Comparisons of diabetic retinopathy events associated with glucose-lowering drugs in patients with type 2 diabetes mellitus: a network meta-analysis

Running title: Glucose-lowering drugs and diabetic retinopathy risk

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ABSTRACT

Aim: To assess the comparative effects of glucose-lowering drugs (GLDs) on diabetic retinopathy (DR) risk in patients with type 2 diabetes mellitus (T2DM).

Methods: We systematically searched Cochrane Central Register of Controlled Trials, PUBMED, and EMBASE from each database's inception to January 17, 2017 to identify randomized controlled trials (RCTs) that reported DR events among the T2DM patients receiving any GLD. Random-effects pairwise and network meta-analyses were performed to calculate the odds ratios (ORs) with 95% confidence intervals (CIs).

Results: A total of 37 independent RCTs with 1,806 DR events among 100,928 patients with T2DM were included. The mean duration of diabetes was 8.7 years and mean baseline HbA1c was 8.2% (SD, 0.5%). Our network meta-analysis found that DPP-4i (OR, 1.20; 95% CI, 0.87 to1.65), GLP-1RA (OR, 1.19; 95% CI, 0.94 to1.52), and SGLT2 inhibitors (OR, 0.79; 95% CI, 0.49 to 1.28) were not associated with a higher risk of DR than placebo; however, a significantly increased risk of DR was associated with DPP-4i in the pairwise meta-analysis (OR, 1.27; 95% CI, 1.05 to 1.53). Sulfonylureas, on the other hand, were associated with a significantly increased risk of DR compared to placebo (OR, 1.67; 95% CI, 1.01 to 2.76).

Conclusions: Current evidence indicates that the association between DPP-4i, GLP-1RA, or SGLT2 inhibitors and risk of DR remains uncertain in patients with T2DM. Some evidence suggests that sulfonylureas may be associated with increased risk of DR. However, given that DR events were not systematically assessed, these effects should be explored further in large-scale, well-designed studies.

KEYWORDS

Antidiabetic drug, diabetic retinopathy, type 2 diabetes, network meta-analysis

1 **INTRODUCTION**

Diabetic retinopathy (DR) is the most common microvascular complication in patients with diabetes mellitus (DM) and the most frequent cause of blindness in adults [1-3]. Studies demonstrate that intensive glycaemic control reduces the risk of long-term complications such as retinopathy, neuropathy, and nephropathy [4-6]. Improving glycaemic control also reduces DR progression [7]. However, a recent clinical trial of semaglutide (SUSTAIN - 6) [8] showed an increased risk of developing DR and complications of DR (defined as the need for retinal photocoagulation or treatment with intravitreal agents, vitreous hemorrhage, or onset of blindness) among subjects treated with semaglutide compared to subjects on placebo. In addition, some observational studies found that use of thiazolidinediones was associated with an increased risk of diabetic macular edema (DME) [9, 10]. In contrast, a pre-clinical study showed that control of hyperglycaemia with ipragliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, slowed the progression of retinopathy, nephropathy, and neuropathy [11].

The effect of GLDs on the risk of DR remains uncertain. We therefore performed a meta-analysis of all available randomized controlled trials (RCTs) to test the effect of each class of GLDs (including dipeptidyl peptidase 4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1RA), SGLT2 inhibitors, glinides, α-glucosidase inhibitors, thiazolidinediones, sulfonylureas, metformin, insulin) on DR risk in patients with T2DM. Additionally, to distinguish the potential risk for developing DR among different classes of GLDs, we carried out this meta-analysis to evaluate the comparative safety of different classes of GLDs on risk of DR in these populations.

2 METHODS

This network meta-analysis was conducted according to the PRISMA extension statement for the reporting of systematic reviews incorporating network meta-analyses of health care interventions[12] and registered with PROSPERO (number CRD 42017057945).

2.1 Search strategy and study selection

We comprehensively searched PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Clinicaltrials.gov from inception to January 17, 2017 to identify eligible RCTs. A detailed search strategy that included electronic databases and key terms is presented in **Appendix 1**. There were no restrictions regarding the language, date, or publication. In addition, we also identified other potential trials by manually searching the reference lists of included trials and relevant meta-analyses.

Two reviewers (YZ and GL) independently selected the trials based on the following inclusion criteria: 1) RCTs that compared one or more GLDs with placebo, no treatment, or active treatments (including DPP-4i, GLP-1RA, SGLT2 inhibitors, glinides, α-glucosidase inhibitors, thiazolidinediones, sulfonylureas, metformin, and insulin). When background therapy was specified, we required the background therapy to be identical between the intervention and control groups; 2) trial durations ≥ 24 weeks; and 3) trials reporting safety outcomes of DR (DR events include DR, macular edema, vitreous hemorrhage, onset of diabetes-related blindness, and the need for treatment with an intravitreal agent or retinal photocoagulation). Authors were contacted for further information if necessary. Data from the large trials (EMPA-REG OUTCOME [13], LEADERS [14], SUSTAIN-6 [8]) showed that the incidence of DR ranged from 3 to 14.9

cases/1000 person-years. In studies with a population >1000 patients and no reported DR events, we assumed that DR events were underreported. In these cases, we contacted study authors to inquire about DR events. Six of 20 authors contacted responded back; five provided additional data, and one clarified data.

2.2 Data extraction and quality assessment

Two reviewers (YZ and GL) independently extracted data from original trial reports using a standardized form. Data extracted included study characteristics (first author, publication year, NCT number, and duration of follow-up) and characteristics of patients (inclusion criteria, background treatments, mean age, proportion of men, duration of T2DM, baseline HbA1c%, and body mass index [BMI]), any GLD, comparators, and the incidence of DR). If multiple reports from the same population were retrieved, only the most complete and/or most recently reported data were used. If DR events were not reported in the manuscripts, we extracted the data from the "Serious Adverse Events" section on ClinicalTrials.gov. When both the publication and the clinicalTrials.gov of the same trial reported DR event, but data were not consistent, we contacted the authors for verification.

