Glucagon-Like Peptide-1 Receptor Agonists and the Risk of Incident Diabetic Retinopathy

Antonios Douros,[1,2,3] Kristian B. Filion,[1,2,4] Hui Yin,[1] Oriana Hoi Yu,[1,5] Mahyar Etminan,[6] Jacob A. Udell,[7,8] and Laurent Azoulay[1,2,9]

https://doi.org/10.2337/dc17-2280

OBJECTIVE

Previous studies suggested that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) may initially worsen and possibly increase the risk of diabetic retinopathy. However, data on this possible association remain limited. Thus, this population-based study aimed to determine whether use of GLP-1 RAs is associated with an increased risk of incident diabetic retinopathy.

RESEARCH DESIGN AND METHODS

Using the U.K. Clinical Practice Research Datalink, we conducted a cohort study among 77,115 patients with type 2 diabetes initiating antidiabetic drugs between January 2007 and September 2015. Adjusted hazard ratios (HRs) and 95% CIs of incident diabetic retinopathy were estimated using time-dependent Cox proportional hazards models, comparing use of GLP-1 RAs with current use of two or more oral antidiabetic drugs. In an ancillary analysis, new users of GLP-1 RAs were compared with new users of insulin.

RESULTS

During 245,825 person-years of follow-up, 10,763 patients were newly diagnosed with diabetic retinopathy. Compared with current use of two or more oral antidiabetic drugs, use of GLP-1 RAs was not associated with an increased risk of incident diabetic retinopathy overall (HR 1.00, 95% CI 0.85–1.17). Compared with insulin, GLP-1 RAs were associated with a decreased risk of diabetic retinopathy (HR 0.67, 95% CI 0.51–0.90).

CONCLUSIONS

The associations with diabetic retinopathy varied according to the type of comparator. When compared with use of two or more oral antidiabetic drugs, use of GLP-1 RAs was not associated with an increased risk of incident diabetic retinopathy. The apparent lower risk of diabetic retinopathy associated with GLP-1 RAs compared with insulin may be due to residual confounding.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are injectable incretin-based drugs recommended as second- or third-line treatments in type 2 diabetes (1). These drugs have been shown to have neutral or favorable risk profiles with regard to cardiovascular outcomes in recent large randomized controlled trials (RCTs) (2–5). Paradoxically, earlier data had suggested that GLP-1 RAs may initially worsen diabetic retinopathy (6–8), a common diabetes-related microvascular complication. This possible association is supported by the findings of two of the four large RCTs of GLP-1

[1]Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, Quebec, Canada
[2]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada
[3]Institute of Clinical Pharmacology and Toxicology, Charité–Universitätsmedizin Berlin, Berlin, Germany
[4]Division of Clinical Epidemiology, Department of Medicine, McGill University, Montreal, Quebec, Canada
[5]Division of Endocrinology, Jewish General Hospital, Montreal, Quebec, Canada
[6]Department of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, British Columbia, Canada
[7]Women's College Research Institute and Cardiovascular Division, Department of Medicine, Women's College Hospital, University of Toronto, Toronto, Ontario, Canada
[8]Cardiovascular Division, Department of Medicine, Peter Munk Cardiac Centre, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada
[9]Gerald Bronfman Department of Oncology, McGill University, Montreal, Quebec, Canada

Corresponding author: Laurent Azoulay, laurent.azoulay@mcgill.ca.

Received 31 October 2017 and accepted 29 July 2018.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-2280/-/DC1.

RAs (3,4). In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, there was a nonsignificant but numerically higher rate of diabetic retinopathy complications (need for retinal photocoagulation or treatment with intravitreal agents, vitreous hemorrhage, or diabetes-related blindness) with liraglutide compared with placebo after a median follow-up of 3.8 years (106 of 4,668 [2.3%] vs. 92 of 4,672 [2.0%]; hazard ratio [HR] 1.15, 95% CI 0.87–1.52) (3). In the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), semaglutide was significantly associated with an increased risk of diabetic retinopathy complications (same definition as in the LEADER trial) compared with placebo after a median follow-up of 2.1 years (50 of 1,648 [3.0%] vs. 29 of 1,649 [1.8%]; HR 1.76, 95% CI 1.11–2.78) (4). These included eight versus five events of incident diabetic retinopathy, respectively.

The association between GLP-1 RAs and diabetic retinopathy is biologically plausible. One mechanism may relate to the rapid decrease in glycemic levels with GLP-1 RAs; this has been previously reported with other antidiabetic treatments that rapidly improve glycemic levels, such as insulin (9,10). Another mechanism may involve a direct effect of these drugs on the retina, given the expression of GLP-1 receptors in human retinal cells (11). To date, however, this association has not been investigated in the natural setting of clinical practice. Thus, the objective of this population-based study was to determine whether the use of GLP-1 RAs is associated with an increased risk of incident diabetic retinopathy in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Data Sources

This study was conducted using the U.K. Clinical Practice Research Datalink (CPRD), which was linked to the Hospital Episode Statistics (HES) repository. The CPRD contains the medical records of more than 14 million people enrolled across 700 general practices (12). Medical diagnoses and procedures are recorded using the Read code classification, and drugs prescribed by general practitioners are coded using the U.K. Prescription Pricing Authority dictionary. The CPRD contains information on anthropometric variables (e.g., BMI) and lifestyle variables (e.g., smoking), and diagnoses recorded in this database have been previously validated and shown to be of high quality (13). The HES contains all inpatient admissions, including primary and secondary diagnoses (coded using the ICD-10) and hospital-related procedures. The linkage of the CPRD to the HES is possible from 1 April 1997 onward and is limited to general practices in England that have consented to the linkage scheme (currently representing 75% of all practices in England) (13). The study protocol was approved by the CPRD Independent Scientific Advisory Committee (protocol number 16_287R) and by the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

Study Population

We first identified a base cohort of patients newly treated for type 2 diabetes. This included all patients, at least 18 years of age, initiating a new noninsulin antidiabetic drug (metformin, sulfonylureas, prandial glucose regulators, acarbose, thiazolidinediones, dipeptidyl peptidase-4 [DPP-4] inhibitors, GLP-1 RAs, and sodium-glucose cotransporter-2 inhibitors) between 1 April 1998 and 30 September 2015. All patients were required to have at least 1 year of medical history recorded in the CPRD before their first prescription. We excluded patients initially treated with insulin (because these patients are likely to have advanced disease) and women with a history of polycystic ovarian syndrome or a history of gestational diabetes in the last year (other known metformin indications).

