Glucagon-Like Peptide 1 Receptor Agonists and Risk of Diabetic Retinopathy Complications: Cohort Study in Nationwide Registers From Two Countries

Diabetes Care 2019;42:e92–e94 | https://doi.org/10.2337/dc18-2532

Peter Ueda,[1] Björn Pasternak,[1,2] Björn Eliasson,[3] Ann-Marie Svensson,[4] Stefan Franzén,[4,5] Soffia Gudbjörnsdottir,[3,4] Kristian Hveem,[6,7] Christian Jonasson,[6,7] Mads Melbye,[2,8,9] and Henrik Svanström[1,2]

Post hoc analyses of the Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) showed an increased risk of diabetic retinopathy complications associated with semaglutide versus placebo among patients with a history of retinopathy, especially among those with insulin use (1). Although concerns have been raised regarding the safety of glucagon-like peptide 1 (GLP-1) receptor agonists in patients with existing retinopathy, subgroup analyses by retinopathy status at baseline have not been presented for other trials of GLP-1 receptor agonists; the two observational studies on GLP-1 receptor agonists and diabetic retinopathy performed to date have excluded patients with a history of retinopathy (2) or treatment of retinopathy (3).

We conducted a cohort study (January 2010 to December 2016) of patients with existing retinopathy using nationwide data in Sweden and Denmark from the prescription registers, patient registers, population registers, the national bureaus of statistics, and the Swedish National Diabetes Register. Data sources and general methods used have been described in detail elsewhere (4,5). We included patients, aged 35–84 years, who filled their first prescription for either a GLP-1 receptor agonist or a dipeptidyl peptidase 4 (DPP-4) inhibitor (active comparator) during the study period and had a history of diabetic retinopathy (retinal photocoagulation, treatment with intravitreal agents, vitreous hemorrhage, vitrectomy, retinal detachment, retinal bleeding, and diabetic eye complications/retinopathy). We excluded patients who had previously filled prescriptions for any of the study drugs; had no hospital contact or prescription drug in the past year; had dialysis, renal transplantation, severe pancreatic disorders, end-stage illness, or drug misuse; or were hospitalized for any reason or had a hospital contact for diabetic retinopathy within 30 days before cohort entry. Using logistic regression, we estimated propensity scores for the probability of starting a GLP-1 receptor agonist versus a DPP-4 inhibitor given the status of 60 covariates, including sociodemographic characteristics, comorbidities, comedications, and health care utilization, at cohort entry; two-way interaction terms between country and each covariate were included in the model. Patients with a propensity score outside the overlapping area of the distribution for the two study drug groups were excluded.

Patients were considered exposed to the study drugs as long as prescriptions were refilled before the estimated end date of the most recent prescription, including a grace period of 180 days. The primary outcome, retinopathy complications, was a composite of retinal photocoagulation, treatment with intravitreal agents, vitreous hemorrhage, vitrectomy, retinal detachment, or retinal bleeding, which were identified by procedure and diagnostic codes. Patients were followed from cohort entry to end of exposure to the study drug, crossover to the other study drug, the outcome event, death, emigration, 5 years since cohort entry, or end of study period. Cox proportional hazards regression was used to calculate hazard ratios (HRs). Adjusted HRs were calculated using propensity score weighting.

[1]Clinical Epidemiology Division, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden
[2]Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark
[3]Department of Molecular and Clinical Medicine, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden
[4]Swedish National Diabetes Register, Västra Götalandsregionen, Gothenburg, Sweden
[5]Health Metrics, Department of Public Health and Community Medicine, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden
[6]K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, Faculty of Medicine and Health Science, NTNU–Norwegian University of Science and Technology, Trondheim, Norway
[7]Faculty of Medicine, HUNT Research Center, NTNU–Norwegian University of Science and Technology, Levanger, Norway
[8]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[9]Department of Medicine, Stanford University School of Medicine, Stanford, CA

Corresponding author: Peter Ueda, peter.ueda@ki.se

Received 11 December 2018 and accepted 14 March 2019

The study was approved by the Regional Ethical Review Board in Stockholm, Sweden, and the Danish Data Protection Agency.