Study quality was assessed by two reviewers using the Cochrane risk of bias tool as described in the Cochrane Collaboration Handbook [15]. In cases of disagreement, a third reviewer (TW) was consulted to reach a consensus. We assessed the risk of bias based on the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). We generated the risk of bias graphs with the Review Manager 5.3 software, with each domain judged as low risk, high risk, or unclear risk.

2.3 Statistical analysis

Direct meta-analysis was carried out using Mantel-Haenszel's method with random effects models to calculate the odds ratio (ORs) and 95% confidence intervals (CIs) for direct comparisons between therapeutic regimens. Statistical heterogeneity was assessed using the I^2 statistic, with I^2 of < 25%, ≥ 25 and < 75% , and ≥ 75% indicating low, medium, and high heterogeneity, respectively [16]. For the comparisons including more than ten trials, publication bias was evaluated with funnel-plot symmetry and using the Egger regression. A sensitivity analysis using the person-years was performed to test the robustness of the results.

For indirect and mixed comparisons, a network meta-analysis with a random-effects model using the "mvmeta" command and programmed STATA routines was used to calculate the ORs and 95% CIs between different interventions [17, 18]. For zero-event RCTs, a 0.5 zero-cell correction was applied before meta-analysis [19]. The relative ranking of GLDs on DR events was assessed by using their surface under the cumulative ranking curve (SUCRA), which represents their likelihood of being ranked safest. In this study, larger SUCRA probabilities indicate lower risk of DR events [20]. The heterogeneity variance (tau) estimated by a restricted maximum likelihood method was employed to investigate between-study heterogeneity in the network meta-analysis [21].To check for the presence of inconsistency, a loop inconsistency–specific approach was introduced to evaluate the difference between direct and indirect estimates for a specific comparison [22].To check the assumption of consistency in the entire network, a designby-treatment interaction model using the $\chi 2$ test was used [23]. Finally, a comparison-adjusted funnel plot was used to assess small study effects within a network of interventions [24].

We performed a regression analysis to examine the relationship between trial characteristics and effect size by using the following factors: duration of diabetes, difference in glycaemic control change between groups, the absolute glycaemic control achieved in the experimental treatment group, and baseline systolic blood pressure. All meta-analyses were performed with STATA (Version 14; Stata Corp., College Station, TX) and SAS version 9.4 (SAS Institute, Cary, NC). A two-tailed $P < 0.05$ was considered statistically significant.

3 RESULTS

3.1 Study selection and Study characteristics

Figure 1 shows the process of identifying eligible trials. We retrieved 11,428 studies through our electronic search and selected 1,692 potential trials. Eight months after our formal search, the results of the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) were published in September 2017 [57]. We incorporated data from this large trial, and our final analysis included 36 manuscripts involving 37 trials [13, 14, 25-57] (**Figure 1**). These included 34 two-group trials, 2 three-group trials [45, 47], and 1 four-group trial [56]. The available direct comparisons and network of trials are shown in **Figure 2**.

We summarize the study characteristics in **Table 1 and Appendix 2**. A total of 100,928 patients with T2DM from 37 independent trials were randomly assigned to a GLD or placebo. A total of 1,806 DR events were reported. Mean sample size was 2,728 (range: 257 - 16,492), and the mean duration of follow-up ranged between 0.5-5.5 years (median, 1.5, interquartile range: 0.8-3.0). Participants were generally middle-aged (mean age: 58.3 years), with a mean diabetes duration of 8.7 years (interquartile range, 6.2-11.4 years), and a mean baseline HbA1c level is 8.2% (SD, 0.5%). Mean baseline and end-of-study HbA1c% values are presented in **Appendix 3**.

The risk of bias for the 37 RCTs is summarized as follows (**Appendix 4**): A total of 19 RCTs reported adequate random sequence generation, and 23 RCTs reported adequate allocation concealment. Masking conditions were high in 6 RCTs, and 3 RCTs were judged as high risk for incomplete outcome data due to high loss to follow-up (24.0%, 34.4%, and 44.8%, respectively). Only two trials that predefined and adjudicated DR events had a low risk of other bias [8, 14].

3.2 Pairwise meta-analysis

Results of pairwise meta-analysis are presented in **Appendix 5**. DPP-4i were associated with a significantly increased risk of DR events as compared with placebo (OR, 1.27; 95% CI, 1.05 to 1.53) (**Table 2**). However, there were no significant differences found with GLP-1RA and SGLT2 inhibitors compared with placebo (OR, 1.15; 95% CI, 0.93 to 1.43) and (OR, 0.78; 95% CI, 0.54 to 1.12), respectively (**Table 2**). No statistically significant difference was observed in other head-to-head comparisons; effect estimates are imprecise due to the low number of events (including 0 events in some trials). Overall, there was no evidence of significant heterogeneity observed, with one exception found between SGLT2 inhibitors and sulfonylureas (I^2 =

69.1%). A sensitivity analysis using the numbers of person-years indicated all results were consistent (**Appendix 6**). There was no evidence of publication bias in the comparison of GLP-1RA and placebo, based on Egger's test (P = 0.67), Begg's test (P = 0.63) and visual inspection of the funnel plot (**Appendix 7)**.

3.3 Network meta-analysis

In the network meta-analysis (**Appendix 8**), sulfonylureas were associated with a significantly increased risk of DR as compared with both placebo (OR, 1.67; 95% CI, 1.01 to 2.76) and SGLT2 inhibitors (OR, 2.11; 95% CI, 1.07 to 4.17) (**Table 2**). There was no significant difference between DPP-4i (OR, 1.20; 95% CI, 0.87 to 1.65) or GLP-1RA (OR, 1.19; 95% CI, 0.94 to 1.52) and placebo. Consistent with the results from pairwise meta-analysis, the risk of DR in SGLT2 inhibitors was similar to placebo (OR, 0.79; 95% CI, 0.49 to 1.28). We generated hierarchies of treatment effects based on the SUCRA probabilities (**Appendix 9**). SGLT2 inhibitors were associated with the lowest probability for DR complications (SUCRA, 90.6%), followed by GLP-1RA (SUCRA, 59.6%), DPP-4i (SUCRA, 58.8%), insulin (SUCRA, 55.4%), thiazolidinediones (SUCRA, 41.9%), glinides (SUCRA, 36.3%), metformin (SUCRA, 33.7%), sulfonylureas (SUCRA, 30.9%), and α-glucosidase inhibitors (SUCRA, 12.9%). There was low between-study heterogeneity (tau ≈ 0.18), no inconsistency between direct and indirect estimates (all 95%CIs across zero) (**Appendix 10**), and no global inconsistency within any network (P = 0.80). In addition, the comparison-adjusted funnel plot indicated the absence of small-study effects (**Appendix 11**).