Using this base cohort, we assembled a study cohort of all patients initiating a new antidiabetic drug class on or after 1 January 2007; the first GLP-1 RA, exenatide, was approved in the U.K. on 20 November 2006 (14). These patients included those newly treated with a noninsulin antidiabetic drug as well as those who switched to or added on an antidiabetic drug from a class not previously used in their treatment history. Cohort entry was defined by the date of this new prescription.

We excluded patients previously diagnosed with any retinal disease (codes available upon request) or with medical conditions associated with retinopathy (HIV infection, history of bariatric surgery), and those previously using drugs associated with retinopathy (imatinib, acitretin, nicotinic acid, rituximab, taxanes, interferon, zilovudine, rifabutine, and fingolimod) (10,15,16).

Patients were monitored until the earliest of the following events: incident diagnosis of diabetic retinopathy recorded in the outpatient or inpatient setting (Read and ICD-10 codes listed in Supplementary Table 1), end of registration with the general practice, death from any cause, or end of the study period (30 September 2015).

Exposure Definition

We used a time-varying exposure definition, in which each person-day of follow-up was classified hierarchically into one of the following four mutually exclusive categories: current use of GLP-1 RAs (exenatide, liraglutide, lixisenatide; alone or in combination with other antidiabetic drugs other than insulin), current use of DPP-4 inhibitors (alone or in combination with other antidiabetic drugs other than insulin), current use of two or more oral antidiabetic drugs, and others, which included current use of other antidiabetic drugs and treatment combinations as well as no current use of antidiabetic drugs. Current use refers to each patient's exposure category on the day of follow-up included in the risk set. For all exposure categories, we defined exposed person-time by the prescription duration plus a 30-day grace period. Thus, continuous use was assumed if the prescription duration overlapped with the date of the next prescription, allowing for the 30-day grace period in the case of two nonoverlapping successive prescriptions. Because GLP-1 RAs are recommended as second- or third-line treatment in the management of type 2 diabetes (1), the reference category for our analyses consisted of current use of two or more oral antidiabetic drugs.

Potential Confounders

All models were adjusted for potential confounders assessed at study cohort entry. These included year of cohort entry, age, sex, quintiles of the Index of Multiple Deprivation (17), smoking status, BMI category (<25 kg/m^2, 25–29 kg/m^2, ≥ 30 kg/m^2, unknown), hemoglobin A_{1c} (HbA_{1c}) level ($\leq 7\%$ or ≤ 53 mmol/mol, 7.1–8.0% or 54–64 mmol/mol, $>8\%$ or >64 mmol/mol, unknown; last measurement before cohort entry), systolic and diastolic blood pressure (last measurement

before cohort entry), and duration of treated diabetes. Age and duration of treated diabetes were modeled flexibly (i.e., restricted cubic splines with five interior knots) as continuous variables to account for potentially nonlinear relationships with the outcome (18). Due to expected missing data, BMI and HbA_{1c} were modeled as categorical variables. The models were also adjusted for the following variables recorded at any time before cohort entry: alcohol-related disorders, dyslipidemia, diabetic arterial complications (neuropathy, nephropathy, peripheral arteriopathy, myocardial infarction, ischemic stroke), history of cataract surgery, albuminuria or proteinuria, uveitis, and sickle cell disease. We adjusted for the use of statins, fibrates, antihypertensive drugs, ophthalmic agents, antimalarial drugs, fluconazole, and tamoxifen in the year before cohort entry. Finally, we also adjusted for the overall number of nonantidiabetic drugs and the number of physician visits in the year before cohort entry.

Statistical Analysis

We used descriptive statistics to summarize the characteristics of the cohort. We calculated crude incidence rates, with 95% CIs based on the Poisson distribution, of diabetic retinopathy overall and for each exposure category. Cox proportional hazards regression models using the time-varying exposure definition were used to estimate adjusted HRs with 95% CIs of incident diabetic retinopathy associated with current use of GLP-1 RAs, compared with current use of two or more oral antidiabetic drugs. All models were adjusted for the potential confounders listed above.

Secondary Analyses

We conducted three prespecified secondary analyses. First, to explore whether the use of GLP-1 RAs is associated with a transient increased risk of diabetic retinopathy, current use was further categorized according to three predefined continuous durations of use ($\leq$6 months, 6.1–12 months, $>$12 months). The *P* value for heterogeneity across the HRs of the different durations of use was calculated using a χ^2 test. Second, we assessed the association with individual GLP-1 RAs (liraglutide and exenatide; no lixisenatide-specific analyses were conducted due to the low number of exposed patients). Finally, we assessed whether duration of treated diabetes modified the association by including an interaction term between duration of treated diabetes ($<$5 vs. $\geq$5 years) and exposure to GLP-1 RAs.

We also conducted three post hoc secondary analyses. In the first two analyses, we assessed whether arterial hypertension (defined as systolic blood pressure $\geq$140 mmHg or diastolic blood pressure $\geq$90 mmHg or use of any antihypertensive medication) or use of ACE inhibitors or angiotensin receptor blockers (ARBs) modified the association. Finally, also assessed whether baseline HbA_{1c} level ($\leq$7% or $\leq$53 mmol/mol, 7.1–8.0% or 54–64 mmol/mol, $>$8% or $>$64 mmol/mol) modified the association. For this analysis, exposure was defined based on the drugs received at cohort entry with a maximum follow-up of 1 year.

