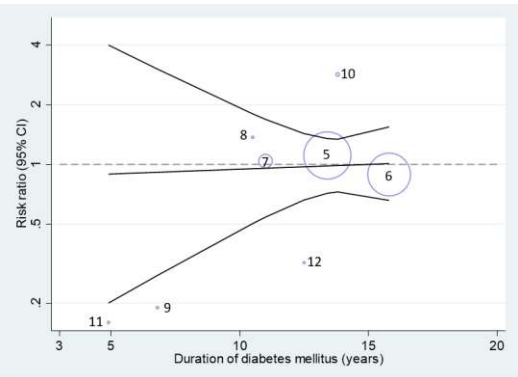


D. Retinopathy events and reduction in SBP

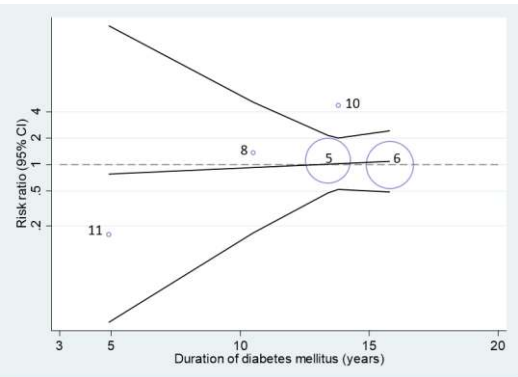


C. Meta-regression of RR for eye-related AEs according to reduction in systolic blood pressure (SBP) with regression coefficient of 0.21 [95% CI, -0.07 to 0.48];*P* = .12[4-12].D. Meta-regression RR for retinopathy events according to reduction in SBP with regression coefficient of 0.20 [95% CI, -0.23 to 0.62];*P* = .27.[4-6,8,10,11] Effects of SGLT-2 inhibitor on magnitude of reduction in SBP were assessed with the use of mixed models in sdudies;[4-6] fixed model in sdudies;[8,9,11] least-squares in study;[7,10] unknown in study.[12]

E. Eye-related AEs and duration of DM

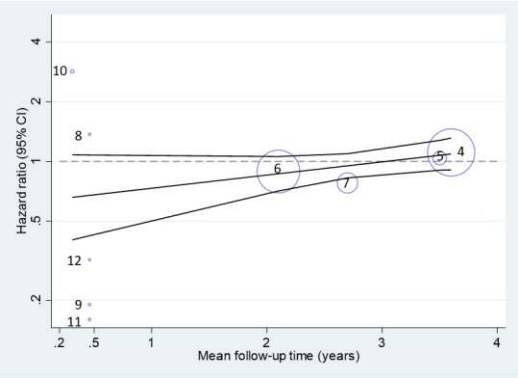


F. Retinopathy events and duration of DM

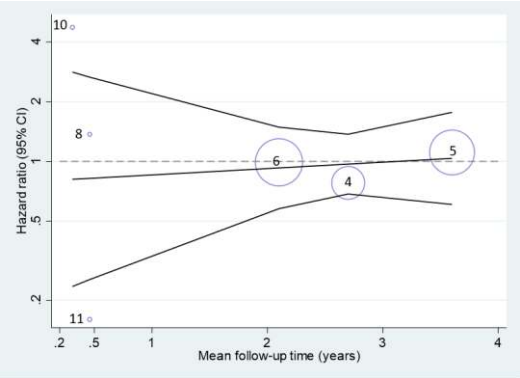


E. Meta-regression of RR for eye-related AEs according to duration of DM with regression coefficient of 0.01 [95% CI, -0.13 to 0.14];*P* = .91.[5-7,8-12] F. Meta-regression RR for retinopathy events according to duration of DM with regression coefficient of 0.01 [95% CI, -0.21 to 0.23];*P* = .87.[5,6,8,10,11]