3.4 Regression analysis

In the multivariate regression of 11 trials (studies with missing variables were excluded from the multivariate regression), none of the pre-specified factors were found to be significant (**Appendix 12**). In the univariate regression of 22 trials, the risk of DR was associated with difference in HbA1c% change between groups (P = 0.04) (**Figure 3**).

4 DISCUSSION

Our study is the first network meta-analysis to address the safety of GLDs on DR events. We included 37 RCTs that reported 1,806 events among 100,928 patients with T2DM. In the network meta-analysis based on the direct and indirect evidence, we found that the risks of DR events in both DPP-4i and GLP-1RA were similar to placebo. However, in the pairwise meta-analysis, there was a significantly increased risk of DR associated with DPP-4i alone. There was also no significant association found between SGLT2 inhibitors and the risk of DR. In contrast, sulfonylureas were associated with a significantly increased risk of DR compared to placebo and SGLT2 inhibitors. Our univariate regression showed the difference in HbA1c% change between groups might be associated with DR risk (that is the greater reduction in HbA1c%, the lower the risk of DR). This finding is consistent with the current evidence [7, 58] and confirms the importance of achieving good glycaemic control to reduce the risk of DR. However, none of these pre-specified factors were found to significant in the multivariate regression. This might be due in large part, to the limited number of trials included in our meta-analysis.

In contrast to the results from SUSTAIN - 6 [8] and TECOS [25], the results from our network meta-analysis found no significant increase in the risk of DR in patients taking

DPP-4i or GLP-1RA, although an increased risk of DR associated with DPP-4i was detected in the pairwise meta-analysis, which was largely driven by TECOS [25]. Recent evidence about the effects of incretin therapies on the microcirculation is scarce. Preclinical data demonstrated beneficial pleiotropic effects of incretin therapies in DR, independent of the glucose-lowering effect by reducing blood–retinal barrier breakdown, inflammation, and neuronal cell death [59-62]. Topical administration of DPP-4i was shown to prevent neurodegeneration and vascular leakage in db/db mice by enhancing GLP-1[63]. The results in patients with T2DM remains inconsistent. In two small clinical studies, DPP-4i (saxagliptin and vildagliptin) were found to reduce retinal capillary blood blow and improve vasodilation [64, 65]. In contrast, some GLP-1RA (liraglutide and exenatide) and DPP-4i (sitagliptin) had no effect on capillary perfusion in patients with T2DM [66]. Although some experimental studies and small clinical trials indicated overall beneficial effects on the development of DR with GLP-1RA and DPP-4i, this is balanced by evidence of progressive worsening or a net neutrality of these agents on DR [67]. Varadhan et al., found a progressive worsening of DR in patients treated for at least 6 months with exenatide [68].The authors suggested that the worsening of DR might be due to the sudden and substantial reduction in HbA1c levels (initial HbA1c decrease of ≥ 1.5%) caused by treatment [69] and subsequently found this effect to be transient and continued therapy with exenatide was associated with a reversal of this phenomenon [68]. Several possible reasons to account for this observed phenomenon may lie in the short follow-up. Generally, five years is considered sufficient time to separate the incidence of DR between intervention and control groups [67]. However the median duration of follow-up of the included RCTs was 1.5 years (range: 0.5 - 5.5 years). Finally, lack of data on the grading of DR at baseline and during the follow-up were reported in the clinical trials [67]. Further studies are required to clarify the risk of DR associated with DPP-4i or GLP-1RA.

Our meta-analysis found SGLT2 inhibitors were similar to placebo in the risk of DR. However, SGLT2 inhibitors were associated with the lowest risk among the GLDs in our network meta-analysis. Recently, a few studies explored the mechanism behind the beneficial effect of SGLT2 inhibitors on DR. One small trial involving 59 patients found that dapagliflozin, 10 mg/day administered for six weeks, significantly lowered retinal capillary flow compared to little change in the placebo group [70]. In addition, dapagliflozin appeared to prevent changes to the structure of the retinal arterioles [70]. The beneficial effects of SGLT2 inhibitors may be partly due to their blockade of renin–angiotensin system [71, 72], improved glycaemic control, and reduced blood pressure. However, these results are inconclusive and require further research to explore the risk of DR associated with SGLT2 inhibitors.

Our network meta-analysis results also showed that sulfonylureas might be associated with a higher risk of DR compared to placebo, although the lower limit of the confidence interval is very close to the null. This result is inconsistent with direct evidence from the individual trials. The inconsistency might be partly due to lack of power to detect a statistical difference in the pairwise meta-analysis. In the UKPDS, each 1% reduction in HbA1c with intensive glucose therapies (sulfonylurea or insulin) was associated with a 37% reduction in the risk of retinopathy [5]. However, to our knowledge, no studies have assessed sulfonylurea monotherapy and the risk of retinopathy [73, 74]. Thus, future studies are warranted to confirm our findings.

Two previous observational studies [9, 10] found an increased risk of macular edema associated with thiazolidinedione therapy, which had considerable limitations such as a lack of duration of individual patient exposure to thiazolidinediones. Our analysis did not observe an association between DR risk and thiazolidinediones, which is consistent with the ACCORD eye study [75, 76]. Further studies are needed to examine the risk of DR for thiazolidinediones.