Sensitivity Analyses

We conducted seven prespecified sensitivity analyses to assess the robustness of our findings:

1. To assess possible exposure misclassification, we repeated the primary analysis by lengthening the grace period to 90 days between prescriptions that did not overlap.
2. To adjust further for potential confounding by disease severity, we additionally adjusted for the use of antidiabetic drugs in the year before cohort entry.
3. Because an association between thiazolidinediones and macular edema has been suggested (16), we redefined our exposure variable by removing current use of thiazolidinediones from the GLP-1 RA and reference (two or more oral antidiabetic drugs) exposure groups and including such use in the "other treatment combinations" group.
4. We used multiple imputations for variables with missing information (BMI, HbA_{1c} level, smoking status, Index of Multiple Deprivation).
5. We used the high-dimensional disease risk score approach as an alternate means to control for confounding (19). This method uses an algorithm that empirically selects covariates along with prespecified covariates for the statistical analysis and is recommended in settings similar to our study where the exposure of interest is relatively rare but the outcome of interest is common (20).
6. We repeated the analyses to account for competing risk due to deaths from any cause (21).
7. To assess the possible inclusion of prevalent retinopathy events (i.e., patients who had the condition before study cohort entry but were not yet diagnosed), we stratified the cohort based on the presence of at least one retinopathy screening visit in the year before cohort entry (the recommended screening regimen according to U.K. guidelines [22]).

Finally, in a post hoc analysis, we assessed the potential effect of residual confounding on our point estimates using the approach proposed by Ding and VanderWeele (23), a model that does not impose any assumptions on the unmeasured confounder or confounders, such as having an unmeasured confounder that is binary, or having no interaction between the effects of the exposure and the confounder on the outcome, or having only one unmeasured confounder.

Negative and Positive Control Exposures

To further assess the validity of our findings, we conducted two additional analyses using negative and positive control exposures (24). For the negative control exposure, we repeated the analyses comparing current use of DPP-4 inhibitors with current use of two or more oral antidiabetic drugs; the former are incretin-based drugs, but have not been associated with diabetic retinopathy in previous large RCTs (25–27). For the positive control exposure, we repeated the analyses comparing current use of insulin with current use of two or more oral antidiabetic drugs; the former has been previously associated with a transient increased risk of diabetic retinopathy (9).

Ancillary Analysis

We conducted a post hoc ancillary analysis head-to-head comparison of new users of GLP-1 RAs with new users of insulin. For this analysis, we identified patients in our base cohort initiating a GLP-1 RA or insulin after January 2007. Cohort entry was defined as the date of the first prescription of GLP-1 RA or insulin. We then estimated propensity scores using multivariate logistic regression to estimate the predicted probability of receiving a GLP-1 RA versus insulin,

conditional on the variables listed above. Patients with nonoverlapping propensity score distributions were trimmed from the analysis. The remaining patients were monitored from cohort entry until they switched from GLP-1 RAs to insulin or vice versa, discontinued treatment, or experienced the outcome, whichever occurred first. Finally, the HR of incident diabetic retinopathy was estimated using a Cox proportional hazards model adjusted for the propensity score, which was included in the model as an interaction term between propensity score deciles and the propensity score as a continuous variable. All analyses were conducted with SAS 9.4 software (SAS Institute, Cary, NC).

RESULTS

The cohort included 77,115 new users of antidiabetic drugs (Fig. 1). The median duration of follow-up was 2.8 (maximum 8.8) years, generating 245,825 person-years. During follow-up, 3,047 patients received GLP-1 RAs (97% in combination therapy), with the median duration of use being 0.8 (maximum 7.3) years (median duration of use for the comparator group, i.e., two or more oral antidiabetic drugs, was 0.6 [maximum 8.7] years). Overall, 10,763 patients were newly diagnosed with diabetic retinopathy during follow-up, corresponding to an overall incidence rate of 43.8 (95% CI 43.0–44.6) per 1,000/year.

Table 1 presents the characteristics of patients who received GLP-1 RAs versus two or more oral antidiabetic drugs at cohort entry. Compared with users of two or more oral antidiabetic drugs, users of GLP-1 RAs were younger, more likely to be women, and more likely to be obese. They were also more likely to have elevated HbA_{1c} levels (>8% or >64 mmol/mol), have a history of neuropathy, nephropathy, or proteinuria, and to have used antihypertensive drugs.

Table 2 presents the results related to the use of GLP-1 RAs. Compared with current use of two or more oral antidiabetic drugs, current use of GLP-1 RAs was not associated with an overall higher risk of diabetic retinopathy (crude incidence rates, 40.4 vs. 49.0 per 1,000/year; adjusted HR 1.00, 95% CI 0.85–1.17). However, there was a suggestion of heterogeneity across the duration categories. A duration of use ranging between 6.1 and 12 months was associated with a 44% increased risk of diabetic retinopathy (crude incidence rates, 56.6 vs. 45.9 per 1,000/year; adjusted HR 1.44, 95% CI 1.06–1.95). This association was not observed for shorter and longer durations of use of ≤6 months (crude incidence rates, 38.2 vs. 51.3 per 1,000/year; adjusted HR 0.94, 95% CI 0.76–1.17) and >12 months (crude incidence rates, 33.2 vs. 47.4 per 1,000/year; adjusted HR, 0.83; 95% CI, 0.60–1.15) (*P* for heterogeneity = 0.07). Drug-specific analyses revealed similar overall and duration patterns for liraglutide and exenatide, but these did not achieve statistical significance due to the smaller number of exposed events (Supplementary Table 2). Duration of treated diabetes and HbA_{1c} level did not modify the association between GLP-1 RA use and risk of diabetic retinopathy (Supplementary Tables 3 and 4). However, the risk of GLP-1 RA–associated diabetic retinopathy was increased among patients with arterial hypertension or use of ACE inhibitors or ARBs (Supplementary Tables 5 and 6).

