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RESEARCH LETTER

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Early uptake of semaglutide for type 2 diabetes in Scandinavia and characteristics of initiators in Denmark: A register-based drug utilization study

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1 | INTRODUCTION

The use of glucose-lowering drugs has changed considerably during the last decade.[1,2] To understand the role of semaglutide in the treatment of type 2 diabetes, we aimed firstly to describe the uptake in adults in the early phases after launch in three Scandinavian countries, including the impact of semaglutide on the use of other glucagon-like peptide-1 receptor agonists (GLP-1RAs) indicated for treatment of type 2 diabetes. Secondly, we aimed to compare the characteristics of semaglutide initiators with those of initiators of liraglutide and other glucose-lowering drugs and to compare early versus late initiators of subcutaneous semaglutide in Denmark.

2 | METHODS

2.1 | Data sources

We used nationwide data on filled prescriptions in Denmark, Norway and Sweden.[3] Data included dispensing date, Anatomical Therapeutic Chemical (ATC) code,[4] drug ID, dispensed drug volume in defined daily doses (DDDs),[4] and type of prescriber (in Denmark). Population counts were extracted from national statistics. To characterize Danish initiators of semaglutide we used information on diagnoses from the National Patient Register[5] and laboratory values of estimated glomerular filtration rate (eGFR).[6]

2.2 | Study population

Semaglutide was introduced in Scandinavia in October 2018 (Ozempic® [subcutaneous]) and in March 2020 (Rybelsus® [oral]). We identified individuals aged ≥18 years who filled at least one prescription of semaglutide, liraglutide, or other GLP-1RA in the period 1 January 2018 to 30 September 2022 in Sweden and Norway and to 30 June 2023 in Denmark. For Denmark we also included individuals aged ≥18 years who were new users of sodium-glucose cotransporter-2 (SGLT2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, insulin, and sulphonylureas (SUs) between 1 January 2018 and 30 June 2023. We excluded GLP-1RAs indicated for weight management. Combination products were split into their individual components (Appendix S1).

2.3 | Analyses

We calculated the quarterly incidence rate, prevalence proportion, and total annual quantity of dispensed semaglutide, liraglutide and

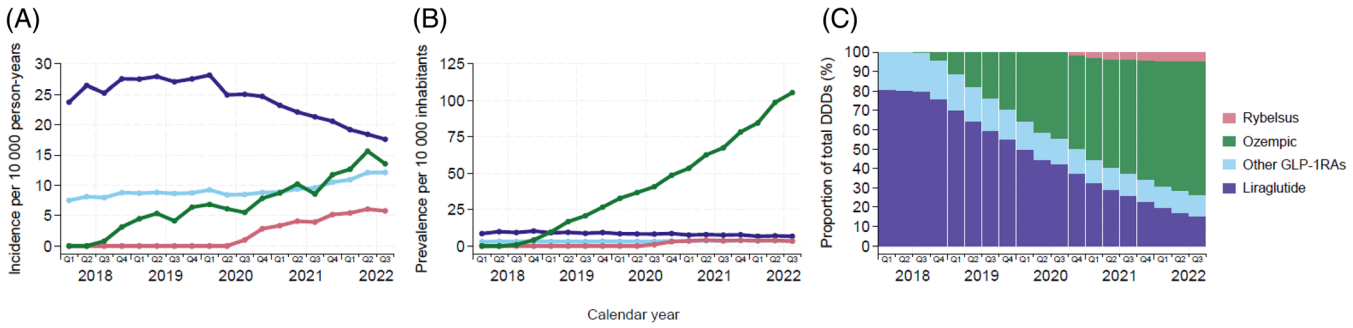

FIGURE 1 (A) Quarterly incidence rate (per 10 000 person-years), (B) prevalence proportion (per 10 000 inhabitants) and (C) proportional distribution in total defined daily doses (DDDs; in millions) of semaglutide (Ozempic® and Rybelsus®), liraglutide, and other glucagon-like peptide-1 receptor agonists (GLP-1RAs) for the period 1 January 2018 to 30 September 2022 in Scandinavia.

other GLP-1RAs in Scandinavia from 1 January 2018 to 30 September 2022. The incidence rate was calculated as the number of new users in the given quarter of the year divided by the total population follow-up time (using the total population count on 1 January as an approximation of the person-time at risk). 'New users' had no dispensation of the specific glucose-lowering drugs during the last 10 years or since market approval. The prevalence proportion was calculated as the number of users in the given quarter divided by the total population count on 1 January in the given year. Drug use was defined as the filling of at least one prescription. In additional analyses, the incidence and prevalence were stratified by age (18–39, 40–59, 60–79 and ≥80 years), and analyses were performed separately for each country.