The study population included 6,650 new users of GLP-1 receptor agonists (liraglutide, 91.6%; exenatide, 4.3%; dulaglutide, 2.7%; and lixisenatide, 1.4%) and 11,630 new users of DPP-4 inhibitors with history of retinopathy.

After propensity score weighting, the treatment groups were well balanced on baseline characteristics (data on file). Use of GLP-1 receptor agonists was not associated with a statistically significant increase in risk of diabetic retinopathy complications (adjusted HR 1.07 [95% CI 0.95–1.20]). Adjusted HRs in subgroup analyses by country, sex, age-group, insulin treatment, and glycated hemoglobin level at cohort entry (for patients in Sweden) were similar to those observed in the primary analyses (Table 1). The findings were similar in an additional analysis in which the follow-up time was truncated at 6 months after cohort entry and in sensitivity analyses applying an intention-to-treat exposure definition, truncation of large weights, or additional adjustments for glycated hemoglobin, blood pressure, albuminuria, estimated glomerular filtration rate, BMI, and smoking in the Swedish part of the cohort (Table 1).

In this nationwide cohort study of patients with existing retinopathy from two countries, we found no association between use of GLP-1 receptor agonists and diabetic retinopathy complications in analyses using DPP-4 inhibitors as the active comparator. Liraglutide comprised the majority (91.6%) of GLP-1 receptor agonist use in our study, and examination of individual GLP-1 receptor agonists remains a topic for future studies.

Data from the placebo-controlled SUSTAIN-6 trial suggest that retinopathy complications associated with semaglutide may occur due to early worsening of existing retinopathy following rapid improvement of glycemic control (1). We found no evidence of a risk increase associated with use of GLP-1 receptor agonists versus DPP-4 inhibitors among patients who might have a higher likelihood of experiencing a rapid improvement of glycemic control, including those

Table 1—Analyses of association between use of GLP-1 receptor agonists versus DPP-4 inhibitors and risk of diabetic retinopathy complications

	GLP-1 receptor agonists			DPP-4 inhibitors				
	N	Events	Events per 1,000 patient-years	*N*	Events	Events per 1,000 patient-years	Unadjusted HR (95% CI)	Adjusted HR[b] (95% CI)
Primary analysis								
Total cohort[a]	6,650	909	69.4	11,630	1,162	59.3	1.25 (1.15–1.36)	1.07 (0.95–1.20)
Subgroup analyses								
Country								
Denmark	2,821	370	53.7	3,497	322	47.9	1.25 (1.08–1.45)	1.02 (0.82–1.26)
Sweden	3,829	539	86.6	8,133	840	65.2	1.34 (1.20–1.49)	1.12 (0.98–1.28)
Sex								
Women	2,762	354	64.5	4,739	448	58.7	1.20 (1.05–1.38)	1.04 (0.87–1.25)
Men	3,888	555	72.8	6,891	714	59.7	1.29 (1.15–1.44)	1.08 (0.93–1.25)
Age (years)								
$<$65	3,942	589	71.7	4,266	521	68.4	1.12 (0.99–1.26)	1.00 (0.87–1.15)
$\geq$65	2,708	320	65.5	7,364	641	53.5	1.28 (1.12–1.47)	1.13 (0.94–1.35)
Insulin use								
No	1,554	158	48.3	7,190	606	46.4	1.12 (0.94–1.33)	1.18 (0.95–1.45)
Yes	5,096	751	76.4	4,440	556	84.9	1.00 (0.89–1.11)	0.98 (0.86–1.11)
Glycated hemoglobin (Sweden)[c]								
$<$8.7% (72 mmol/mol)	—	—	—	—	—	—	—	1.17 (0.94–1.46)
$\geq$8.7% (72 mmol/mol)	—	—	—	—	—	—	—	1.04 (0.87–1.26)
Additional analysis								
Truncated follow-up time at 6 months after cohort entry	6,650	410	135.9	11,630	602	116.7	1.17 (1.03–1.33)	1.04 (0.88–1.24)
Sensitivity analyses								
Intention-to-treat exposure definition[d]	6,650	1,159	62.4	11,630	1,515	53.3	1.23 (1.14–1.33)	1.03 (0.93–1.14)
Truncated weights[e]	6,650	909	69.4	11,630	1,162	59.3	1.25 (1.15–1.36)	1.08 (0.97–1.20)
Additionally adjusted model (Sweden)[f]	3,829	539	86.6	8,133	840	65.2	1.34 (1.20–1.49)	1.09 (0.95–1.25)