Figure 2 summarizes the results of the sensitivity analyses (presented in detail in Supplementary Tables 7–14). The results remained consistent with those of the primary and secondary analyses in overall use and duration of use. With respect to the latter, GLP-1 RA durations ranging between 6.1 and 12 months were consistently associated with an increased risk of diabetic retinopathy across the different sensitivity analyses. Based on a post hoc analysis, these findings are unlikely to be the result of an unmeasured confounder under most plausible exposure-confounder and confounder-outcome associations (Supplementary Table 15).

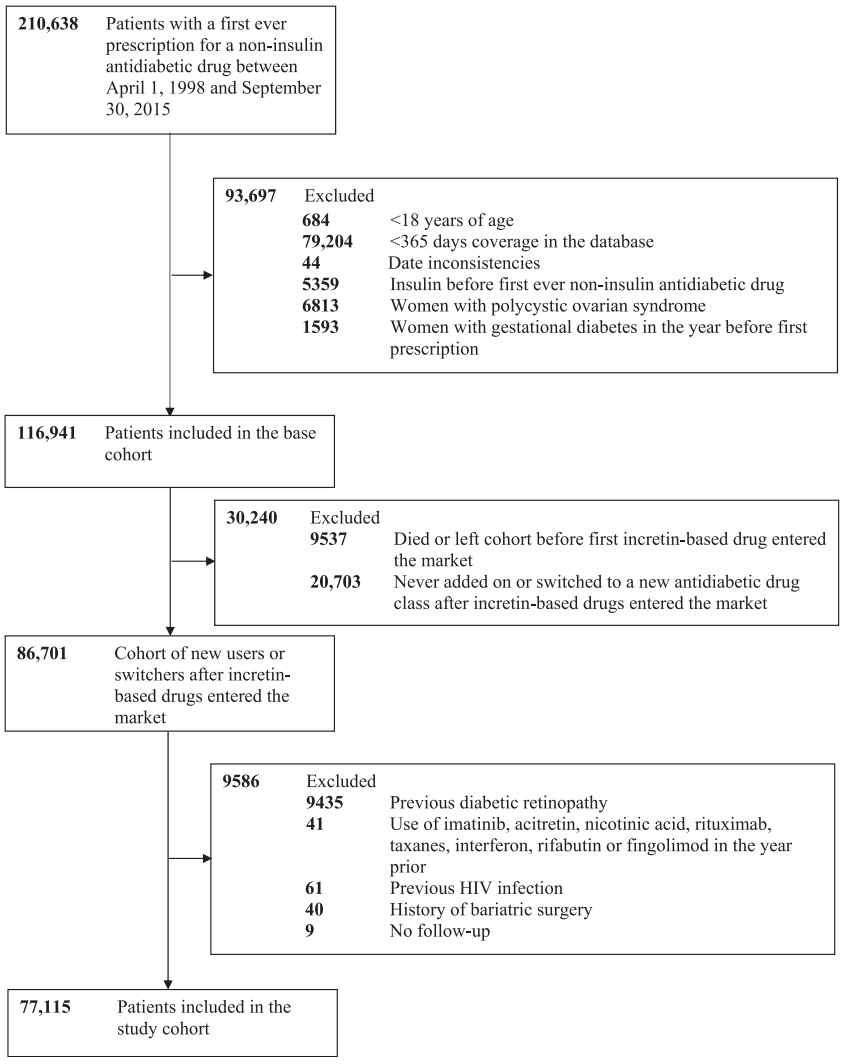

Figure 1—Flowchart describing the construction of base and study cohorts.

Table 1—Baseline demographics and clinical characteristics of the cohort and stratified by drug use at cohort entry

Characteristic	Entire cohort (*N* = 77,115)	Use at Cohort Entry[a]	
		GLP-1 RAs (*n* = 444)[b]	≥2 oral antidiabetic drugs (*n* = 10,431)
Age, mean (SD) years	61.6 (13.6)	56.8 (10.5)	63.3 (12.4)
Male, *n* (%)	44,155 (57.3)	245 (55.2)	6,331 (60.7)
Index of Multiple Deprivation, *n* (%)			
Quintile 1	14,799 (19.2)	73 (16.4)	2,097 (20.1)
Quintile 2	15,947 (20.7)	77 (17.3)	2,210 (21.2)
Quintile 3	15,993 (20.7)	86 (19.4)	2,170 (20.8)
Quintile 4	15,732 (20.4)	113 (25.5)	2,031 (19.5)
Quintile 5	14,595 (18.9)	95 (21.4)	§
Unknown	49 (0.1)	0 (0.0)	§
Alcohol-related disorders, *n* (%)	10,671 (13.8)	72 (16.2)	1,535 (14.7)
Smoking status, *n* (%)			
Current	12,434 (16.1)	66 (14.9)	1,513 (14.5)
Past	28,540 (37.0)	188 (42.3)	4,091 (39.2)
Never	35,864 (46.5)	190 (42.8)	4,800 (46.0)
Unknown	277 (0.4)	0 (0.0)	27 (0.3)
BMI, *n* (%)			
<25 kg/m^2	8,484 (11.0)	§	1,273 (12.2)
25–30 kg/m^2	22,938 (29.8)	30 (6.8)	3,378 (32.4)
≥30 kg/m^2	43,730 (56.7)	411 (92.6)	5,662 (54.3)
Unknown	1,963 (2.5)	§	118 (1.1)
HbA_{1c}, *n* (%)			
≤7.0% or ≤53 mmol/mol	13,453 (17.4)	51 (11.5)	1,089 (10.4)
7.1–8.0% or 54–64 mmol/mol	16,658 (21.6)	103 (23.2)	3,169 (30.4)
>8.0% or >64 mmol/mol	24,031 (31.2)	284 (64.0)	5,446 (52.2)
Unknown	22,973 (29.8)	6 (1.4)	727 (7.0)
Blood pressure, *n* (%)			
Systolic <140 mmHg and diastolic <90 mmHg	39,307 (51.0)	242 (54.5)	5,793 (55.5)
Systolic ≥140 mmHg or diastolic ≥90 mmHg	32,196 (41.7)	187 (42.1)	4,235 (40.6)
Unknown	5,612 (7.3)	15 (3.4)	403 (3.9)
Dyslipidemia, *n* (%)	17,931 (23.3)	123 (27.7)	2,923 (28.0)
Duration of treated diabetes, mean (SD) years	1.0 (2.4)	6.6 (2.9)	3.9 (2.8)
Neuropathy, *n* (%)	7,364 (9.5)	114 (25.7)	1,969 (18.9)
Nephropathy, *n* (%)	25,476 (33.0)	160 (36.0)	4,108 (39.4)
Peripheral arteriopathy, *n* (%)	3,056 (4.0)	19 (4.3)	493 (4.7)
Myocardial infarction, *n* (%)	5,774 (7.5)	27 (6.1)	788 (7.6)
Ischemic stroke, *n* (%)	3,778 (4.9)	10 (2.3)	542 (5.2)
Cataract surgery, *n* (%)	5,800 (7.5)	12 (2.7)	838 (8.0)
Albuminuria or proteinuria, *n* (%)	6,339 (8.2)	125 (28.2)	1,674 (16.1)
Uveitis, *n* (%)	302 (0.4)	§	49 (0.5)
Sickle cell disease, *n* (%)	123 (0.2)	0 (0.0)	17 (0.2)
Statins, *n* (%)	47,765 (61.9)	367 (82.7)	8,189 (78.5)
Fibrates, *n* (%)	1,231 (1.6)	20 (4.5)	264 (2.5)
Antihypertensive drugs, *n* (%)			
Calcium-channel blockers	20,705 (26.8)	140 (31.5)	3,150 (30.2)
ACE inhibitors	29,310 (38.0)	227 (51.1)	5,150 (49.4)
ARB	10,161 (13.2)	104 (23.4)	1,729 (16.6)
β-Blockers	17,524 (22.7)	122 (27.5)	2,561 (24.6)
Diuretics	22,781 (29.5)	187 (42.1)	3,394 (32.5)
Mineralocorticoid receptor antagonists	1,671 (2.2)	9 (2.0)	213 (2.0)
Other antihypertensive drugs	742 (1.0)	10 (2.3)	132 (1.3)
Ophthalmic agents	1,758 (2.3)	5 (1.1)	241 (2.3)
Antimalarial drugs	258 (0.3)	§	31 (0.3)
Fluconazole	1,897 (2.5)	22 (5.0)	257 (2.5)
Tamoxifen	306 (0.4)	0 (0.0)	40 (0.4)