Our meta-analysis of 37 randomized trials has several strengths. First, we used rigorous methodology to systematically identify and synthesize data. Second, in addition to published reports, our study also included 8 trials that were not published in peer-reviewed journals, but were only identified from ClinicalTrials.gov. Third, we carefully checked the data in journal publications and clinicaltrials.gov for consistency, and contacted authors to ensure the data were accurate.

Our meta-analysis has limitations as well. Firstly, none of the included trials were systematically designed to evaluate DR events. Only 5 trials clearly predefined a DR outcome [8, 13, 14, 25, 57] and the rest may have underreported DR events. Most data for DR endpoints come from adverse event reporting rather than the trial data itself. Such limitations decrease the validity of our meta-analysis. Second, due to the short-term follow up in the included clinical trials (median, 1.5 years), there may be insufficient follow up to fully assess the incidence of DR between intervention and control groups [67]. Furthermore, since prior research suggested that a rapid reduction of HbA1c was associated with progression of microvascular disease followed by a resolution of symptoms, the current data included in our meta-analysis might overestimate this risk and underestimate the long-term overall benefits of HbA1c reduction. Third, lacking of data on grading of DR at baseline and during the trials made it difficult to calculate the actual number of new adverse events. Fewer new events of DR would be reported if a study arm contained a disproportionate number of participants with previously treated retinopathy. In our meta-analysis only 5 trials with a predefined DR outcome [8, 13, 14, 25, 57], however, the methods used to detect and report DR were not clarified. Although it is more likely that only severe DR would be reported (i.e. less severe DR like mild or moderate non-proliferative DR were probably not reported), the unclear outcome definition from the included trials might weaken our internal validity. Finally, given the limited number of studies about metformin, α-glucosidase inhibitors, SGLT2 inhibitors, glinides, thiazolidinediones, and sulfonylureas included in our meta-analysis, the risk of DR for these classes of drugs remains uncertain.

Our meta-analysis based on current evidence suggests that the DR risk associated with DPP-4i or GLP-1RA remains uncertain, while some evidence indicates that sulfonylureas may be associated with increased risk of DR. There was no significant difference between SGLT2 inhibitors and risk of DR. However, given that these events are may be underreported and DR was not systematically assessed as an endpoint, further data from large-scale, well-designed studies and real- world settings are warranted.

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Author contributions

TW designed the study. GL, and YZ identified and acquired reports of trials and extracted data. HT, GL, and TW performed all data analyses, checked for statistical inconsistency, and interpreted data. HT, GL, YZ, FW, EG, LS, and TW contributed to data interpretation. HT drafted the paper, and all other authors (GL, YZ, FW, EG, LS, and TW) critically reviewed the paper.

Declaration of conflicting interests

We declare no competing interests.

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Table1 Baseline characteristics of included randomized controlled trials

First author (year)	Study ID ClinicalTrial.gov	Name	Patients	Intervention	Control	Background treatments	Follow -up (years)	Number of patients	Age (years)	Male (%)	BMI	HbA1c (%)	Duration of diabetes (years)
Green (2015)[25]	NCT00790205	TECOS	Patients with T2DM and established cardiovascular disease; excluded patients with a history of two or more episodes of severe hypoglycemia during the preceding 12 months or eGFR was < 30 ml/min/1.73 m^2.	Sitagliptin	Placebo	one or two OADs (MET, pioglitazone, or SU) OR insulin ± MET	3.0	14671	65.5	10347 (70.7)	30.2	7.2	11.6
White (2013)[26]	NCT00968708	EXAMINE	Patients with T2DM and an acute coronary syndrome within 15 to 90 days before randomization; excluded patients with unstable cardiac disorders (e.g., New York Heart Association class IV heart failure, refractory angina, uncontrolled arrhythmias, critical valvular heart disease, or severe uncontrolled hypertension), and dialysis within 14 days before screening.	Alogliptin	Placebo	GLDs (with the exception of a DPP-4 inhibitor or GLP-1 analogue)	1.5	5380	60.9	3651 (67.9)	29.5	8.0	9.2
Owens (2011)[27]	NCT00602472		Patients with T2DM and inadequate glycemic control with MET and SU; excluded patients with myocardial infarction, stroke or transient ischaemic attack within 6 months before enrolment, impaired hepatic function, renal failure or renal impairment.	Linagliptin	Placebo	MET + SU	0.5	1055	58.1	498 (47.2)	28.3	8.1	Up to 1 year 29 (2.8) 1–5 years 249 (23.9) > 5 years 762 (73.3)
Scirica (2013)[28]	NCT01107886	SAVOR-TIMI 53	Patients with T2DM and either a history of established cardiovascular disease or multiple risk factors for vascular disease; excluded patients with end-stage renal disease and were undergoing long-term dialysis, had undergone a renal transplantation, or had a serum creatinine level > 6.0 mg/dl (530 μmol/L).	Saxagliptin	Placebo	MET or SU or TZD or insulin	2.1	16492	65.1	11037 (66.9)	31.1	8.0	10·3
Barnett (2013)[29]	NCT00757588		Patients with T2DM and inadequate glycemic control with insulin and MET; excluded patients with history of diabetic ketoacidosis or hyperosmolar nonketoticcoma, history of significant cardiovascular disease or hemoglobinopathy.	Saxagliptin	Placebo	Insulin ± MET	1.0	455	57.2	188 (41.3)	32.3	8.7	11.9
YKI-JÄRVINEN (2013)[30]	NCT00954447		Patients with T2DM and inadequate glycemic control with basal insulin, alone or in combination with metformin and/or pioglitazone, for≥12 weeks; excluded patients with a myocardial infarction, stroke, or transient ischemic attack within 6 months before informed consent; impaired hepatic function.	Linagliptin	Placebo	basal insulin ± MET ± pioglitazone	1.0	1261	60.0	658 (52.2)	31.0	8.3	Up to 1 year 26 (2.1) 1–5 years 152 (12.1) > 5 years 1057 (83.8)
Ferreira (2013)[31]	NCT00509262		Patients with T2DM and had moderate to severe chronic renal insufficiency (eGFR＜50 mL/min/1.73 m2); excluded patients with history of ketoacidosis, acute renal disease,	Sitagliptin	Glipizide	None	1.1	422	64.2	253 (59.8)	26.8	7.8	10.4