G. Eye-related AEs and mean follow-up time

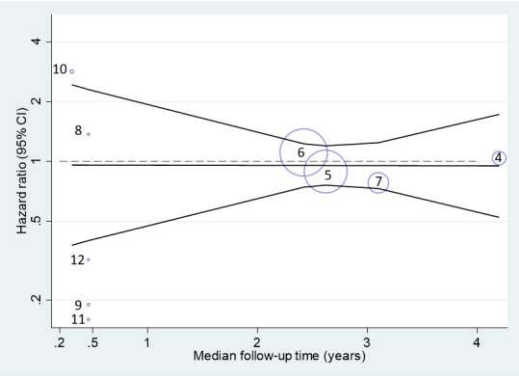


H. Retinopathy events and mean follow-up time

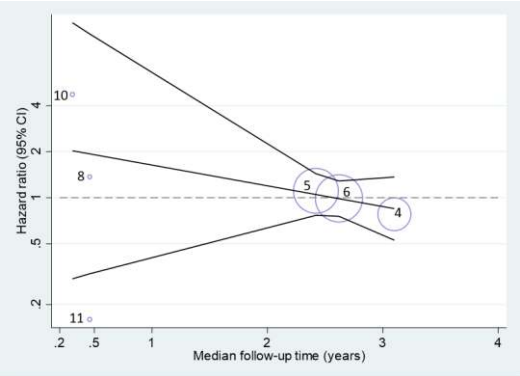


G. Meta-regression of RR for eye-related events according to mean follow-up time with regression coefficient of 0.16 [95% CI, -0.04 to 0.36];*P* = .0.10.[4-12] H. Meta-regression RR for retinopathy events according to mean follow-up time with regression coefficient of 0.13 [95% CI, -0.34 to 0.60];*P* = .49.[4-6,8,10,11]

I. Eye-related AEs and median follow-up time

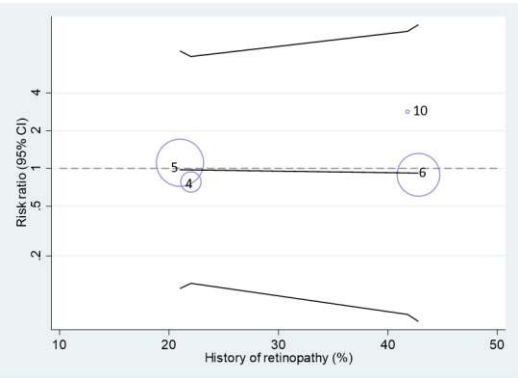


J. Retinopathy events and median follow-up time

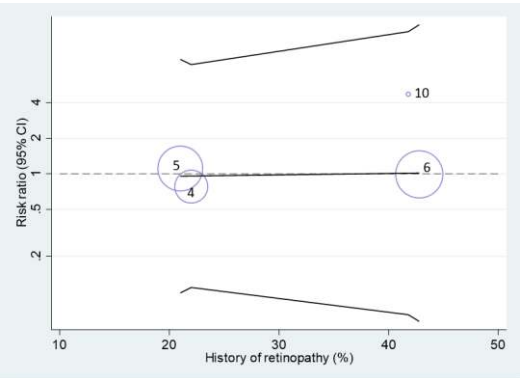


I. Meta-regression of RR for eye-related AEs according to median follow-up time with regression coefficient of 0.04 [95% CI, -0.35 to 0.43];*P* = .0.83.[4-12] J. Meta-regression RR for retinopathy events according to median follow-up time with regression coefficient of 0.22 [95% CI, -0.91 to 0.48];*P* = .0.43.[4-6,8,10,11]

K. Eye-related AEs and history of retinopathy

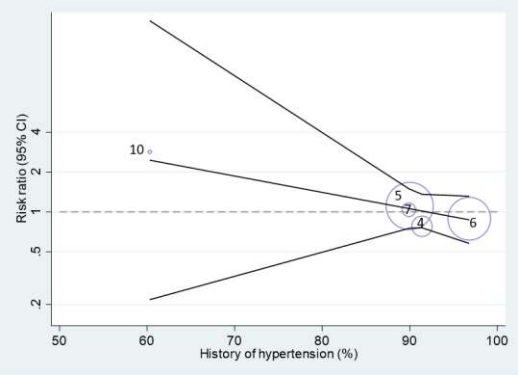


L. Retinopathy events and history of retinopathy

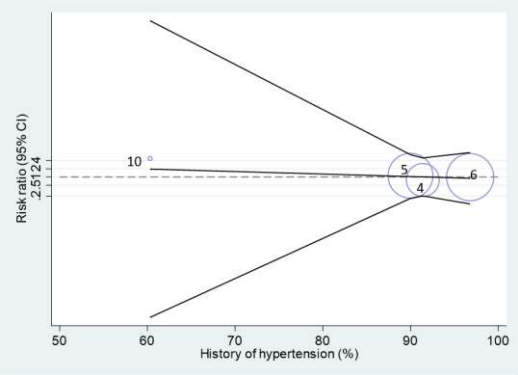


K. Meta-regression of RR for eye-related AEs according to history of retinopathy with regression coefficient of -0.01 [95% CI, -0.06 to 0.05];*P* = .78.[4-6,10] L. Meta-regression RR for retinopathy events according to history of retinopathy with regression coefficient of -0.002 [95% CI, -0.05 to 0.06];*P* = .91.[4-6,10]