Continued on p. 6

Table 1—Continued

Characteristic	Entire cohort (*N* = 77,115)	Use at Cohort Entry[a]: GLP-1 RAs (*n* = 444)[b]	Use at Cohort Entry[a]: ≥2 oral antidiabetic drugs (*n* = 10,431)
Nonantidiabetic drugs, mean (SD), *n*	8.0 (6.1)	11.2 (6.0)	8.8 (5.6)
0	3,775 (4.9)	§	228 (2.3)
1	4,327 (5.6)	§	230 (2.2)
2	5,106 (6.6)	7 (1.6)	436 (4.2)
3	5,605 (7.3)	12 (2.7)	522 (5.0)
≥4	58,302 (75.6)	421 (94.8)	9,015 (86.4)
Physician visits, mean (SD), *n*	7.6 (9.1)	9.8 (10.1)	8.4 (9.4)

[a]Data for patients exposed to other antidiabetic drugs at cohort entry (*n* = 72,381) are not included in the table. [b]These 444 patients represent 14.6% of all patients eventually exposed to GLP-1 RAs during the follow-up period. §Numbers <5 are not displayed, as per the confidentiality policies of the CPRD.

With respect to our control exposures (patient characteristics in Supplementary Table 16; results summarized in Supplementary Fig. 1 and presented in Supplementary Tables 17 and 18), the use of DPP-4 inhibitors (negative control exposure) was not associated with an increased risk of diabetic retinopathy overall or by duration of use. In contrast, insulin (positive control exposure) was associated with an increased risk of diabetic retinopathy overall, and with evidence of a duration-response relation. Finally, Table 3 presents the comparison of new users of GLP-1 RAs with new users of insulin (cohort assembly shown in Supplementary Fig. 2, patient characteristics reported in Supplementary Table 19). Overall, the use of GLP-1 RAs was associated with a decreased risk of diabetic retinopathy (HR 0.67; 95% CI 0.51–0.90). The decreased risk was observed after a duration of at least 12 months of use (HR 0.48; 95% CI 0.31–0.76), whereas the HRs were close to the null for shorter durations of ≤6 months (HR 0.84; 95% CI 0.55–1.27) and 6.1–12 months (HR 1.05; 95% CI 0.64–1.72).

CONCLUSIONS

The results of this population-based study indicate that when compared with the use of two or more oral antidiabetic drugs, the use of GLP-1 RAs is not associated with an overall increased risk of diabetic retinopathy. In a secondary analysis, there was a suggestion of a transient 44% increased risk with GLP-1 RA durations ranging 6 and 12 months, an effect that appeared to be more pronounced in patients with arterial hypertension. Compared with insulin, GLP-1 RAs were associated with a 33% decreased risk of diabetic retinopathy.

Although the findings of our primary analysis suggest a null association between GLP-1 RAs and incident diabetic retinopathy overall, the results of our duration-response analyses suggest a potential transient increase risk in this outcome. A possible mechanism for this observation may involve large and rapid improvements in glycemic control, which have previously been linked to a transient worsening of diabetic retinopathy (9,10) via increased insulin-like growth factor levels and retinal ischemia (28,29). Interestingly, in the SUSTAIN-6 and LEADER trials, a divergence in the Kaplan-Meier curves was observed during the 1st year after randomization (4,30). Moreover, the time interval of the increased risk corresponds to when GLP-1 RA users achieve their greatest drops in HbA_{1c} levels (31). The fact that the association decreased with longer durations of use (>12 months) may relate to the depletion of susceptible phenomenon, where patients susceptible of developing retinopathy selected themselves out of the exposure group in the early phase of treatment (32).