We characterized new users of glucose-lowering drugs in Denmark for the period 1 January 2018 to 30 June 2023 according to: (1) sex and age at initiation (index date); (2) previous use (within 6 months before index date) and concomitant use (within 6 months after index date) of glucose-lowering drugs; (3) use of statins, anticoagulants, and antihypertensives within 6 months before or after index date; (4) diagnoses of cardiovascular or renal disease; and (5) the prescriber of the initial glucose-lowering drug prescription. Additionally, we divided new users of Ozempic into groups of 'early' and 'late' initiators. Early initiators initiated Ozempic before 1 September 2019. Users of Ozempic were further characterized on diagnoses used as exclusion criteria in the SUSTAIN 1 and 2 trials[7,8] as available in the data. Diagnoses are available in Appendix S2.

Analyses were performed using Stata Release 17.0 (StataCorp, College Station, TX, USA).

2.4 | Ethical approval

The study was registered in the repository at the University of Southern Denmark (10.940) and required no approval from an ethics review board. Data for Norway provided as aggregated data did not require ethical approval. Ethical approval was given by the Swedish Ethical Review Authority (Dnr 2023–03824-02).

3 | RESULTS

The total dispensed quantity of GLP-1RAs in Scandinavia reached 21 million DDDs, with semaglutide accounting for 74% by the end of September 2022 (Figure 1 and Figure S1). The incidence rate and prevalence proportion of semaglutide use reached 19 per 10 000 person-years and 109 per 10 000 persons in the third quarter of 2022, mainly driven by Ozempic (Figure 1) and use in individuals aged 40–79 years in all countries (Figures S2A–C and S3A–C). Uptake of Rybelsus during the study period was limited.

Semaglutide initiators were younger compared to initiators of other non-GLP-1RA glucose-lowering drugs (Table S1). Initiators of semaglutide less frequently had previous and concomitant use of DPP-4 inhibitors, SUs and insulin compared to initiators of liraglutide. They did, however, use slightly more SGLT2 inhibitors compared to initiators of liraglutide. There were only minor differences between semaglutide and liraglutide initiators in use of comedication. Semaglutide initiators had slightly less cardiovascular and renal disease compared to initiators of liraglutide. General practitioners (GPs) prescribed most initial prescriptions in both semaglutide and liraglutide users, although hospital physicians played a greater role in the prescribing of liraglutide. There were differences in characteristics between users of Ozempic and Rybelsus (Table S1). Users of Rybelsus were older, they more frequently had previous use of other glucose-lowering drugs except for insulin and SUs, they more often used statins and antihypertensives, and almost exclusively had their first prescription issued by a GP.

'Late' initiators of Ozempic were younger and had fewer comorbidities compared to 'early' initiators (Table 1). There were more women among the late versus early (50% vs. 42%) initiators. Late initiators less frequently had previous and concomitant use of other glucose-lowering drugs, they used statins (63% vs. 77%) and antihypertensives (67% vs. 80%) less frequently, and had less cardiovascular and renal disease compared to early initiators. More prescriptions were issued by GPs among late versus early initiators (84% vs. 64%). One-fifth of Ozempic initiators had at least one condition specified as an exclusion criterion in the SUSTAIN trials, with 15% having impaired renal function.

TABLE 1 Characteristics of early and late initiators of Ozempic® in Denmark from marketing in the period 1 September 2018 to 30 June 2023, Denmark.