M. Eye-related AEs and history of hypertension

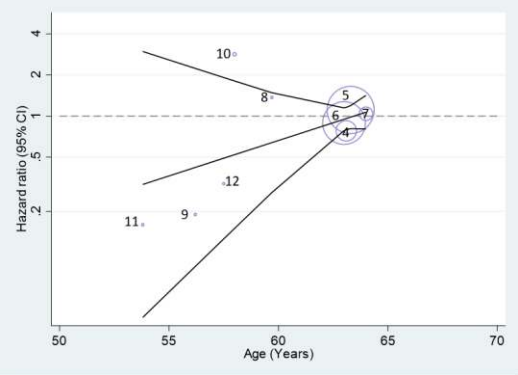


N. Retinopathy events and history of hypertension

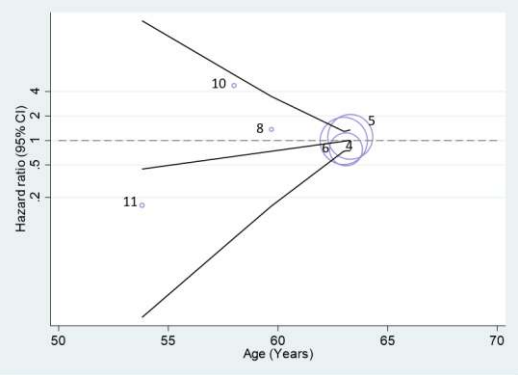


M. Meta-regression of RR for eye-related AEs according to history of hypertension with regression coefficient of -0.02[95% CI, -0.12 to 0.071];*P* = .50.[4-7,10] N. Meta-regression RR for retinopathy events according to history of hypertension with regression coefficient of 0.001 [95% CI, -0.20 to 0.20];*P* = .98.[4-6,10]

O. Eye-related AEs and age at baseline

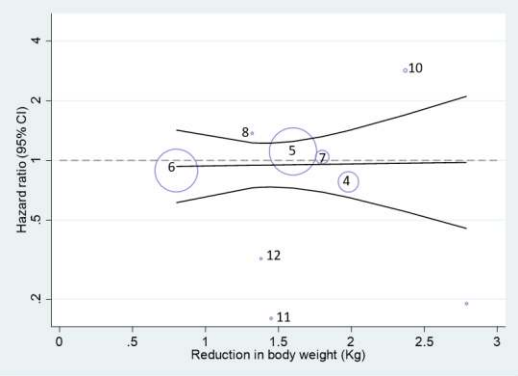


P. Retinopathy events and age at baseline

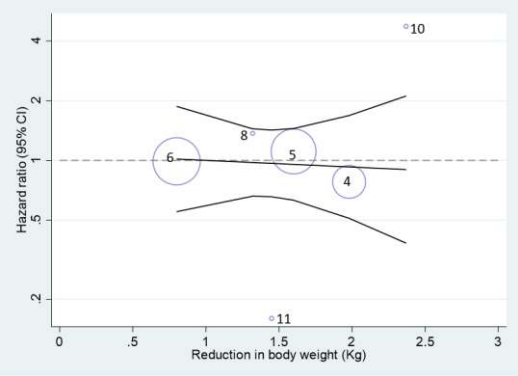


O. Meta-regression of RR for eye-related AEs according to age at baseline with regression coefficient of 0.11 [95% CI, -0.09 to 0.31];*P* = .25[4-12]. P. Meta-regression RR for retinopathy events according to age at baseline with regression coefficient of 0.10 [95% CI, -0.20 to 0.39];*P* = .43.[4-6.10,10,11]