Table 2—Crude and adjusted HRs for the association between the use of GLP-1 RAs compared with the use of two or more oral antidiabetic drugs and the risk of diabetic retinopathy

Exposure[a]	Events	Person-years	Incidence rate (95% CI)[b]	Crude HR (95% CI)	Adjusted HR (95% CI)[c]
≥2 oral antidiabetic drugs	2,386	48,692	49.0 (47.1–51.0)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	173	4,281	40.4 (34.6–46.9)	0.92 (0.78–1.07)	1.00 (0.85–1.17)
≤6 months of use					
≥2 oral antidiabetic drugs	1,203	23,473	51.3 (48.4–54.2)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	88	2,305	38.2 (30.6–47.0)	0.87 (0.70–1.08)	0.94 (0.76–1.17)
6.1–12 months of use					
≥2 oral antidiabetic drugs	394	8,586	45.9 (41.5–50.7)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	47	831	56.6 (41.6–75.2)	1.31 (0.97–1.78)	1.44 (1.06–1.95)
>12 months of use					
≥2 oral antidiabetic drugs	789	16,633	47.4 (44.2–50.9)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	38	1,144	33.2 (23.5–45.6)	0.76 (0.55–1.05)	0.83 (0.60–1.15)
					P for heterogeneity = 0.07

[a]Use of other antidiabetic agents is considered in the model but not presented in the table. [b]Per 1,000 persons per year. [c]Adjusted for year of cohort entry, age, sex, quintiles of the Index of Multiple Deprivation, alcohol-related disorders, smoking status, BMI category, HbA_{1c}, systolic and diastolic blood pressure, dyslipidemia, duration of treated diabetes, neuropathy, nephropathy, peripheral arteriopathy, myocardial infarction, ischemic stroke, history of cataract surgery, albuminuria or proteinuria, uveitis, sickle cell disease, use of statins, fibrates, antihypertensive drugs, ophthalmic agents, antimalarial drugs, fluconazole, or tamoxifen, the number of nonantidiabetic drugs, and the number of physician visits.

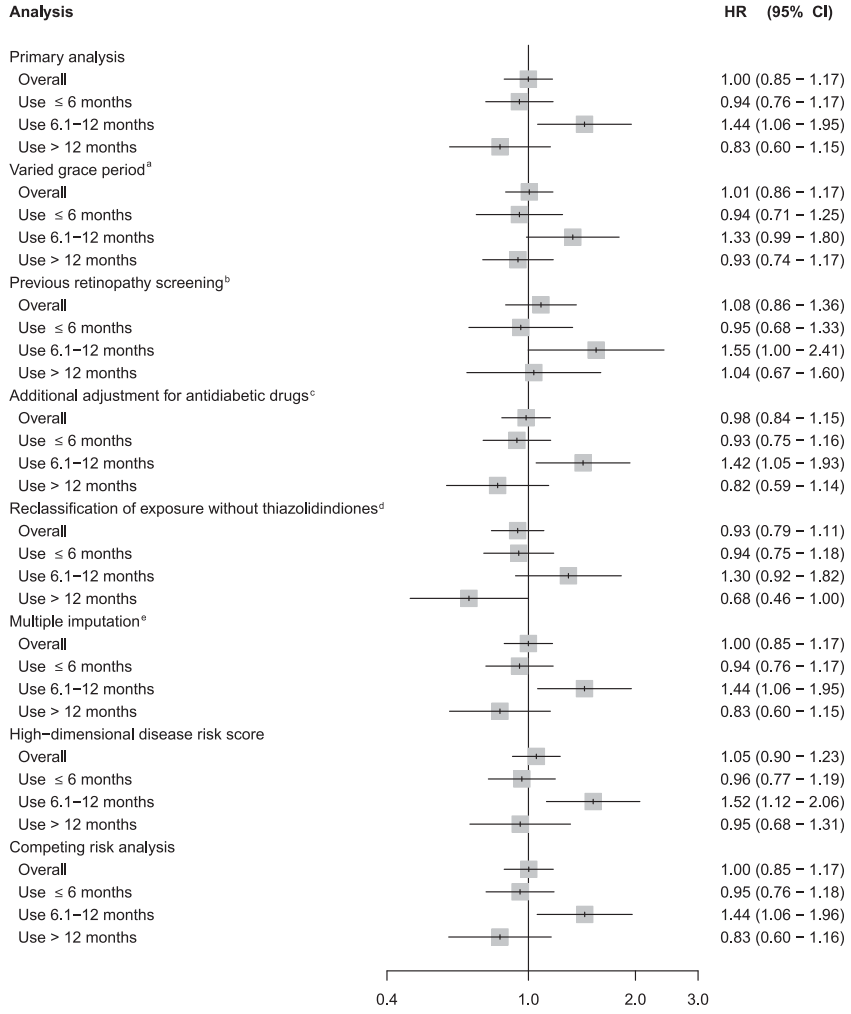

Figure 2—Forest plot summarizing the primary analysis and all sensitivity analyses. [a]90-day grace period. [b]Stratified by diabetic retinopathy screening in the year before cohort entry. [c]Additionally adjusting for use of antidiabetic drugs in the year before cohort entry. [d]Excluding thiazolidinedione users from the two main exposure categories. [e]Multiple imputation for missing values of BMI category, HbA_{1c} level, smoking status, and Index of Multiple Deprivation quintile.

Another possible mechanism might involve a direct drug effect on retinal cells, because GLP-1 receptors have been shown to be abundantly expressed in the retina (11). However, the fact that DPP-4 inhibitors, drugs that increase endogenous GLP-1 levels, were not associated with an increased risk of diabetic retinopathy argues against this hypothesis. Finally, it would be of interest to further investigate the transient increased risk observed in our study by reanalyzing data from the recent large RCTs (e.g., LEADER and SUSTAIN-6 trials) and providing information on temporal patterns of incident diabetic retinopathy (3,4).