			renal transplant, liver disease, a recent (within 3 months) cardiovascular event.										
Ahrén (2013)[32]	NCT00712673	GETG OAL-M	Patients with T2DM inadequately controlled with metformin with a dose of at least 1.5 g/day for at least 3 months; history of unexplained pancreatitis, excluded patients with chronic pancreatitis, pancreatectomy, or inflammatory bowel disease, and history of metabolic acidosis.	Lixisenatide	Placebo	MET	1.5	680	54.7	293 (43.1)	32.9	8.1	6.1
Nauck (2016)[33]	NCT00849017	HARM ONY 2	Patients with T2DM inadequately controlled with diet and exercise; excluded patients with recent cardiovascular and/or cerebrovascular disease.	Albiglutide	Placebo	None	3.2	301	52.9	166 (55.1)	33.5	8.1	4.0
Pfeffer (2015)[34]	NCT01147250	ELIXA	Patients with T2DM and had an acute coronary event within 180 days before screening; excluded patients with percutaneous coronary intervention within the previous 15 days, coronary-artery bypass graft surgery for the qualifying event, planned coronary revascularization procedure within 90 days after screening, an eGFR of less than 30 ml/min/1.73 m^2 .	Lixisenatide	Placebo	MET or SU or Glinide or TZD or insulin as monothera py OR insulin + OAD OR MET + SU OR Other GLDs	2.1	6063	60.3	4207 (69.3)	30.2	7.7	9.3
Marso (2016)[14]	NCT01179048	LEADE R	Patients with T2DM and an age of 50 years or more with at least one cardiovascular coexisting condition or an age of 60 years or more with at least one cardiovascular risk factor; excluded patients with the occurrence of an acute coronary or cerebrovascular event within 14 days.	Liraglutide	Placebo	one or more OADs or insulin or a combinatio n of these agents	3.8	9340	64.3	6003 (64.3)	32.5	8.7	12.9
Marso (2016)[8]	NCT01720446	SUSTAI N-6	Patients with T2DM and an age of 50 years or more with established cardiovascular disease (previous cardiovascular, cerebrovascular, or peripheral vascular disease), chronic heart failure (New York Heart Association class II or III), or chronic kidney disease of stage 3 or higher or an age of 60 years or more with at least one cardiovascular risk factor; excluded patients with a history of an acute coronary or cerebrovascular event within 90 days, planned revascularization of a coronary, carotid, or peripheral artery; or long term dialysis.	Semaglutide	Placebo	a GLD or no more than two OADs, ± basal or premixed insulin	2.1	3297	64.6	2002 (60.7)	32.8	8.7	13.9
Kaku (2011)[35]	NCT00393718		Patients with T2DM and inadequate glycemic control regardless of whether they were previously taking OAD.	Liraglutide	Glibencla mide	± OAD	1.0	400	58.3	269 (67.3)	24.8	9.3	8.3
Wanner (2016)[13]	NCT01131676	EMPA-REG OUTC OME	Patients with T2DM and established cardiovascular disease and an eGFR of at least 30 ml/min/ 1.73 m^2.	Empagliflozin	Placebo	monothera py or dual therapy of GLDs	3.1	7020	63.1	5016 (71.5)	36.6	8.1	≤1 years 180(2.6%) >1 to 5 years 1083(15.4%) >5 to 10 years 1746(24.9%) >10 years 4011(57.1%)
Kovacs (2014)[36]	NCT01210001		Patients with T2DM inadequately controlled with diet and exercise and pioglitazone or	Empagliflozin	Placebo	Pioglitazo ne ± MET	0.5	498	54.5	241 (48.4	29.2	8.1	≤1 year n=65 (13.1); >1–5 years

			pioglitazone plus metformin; excluded patients with estimated glomerular filtration rate of less than 30 mL/min per 1·73 m² (Modified Diet Renal Disease formula)							)			n=214 (43.0) ; >5–10 years n=135 (27.1); >10 years n=84 (16.9)
Cefalu (2013)[37]	NCT00968812	CANTATA-SU	Patients with T2DM inadequately controlled with metformin; excluded patients with estimated glomerular filtration rate of less than 55 mL/min per 1·73 m²	Canagliflozin	Glimepiride	MET	2.0	1450	56.2	756 (52.1)	31.0	7.8	6.6
Ridderstråle (2013)[38]	NCT01167881	EMPA-REG H2H-SU trial	Patients with T2DM inadequately controlled with metformin; excluded patients with estimated glomerular filtration rate of less than 60 mL/min per 1·73 m² (Modified Diet Renal Disease formula)	Empagliflozin	Glimepiride	MET	4.0	1545	55.9	854 (55.3)	30.1	7.9	≤1 years 172 (11.1) >1 to 5 years 677 (43.8) >5 to 10 years 425 (27.5) >10 years 271 (17.5)
Pfützner (2011)[39]	NCT00327015		Patients with T2DM and inadequate glycemic control; excluded patients with cardiovascular event within 6 months before study entry or New York Heart Association stage III/IV congestive heart failure and/or known left ventricular ejection fraction≤40%, significant renal, liver or psychiatric history	Saxagliptin	Metformin	None	0.5	663	52.0	332 (50.1)	30.2	9.5	1.7
Leiter (2014)[40]	NCT01098539		Patients with T2DM, renal impairment(GFR: 15 to 90 mL/min/1.73 m^2) and inadequately controlled glycemia with diet and exercise and/or oral antihyperglycemic medications; excluded patients with recent clinically significant cardiovascular and/or cerebrovascular disease	Albiglutide	Sitagliptin	MET, TZD, SU, or any combination of these OADs	1.2	495	63.3	266 (53.7)	30.4	8.2	11.2
Araki (2015)[41]	NCT01584232		Patients with T2DM and inadequate glycemic control with sulphonylureas and/or biguanides; excluded patients with cardiovascular disease, liver disease, renal disease, poorly controlled hypertension, a history of chronic or acute pancreatitis, obvious clinical signs or symptoms of pancreatitis	Dulaglutide	Insulin glargine	SU ± biguanides	0.5	361	56.8	258 (71.5)	26.0	8.0	8.8
Diamant (2014)[42]	NCT00960661		Patients with T2DM and inadequately controlled with insulin glargine and metformin with or without sulfonylurea	Exenatide	Insulin Lispro	Insulin Glargine + MET	0.6	627	59.5	261 (41.6)	32.5	8.3	11.5
Weissman (2014)[43]	NCT00838916	HARMONY 4	Patients with T2DM inadequately controlled with metformin with or without sulfonylurea; excluded patients with recent significant cardiovascular (within 2 months) or cerebrovascular (within 1 month) events	Albiglutide	Insulin glargine	MET ± SU	3.0	745	55.5	418 (56.1)	33.1	8.3	8.8
Home (2009)_a[44]*	NCT00379769	RECORD	Patients with T2DM inadequately controlled with metformin with or sulfonylurea; excluded patients with hospitalisation for a major cardiovascular event in the 3 months before the trial, planned cardiovascular intervention, and presence, history, or treatment for heart failure.	Rosiglitazone	Sulfonylurea	MET	5.5	2222	57.1	1185 (53.4)	32.8	7.8	6.2
Home (2009)_b[44]*	NCT00379769	RECORD	Patients with T2DM inadequately controlled with metformin with or sulfonylurea; excluded patients with hospitalisation for a major cardiovascular event in the 3 months before the trial, planned cardiovascular intervention, and presence, history, or treatment for heart	Rosiglitazone	Metformin	SU	5.5	2225	59.7	1109 (59.8)	30.2	8.0	7.9