Q. Eye-related AEs and reduction in weight

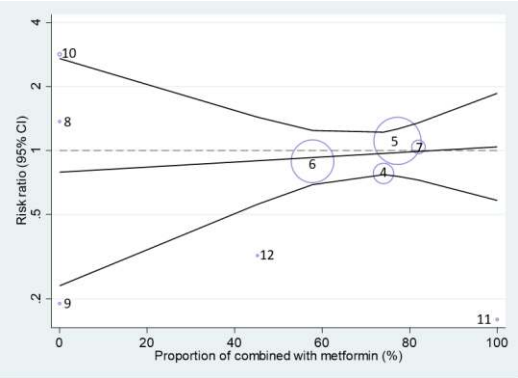


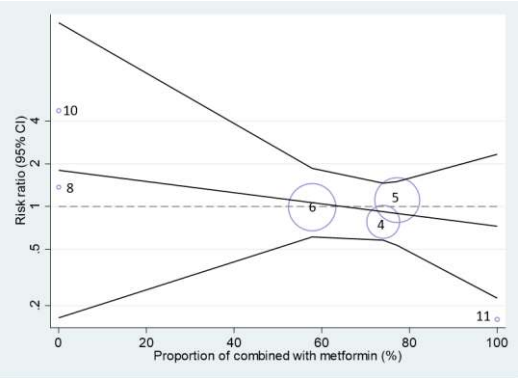
R. Retinopathy events and reduction in weight



Q. Meta-regression of RR for eye-related AEs according to weight with regression coefficient of -0.02 [95% CI, -0.53 to 0.49];*P* = .93.[21-29] R. Meta-regression RR for retinopathy events according to weight with regression coefficient of -0.12 [95% CI, -0.77 to 0.52];*P* = .62.[21,22,24,25,27,28]

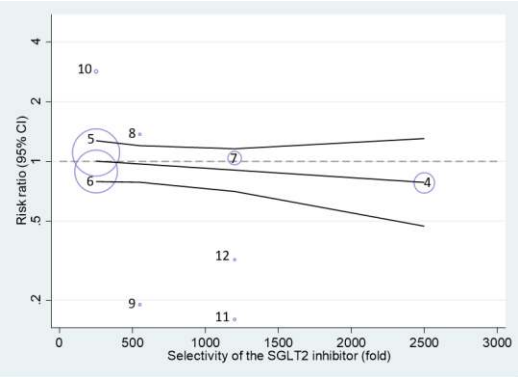
S. Eye-related AEs and proportion of metformin at baseline T. Retinopathy and proportion of metformin at baseline

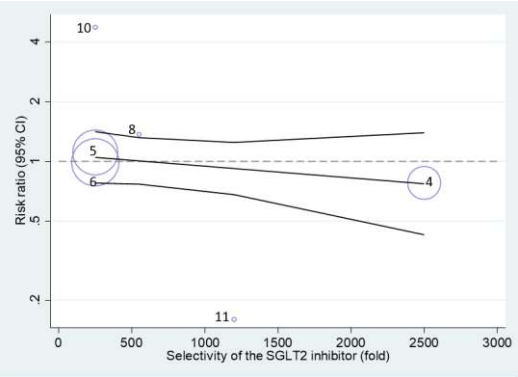




S. Meta-regression of RR for eye-related events according to proportion of combined with metformin with regression coefficient of 0.01 [95% CI, -0.01 to 0.02];*P* = .46.[4-12] T. Meta-regression RR for retinopathy events according to proportion of combined with metformin with regression coefficient of -0.01 [95% CI, -0.04 to 0.03];*P* = .75.[4-6,8,10,11]

U. Eye-related AEs and selectivity of the SGLT2 inhibitor V. Retinopathy and selectivity of the SGLT2 inhibitor





U. Meta-regression of RR for eye-related events according to the selectivity of SGLT2 inhibiotor with regression coefficient of -0.0001 [95% CI, -0.0003 to 0.0001];*P* = .35.[4-12] T. Meta-regression RR for retinopathy events according to the selectivity of SGLT2 inhibiotor with regression coefficient of -0.0001 [95% CI, -0.0003 to -0.0001];*P* =.21.[4-6,8,10,11]

Eye-related AEs was a composite of (1) blindness; (2) retinopathy; (3) macular oedema; (4) vitreous abnormality comprising vitreous haemorrhage or detachment; (5) cataract; (6) glaucoma; (7) requirement for retinal photocoagulation therapy, intravitreal treatment, vitrectomy for no clearing vitreous haemorrhage or tractional detachment of retina, or other eye-related surgery; (8) other ocular complications comprising anterior ischemic optic neuropathy, papilloma, iris rubeosis, ocular movement disorders, corneal oedema, nerve alterations neurotropic ulcers, retinal artery or retinal vein occlusion, retinal arteriolar emboli or, neovascularisation; or (9) other non-specific eye-related AEs including infection, inflammation and bleeding. Retinopathy events outcome was a composite of retinopathy complications comprised of (1), (2), (3), (4) and (7) as described above. Circle sizes indicate the weight given to each study (centred on the intersection of RR for eye-related AEs (left) or retinopathy events (right) and the mean trial value of the metric of interest