[a]Mean follow-up time (SD): 1.8 (1.5) years [2.0 (1.6) years for GLP-1 receptor agonists and 1.7 (1.4) years for DPP-4 inhibitors]. Total follow-up time: 13,105 patient-years for GLP-1 receptor agonists and 19,602 patient-years for DPP-4 inhibitors. [b]Inverse probability of treatment weighting based on a propensity score that included 60 covariates. [c]Analysis of patients in Sweden. There were missing data on glycated hemoglobin, and multiple imputation (Markov chain Monte Carlo method) was used to create 10 imputed data sets. Because each imputation yielded different subgroups of the total population, the number of patients, number of events, incidence rates, and unadjusted HRs are not presented. [d]Patients were considered exposed to the study drug throughout follow-up. [e]Inverse probability of treatment weighting can generate very large weights for patients with low probability of treatment. In this analysis, weights $>$5 were set to 5. [f]Analysis of patients in Sweden additionally adjusted for glycated hemoglobin, blood pressure, albuminuria, estimated glomerular filtration rate, BMI, and smoking. Because there were missing data for all these variables, multiple imputation (Markov chain Monte Carlo method) was used to create 10 imputed data sets.

with a higher glycated hemoglobin and those with insulin treatment at cohort entry. In addition, findings remained similar when follow-up time was truncated at 6 months after cohort entry, although incidence rates in both groups were higher in this time period.

Funding. P.U. was supported by grants from the Swedish Heart-Lung Foundation and the Swedish Society for Medical Research. B.P. was supported by an investigator grant from the Strategic Research Area Epidemiology program at Karolinska Institutet. The study was conducted with research grant support from the Swedish Cancer Society, the Nordic Cancer Union, and the Novo Nordisk Foundation.

The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.
Duality of Interest. B.E. reports personal fees from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Merck Sharp & Dohme, Mundipharma, Navamedic, Novo Nordisk, and RLS Global, Inc., outside the submitted work and grants from Sanofi outside of the submitted work. S.G. reports lecture fees and research grants from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Merck Sharp & Dohme, Novo Nordisk, and Sanofi outside of the submitted work. C.J. reports personal fees from Pfizer and Bayer outside of the submitted work. No other potential conflicts of interest relevant to this article were reported.
Author Contributions. P.U. drafted the manuscript. P.U. and B.P. obtained funding. P.U., B.P., and H.S. were responsible for concept and design. P.U., B.P., B.E., A.-M.S., S.F., S.G., K.H., C.J., M.M., and H.S. were responsible for acquisition, analysis, or interpretation of data and critical revision of the manuscript for important intellectual content. B.P. and H.S. were responsible for study supervision. H.S. was responsible for statistical analysis. P.U., B.P., and H.S. are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Data Availability. Study definitions and descriptive statistics are available upon request.

References

1. Vilsbøll T, Bain SC, Leiter LA, et al. Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. Diabetes Obes Metab 2018;20:889–897
2. Douros A, Filion KB, Yin H, et al. Glucagon-like peptide 1 receptor agonists and the risk of incident diabetic retinopathy. Diabetes Care 2018;41:2330–2338
3. Wang T, Hong J-L, Gower EW, et al. Incretin-based therapies and diabetic retinopathy: real-world evidence in older U.S. adults. Diabetes Care 2018;41:1998–2009
4. Ueda P, Svanström H, Melbye M, et al. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. BMJ 2018;363:k4365
5. Svanström H, Ueda P, Melbye M, et al. Use of liraglutide and risk of major cardiovascular events: a register-based cohort study in Denmark and Sweden. Lancet Diabetes Endocrinol 2019;7:106–114