			failure.										
2016 [45]†	NCT01709305		Patients with T2DM	Acarbose	Repaglinide Gliclazide Glimepiride	MET + sitagliptin	0.9	2195	NR	NR	NR	NR	NR
Yang (2016)[46]	NCT01095666		Patients with T2DM inadequately controlled with stable metformin monotherapy; excluded patients with any of the following cardiovascular/ vascular diseases within 6 months of the enrolment visit: myocardial infarction, cardiac surgery or revascularization, unstable angina or congestive heart failure, transient ischemic attack or significant cerebrovascular disease	Dapagliflozin	Placebo	MET	0.5	444	53.7	241 (54.3)	26.1	8.1	4.9
2016[47] †	NCT00839527		Patients with T2DM	Albiglutide	Pioglitazone Placebo	MET + Glimepiride	3.0	663	55.2	353 (53.2)	NR	NR	NR
2015[48] †	NCT01644500		Patients with T2DM	Dulaglutide	Glimepiride	None	0.5	805	52.8	426 (53.9)	NR	NR	NR
Seino (2016)[49]	NCT01572740		Patients with T2DM inadequately controlled with stable insulin therapy in addition to diet and exercise for ≥12 weeks	Liraglutide	Placebo	insulin	0.7	257	60.5	144 (56.0)	25.6	8.8	14.5
2016[50] †	NCT00849056		Patients with T2DM	Albiglutide	Placebo	pioglitazone ± MET	3.0	301	55.0	180 (59.8)	NR	NR	NR
Rosenstock (2014)[51]	NCT00713830	GETGOAL-S	T2DM inadequately controlled with a sulfonylurea with or without metformin; excluded patients with history of myocardial infarction, stroke, or heart failure requiring hospitalization within the previous 6 months, uncontrolled/inadequately controlled hypertension, end-stage renal disease	Lixisenatide	Placebo	SU ± MET	2.3	859	57.3	434 (50.5)	30.2	8.3	9.3
Pinget (2013)[52]	NCT00763815	GETGOAL-P	Patients with T2DM inadequately controlled with pioglitazone with or without metformin; excluded patients with history of unexplained pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery or inflammatory bowel disease, end-stage renal disease	Lixisenatide	Placebo	Pioglitazone ± MET	2.5	484	55.8	254 (52.5)	33.9	8.1	8.1
Seino (2011)[53]	NCT00395746		Patients with T2DM inadequately controlled with diet therapy and one SU agent; excluded patients with proliferative retinopathy or maculopathy requiring acute treatment, impaired hepatic/renal function, serious heart disease, cancer, uncontrolled hypertension	Liraglutide	Placebo	SU	1.0	264	59.7	169 (64.0)	24.9	8.8	10.3
Rosenstock (2014)[54]	NCT00976391		Patients with T2DM inadequately controlled with basal insulin, excluded patients with recent clinically significant cardiovascular or cerebrovascular disease	Albiglutide	Lispro insulin	insulin glargine in combination with MET or TZD or both or neither	1.2	566	55.6	268 (47.3)	NR(90.05 kg, BMI 20-45)	8.5	11.0

Pratley (2010)[55]	NCT00700817		Patients with T2DM inadequately controlled with metformin; excluded patients with impaired renal or hepatic function, clinically significant cardiovascular disease, recurrent major hypoglycaemia or hypoglycaemic unawareness	Liraglutide	Sitagliptin	MET	0.5	658	55.3	352 (53.5)	32.8	8.4	6.2
Ahrén (2014)[56]	NCT00838903	HARMONY 3	Patients with T2DM inadequately controlled with metformin; excluded patients with recent clinically significant cardiovascular and/or cerebrovascular disease (≤2 months before screening), resting systolic blood pressure ＞ 160mmHg and/or diastolic blood pressure ＜ 100 mmHg	Albiglutide	Sitagliptin Glimepiride Placebo	MET	3.2	1012	54.5	482 (47.6)	32.6	8.1	6.0
Holman (2017)[57]	NCT01144338	EXSCEL	T2DM and a broad range of cardiovascular risk.Recruitment will be constrained such that approximately 30% will not have had a prior CV event and 70% will have had a prior CV event.	Exenatide	Placebo	OADs ± insulin	3.2	14752	62.0	9149 (62.0)	31.7	8.0	12.0

* Data from same study with different background therapy.