In a post hoc ancillary analysis, GLP-1 RAs were associated with a decreased risk of incident diabetic retinopathy compared with insulin. However, this finding should be interpreted with caution. First, insulin users were older and more likely to have a history of diabetes-related complications than GLP-1 RA users. Thus, residual confounding is possible. Moreover, because insulin has been shown to cause a transient worsening of diabetic retinopathy (9), the results could also be a reflection of the increased risk of the comparator drug rather than a decreased risk associated with GLP-1 RAs.

Our study has several strengths. First, with a cohort of more than 77,000 newly treated patients with type 2 diabetes and close to 11,000 events, we had the statistical precision required to robustly assess this important safety question. Second, the use of a time-varying exposure definition eliminated the risk of immortal time bias (33) and was deemed to be an appropriate exposure definition given the dynamic nature of pharmacotherapy in type 2 diabetes. Third, the use of a base cohort eliminated left truncation, thereby allowing us to precisely assess important clinical characteristics, including duration of treated diabetes. Moreover, this method minimized the inclusion of

Table 3—Crude and adjusted HRs for the association between the use of GLP-1 RAs compared with the use of insulin and the risk of diabetic retinopathy

Exposure	Patients	Events	Person-years	Incidence rate (95% CI)[a]	Crude HR (95% CI)	Adjusted HR (95% CI)[b]
Insulin	5,556	226	3,942	57.3 (50.1–65.3)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	2,606	98	2,383	41.1 (33.4–50.1)	0.72 (0.57–0.91)	0.67 (0.51–0.90)
≤6 months of use						
Insulin	3,698	97	837	115.9 (94.0–141.4)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	1,163	37	298	124.3 (87.5–171.4)	0.95 (0.65–1.39)	0.84 (0.55–1.27)
6.1–12 months of use						
Insulin	798	36	561	64.2 (44.9–88.8)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	647	33	459	71.9 (49.5–101.0)	1.10 (0.69–1.77)	1.05 (0.64–1.72)
>12 months of use						
Insulin	1,060	93	2,544	36.6 (29.5–44.8)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	796	28	1,627	17.2 (11.4–24.9)	0.54 (0.35–0.82)	0.48 (0.31–0.76)
						P for heterogeneity = 0.02

[a]Per 1,000 persons per year. [b]Adjusted for propensity score including an interaction term between propensity score decile and propensity score as a continuous variable.

prevalent users (34), because all patients entering the base and study cohorts were required to be new users of antidiabetic drugs.

This study also has some limitations. First, due to its observational nature, it is susceptible to potential residual confounding. However, with treatment guidelines recommending GLP-1 RAs as a second- or third-line therapy (1), the use of oral antidiabetic drug combinations as an active comparator likely reduced this bias while providing a clinically meaningful treatment comparison. Furthermore, to mitigate this potential bias, our models included several variables such as HbA_{1c} level and BMI. Inclusion of these variables along with more than 30 other potential confounders had a minimal effect on the point estimate (crude HR 0.92 vs. adjusted HR 1.00). Moreover, we conducted several sensitivity analyses, such as the use of the high-dimensional disease risk score, which included more than 500 variables and yielded consistent findings.

Second, prescriptions in the CPRD represent those issued by primary care physicians and have not been previously validated. Thus, misclassification of exposure is possible if patient adherence was low or if they were treated by specialists. However, such exposure misclassification is unlikely to have been differential between the exposure groups, because the prescribing of GLP-1 RAs is not restricted to specialists in the U.K. (35).

Third, diagnostic codes of diabetic retinopathy have not been validated in the CPRD and HES. However, since 2003, all U.K. citizens with diabetes are invited for annual retinopathy screens as part of the Diabetic Eye Screening Program (36). Moreover, from 2004 to 2014, the recording of diabetic retinopathy was remunerated as part of the Quality and Outcomes Framework of the National Health Service, a reward and incentive program detailing primary care practice (37). As such, we expect the recording of diabetic retinopathy in the CPRD to have been high during the study period. Furthermore, our overall rate and patterns of diabetic retinopathy according to duration of treated diabetes are comparable to those previously reported (Supplementary Fig. 3) (38,39).

Finally, assessing the association between GLP-1 RAs and various severities of diabetic retinopathy (e.g., nonproliferative vs. proliferative disease) was not possible because these are not well distinguished in the CPRD and HES. Therefore, assessing whether GLP-1 RAs are associated with a worsening of existing diabetic retinopathy will need to be investigated in other settings where this information is routinely recorded.

In summary, the results of this large population-based study indicate that the use of GLP-1 RAs is not associated with an increased risk of diabetic retinopathy overall. Although there was a suggestion of a transient increased risk with durations of use ranging between 6 and 12 months, this finding needs to be interpreted with caution. The apparent lower risk of diabetic retinopathy associated with GLP-1 RAs compared with insulin may be due to residual confounding.

Funding. A.D. received a Research Fellowship from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG). K.B.F. holds a CIHR New Investigator Award. This research was funded by a Canadian Institutes of Health Research Foundation Scheme grant and a New Investigator Award to K.B.F. J.A.U. holds a Heart and Stroke Foundation of Canada National New Investigator/Ontario Clinician Scientist (Phase I) Award. L.A. holds a Chercheur-Boursier Senior Award from the Fonds de recherche du Québec – Santé (FRQS) and is the recipient of a William Dawson Scholar award from McGill University. All authors have completed the International Committee of Medical Journal Editors uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare this study was funded by the Canadian Institutes of Health Research. The sponsors were not directly involved in the design and conduct of the study, the collection, management, analysis, and interpretation of the data, or the preparation, review, or approval of the manuscript.