† No publications were found, and last updated data in clinicaltrials.gov was extracted.

Abbreviation: BMI, Body Mass Index; HbA1c, glycated haemoglobin; T2DM, type 2 diatbetes mellitus; MET, metformin; SU, sulphonylurea; TZD, thiazolidinedione; GLD, glucose-lowering drug; OAD, oral antihyperglycemic drug; ±, with or without; eGFR, estimated glomerular filtration rate

Table 2 Pairwise and network estimates of the effects of glucose-lowering drugs compared with placebo on risk of diabetic retinopathy

Drug	Direct drug comparisons/ participants (n/N)	**Odds ratio (95% CI)**	
		Pairwise meta-analysis	Network meta-analysis
DPP-4i	443/39,717	1.27 (1.05, 1.53)	1.20 (0.87, 1.65)
GLP-1RA	846/37,387	1.15 (0.93, 1.43)	1.19 (0.94, 1.52)
SGLT2 inhibitors	124/7,962	0.78 (0.54, 1.12)	0.79 (0.49, 1.28)
Sulfonylureas	16/408	2.37 (0.53, 10.59)	1.67 (1.01, 2.76)
Thiazolidinediones	20/392	2.44 (0.70, 8.50)	1.50 (0.84, 2.67)
Metformin	–	–	1.70 (0.80, 3.61)
α-glucosidase inhibitors	–	–	10.00 (0.38, 178.08)
Glinides	–	–	3.37 (0.06, 178.08)
Insulin	–	–	1.25 (0.73, 2.15)

Abbreviations: n/N, number of events/number of patients; CI, confidence interval.

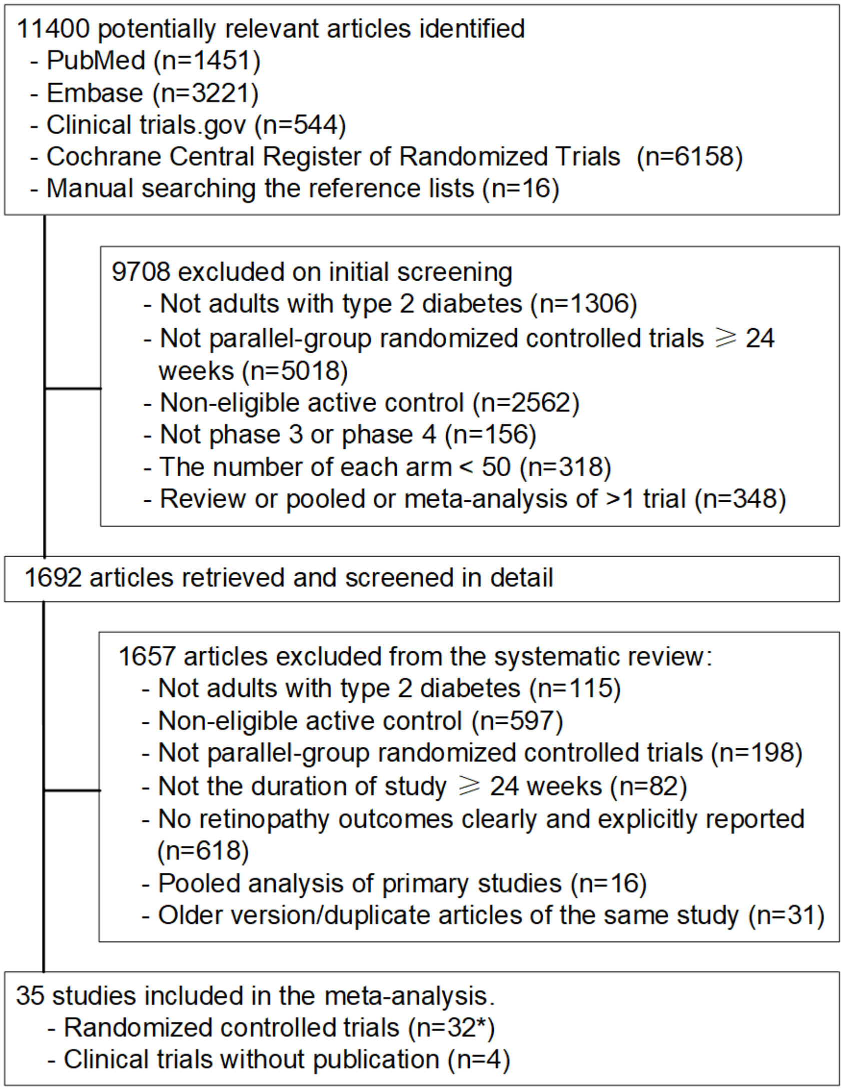
Figure Legends:

Figure 1 Flow chart of study selection.(About eight months after our formal search, the results of the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) were published in September 2017. We incorporated data from this large trial, and our final analysis included 36 studies)

Figure 2 Network of available glucose-lowering drugs for risk of diabetic retinopathy. The size of the nodes corresponds to the number of trials including respective treatments. The directly compared treatments are linked with a line, the thickness of which corresponds to the number of trials that assessed this comparison. Numbers above and below the lines indicate studies and patients respectively.

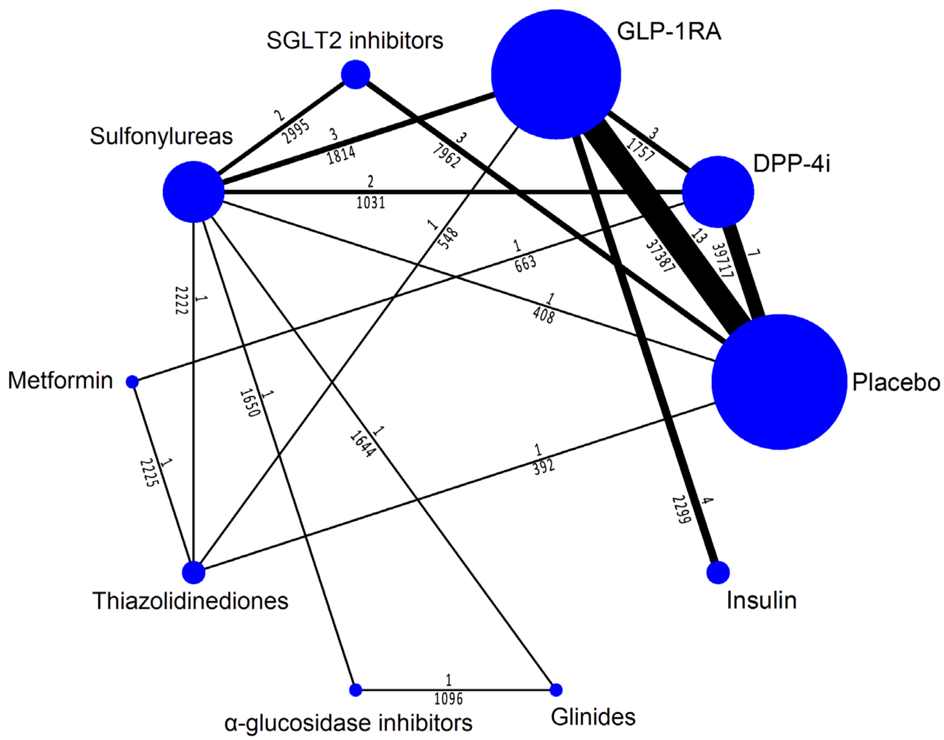
Figure 3 Univariate regression of the relation between HbA1C change and diabetic retinopathy risk.

Figure 1



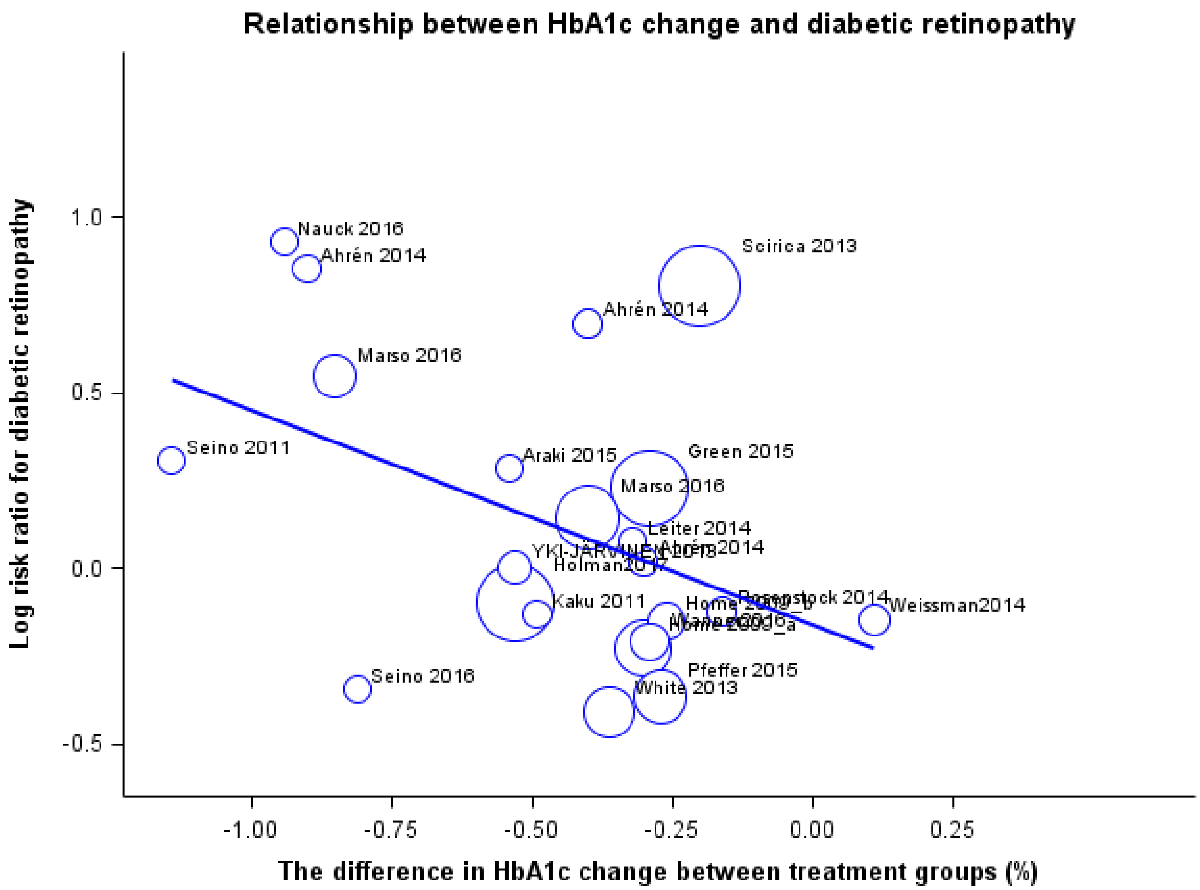
* One study reported by Home 2009 involves two RCTs with different background therapy.

Figure 2



SGLT2 inhibitors
GLP-1RA
Sulfonylureas
DPP-4i
Metformin
Placebo
Thiazolidinediones
Insulin
α-glucosidase inhibitors
Glinides
2
2995
3
1814
3
7962
3
1757
2
1031
1
548
1
663
13
37387
39717
7
1
408
2222
1
1650
1
1644
1
1
392
1
2225
2299
4
1
1096

Figure 3


Relationship between HbA1c change and diabetic retinopathy
Log risk ratio for diabetic retinopathy
1.0
0.5
0.0
-0.5
-1.00
-0.75
-0.50
-0.25
0.00
0.25
The difference in HbA1c change between treatment groups (%)
Nauck 2016
Ahrén 2014
Scirica 2013
Ahrén 2014
Marso 2016
Seino 2011
Araki 2015
Green 2015
Marso 2016
Leiter 2014
Ahrén 2014
Holman2017
Kaku 2011
Rosenstock 2014
Weissman2014
Pfeffer 2015
White 2013
Seino 2016