Duality of Interest. M.E. is a consultant on the finasteride and sexual dysfunction litigation. J.A.U. has consultant or advisory relationships with Amgen, Boehringer-Ingelheim, Janssen, Merck, Novartis, and Sanofi Pasteur, has received research support from Novartis, and has received honoraria for sponsored lectures from Janssen. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. A.D. drafted the manuscript. A.D., K.B.F., H.Y., O.H.Y., M.E., J.A.U., and L.A contributed to study concept and design, to the analysis and interpretation of data, and to critical revision of the manuscript for important intellectual content. A.D., H.Y., and L.A contributed to statistical analysis. L.A. acquired data, obtained funding, and supervised the study. L.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012;55:1577–1596
2. Pfeffer MA, Claggett B, Diaz R, et al.; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247–2257
3. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016; 375:311–322
4. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–1844
5. Holman RR, Bethel MA, Mentz RJ, et al.; EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017;377:1228–1239
6. Brooks AM, Lissett CA. A dramatic deterioration in diabetic retinopathy with improvement in glycated haemoglobin (HbA(1c)) on exenatide treatment. Diabet Med 2009;26:190
7. Varadhan L, Humphreys T, Hariman C, Walker AB, Varughese GI. GLP-1 agonist treatment: implications for diabetic retinopathy screening. Diabetes Res Clin Pract 2011;94:e68–e71
8. Varadhan L, Humphreys T, Walker AB, Varughese GI. The impact of improved glycaemic control with GLP-1 receptor agonist therapy on diabetic retinopathy. Diabetes Res Clin Pract 2014;103:e37–e39
9. Nathan DM, Genuth S, Lachin J, et al.; Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
10. Gorman DM, le Roux CW, Docherty NG. The effect of bariatric surgery on diabetic retinopathy: good, bad, or both? Diabetes Metab J 2016; 40:354–364
11. Hernández C, Bogdanov P, Corraliza L, et al. Topical administration of GLP-1 receptor agonists prevents retinal neurodegeneration in experimental diabetes. Diabetes 2016;65:172–187
12. Walley T, Mantgani A. The UK general practice research database. Lancet 1997;350:1097–1099
13. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol 2010;69:4–14
14. Faillie JL, Yu OH, Yin H, Hillaire-Buys D, Barkun A, Azoulay L. Association of bile duct and gallbladder diseases with the use of incretin-based drugs in patients with type 2 diabetes mellitus. JAMA Intern Med 2016;176:1474–1481
15. Goldberg DE, Smithen LM, Angelilli A, Freeman WR. HIV-associated retinopathy in the HAART era. Retina 2005;25:633–649; quiz 682–633
16. Makri OE, Georgalas I, Georgakopoulos CD. Drug-induced macular edema. Drugs 2013;73: 789–802
17. Ministry of Housing, Communities & Local Government. English indices of deprivation

[Internet]. Available from https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015. Accessed 31 October 2017
18. Durrleman S, Simon R. Flexible regression models with cubic splines. Stat Med 1989;8:551–561
19. Kumamaru H, Gagne JJ, Glynn RJ, Setoguchi S, Schneeweiss S. Comparison of high-dimensional confounder summary scores in comparative studies of newly marketed medications. J Clin Epidemiol 2016;76:200–208
20. Glynn RJ, Gagne JJ, Schneeweiss S. Role of disease risk scores in comparative effectiveness research with emerging therapies. Pharmacoepidemiol Drug Saf 2012;21(Suppl. 2):138–147
21. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509
22. National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults: management [Internet]. Available from https://www.nice.org.uk/guidance/ng28/chapter/1-Recommendations#managing-complications. Accessed 1 February 2017
23. Ding P, VanderWeele TJ. Sensitivity analysis without assumptions. Epidemiology 2016;27:368–377
24. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. Epidemiology 2010;21:383–388
25. Scirica BM, Bhatt DL, Braunwald E, et al.; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317–1326
26. White WB, Cannon CP, Heller SR, et al.; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327–1335
27. Green JB, Bethel MA, Armstrong PW, et al.; TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232–242
28. Grunwald JE, Riva CE, Martin DB, Quint AR, Epstein PA. Effect of an insulin-induced decrease in blood glucose on the human diabetic retinal circulation. Ophthalmology 1987;94:1614–1620
29. Henricsson M, Berntorp K, Fernlund P, Sundkvist G. Progression of retinopathy in insulin-treated type 2 diabetic patients. Diabetes Care 2002;25:381–385
30. U.S. Food and Drug Administration. FDA briefing document. Endocrinologic and Metabolic Drugs Advisory Committee Meeting (EMDAC) Victoza (liraglutide) [Internet], 2017. Available from https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM563334.pdf. Accessed 31 October 2017
31. Wysham CH, MacConell LA, Maggs DG, Zhou M, Griffin PS, Trautmann ME. Five-year efficacy and safety data of exenatide once weekly: long-term results from the DURATION-1 randomized clinical trial. Mayo Clin Proc 2015;90:356–365
32. Moride Y, Abenhaim L. Evidence of the depletion of susceptibles effect in non-experimental pharmacoepidemiologic research [published correction appears in J Clin Epidemiol 2004;57:111]. J Clin Epidemiol 1994;47:731–737
33. Suissa S. Immortal time bias in pharmacoepidemiology. Am J Epidemiol 2008;167:492–499
34. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003;158:915–920
35. Matza LS, Curtis SE, Jordan JB, Adetunji O, Martin SA, Boye KS. Physician perceptions of GLP-1 receptor agonists in the UK. Curr Med Res Opin 2016;32:857–864
36. Harris M. The NHS Diabetic Eye Screening Programme. In *Focus*. London, U.K., The Royal College of Ophthalmologists, 2012
37. Quality and outcomes framework - England, 2004-05: defining QOF indicators [Internet]. Available from http://content.digital.nhs.uk/catalogue/PUB01946/qof-eng-04-05-defi-indi-anx.pdf. Accessed 3 April 2017
38. Thomas RL, Dunstan F, Luzio SD, et al. Incidence of diabetic retinopathy in people with type 2 diabetes mellitus attending the Diabetic Retinopathy Screening Service for Wales: retrospective analysis. BMJ 2012;344:e874
39. Younis N, Broadbent DM, Vora JP, Harding SP; Liverpool Diabetic Eye Study. Incidence of sight-threatening retinopathy in patients with type 2 diabetes in the Liverpool Diabetic Eye Study: a cohort study. Lancet 2003;361:195–200