	Ozempic®		
	All ($n = 107\,983$)	Early ($n = 16\,500$)	Late ($n = 91\,483$)
Age at initiation, years			
Median (IQR)	59 (50–69)	62 (53–70)	59 (50–68)
Mean (SD)	59.3 (13.3)	61.6 (11.8)	58.9 (13.5)
Sex, *n* (%)			
Male	55 411 (51)	9562 (58)	45 849 (50)
Female	52 572 (49)	6938 (42)	45 634 (50)
Previous use of antidiabetics, *n* (%)			
Metformin	70 040 (65)	13 180 (80)	56 860 (62)
SGLT2 inhibitors	30 392 (28)	5406 (33)	24 986 (27)
DPP-4 inhibitors	15 770 (15)	3235 (20)	12 535 (14)
SUs	24 704 (23)	6963 (42)	17 741 (19)
Insulin	5782 (5.4)	1491 (9.0)	4291 (4.7)
Pioglitazone	41 (0.04)	10 (0.06)	31 (0.03)
GLP-1RAs	21 879 (20)	7480 (45)	14 399 (16)
Concomitant use of antidiabetic drugs, *n* (%)			
Metformin	67 582 (63)	12 992 (79)	54 590 (60)
SGLT2 inhibitors	27 937 (26)	4889 (30)	23 048 (25)
DPP-4 inhibitors	5318 (4.9)	1128 (6.8)	4190 (4.6)
SUs	3323 (3.1)	919 (5.6)	2404 (2.6)
Insulin	25 015 (23)	7022 (43)	17 993 (20)
Pioglitazone	40 (0.04)	13 (0.08)	27 (0.03)
Comedication, *n* (%)			
Statins	69 982 (65)	12 647 (77)	57 335 (63)
Anticoagulants	10 624 (9.8)	1757 (11)	8867 (9.7)
Antihypertensives	74 901 (69)	13 195 (80)	61 706 (67)
Prescriber responsible for initiating treatment[a], *n* (%)			
General practitioner	79 658 (81)	9721 (64)	69 937 (84)
Hospital physician	18 102 (18)	5487 (36)	12 615 (15)
Private practicing specialist	604 (0.61)	47 (0.31)	557 (0.67)
Diagnoses[b], *n* (%)			
Cardiovascular disease	28 019 (26)	5231 (32)	22 788 (25)
Heart failure	6251 (5.8)	1284 (7.8)	4967 (5.4)
Renal disease	8863 (8.2)	2158 (13)	6705 (7.3)
Exclusion criteria in SUSTAIN 1 and 2 trials[b], *n* (%)			
At least one of below	22 862 (21)	4234 (26)	18 628 (20)
Impaired renal function	16 116 (15)	3186 (19)	12 930 (14)
eGFR <30 mL/min/1,73 m^2	1424 (1.3)	232 (1.4)	1192 (1.3)
eGFR 30 to <60	14 460 (13)	2927 (18)	11 533 (13)
Based on hospital-diagnosis in individuals with missing eGFR	232 (0.21)	27 (0.16)	205 (0.22)
Chronic or idiopathic acute pancreatitis	2312 (2.1)	343 (2.1)	1969 (2.2)
Acute coronary or cerebrovascular events within 90 days before	564 (0.52)	74 (0.45)	490 (0.54)
Diagnosis of malignant neoplasm in the previous 5 years excl. non-melanoma skin cancer[c]	6518 (6.0)	1075 (6.5)	5443 (5.9)

Note: 'Early' initiators initiated Ozempic before 1 September 2019.

Abbreviations: DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; IQR, interquartile range; SD, standard deviation; SGLT2 inhibitors, sodium-glucose cotransporter-2; SU, sulphonylurea.

[a]Prescriptions with missing prescriber information were excluded (9%).

[b]Based on all time available before index date unless otherwise specified. Renal disease is only based on International Classification of Diseases, Tenth Revision diagnosis codes.

[c]Not an exclusion criterion in SUSTAIN 1.

4 | CONCLUSION

The early uptake of semaglutide in Scandinavia has been considerable, mainly at the expense of liraglutide. Initiators of semaglutide and liraglutide differed only slightly in patient characteristics. The small differences in characteristics may stem from the use of Ozempic for indications other than type 2 diabetes.

Late initiators of Ozempic had less cardiovascular drug use and comorbidity compared to early initiators, in line with previous findings from Denmark showing less cardiovascular comorbidity over time among initiators of GLP-1RAs, and also included fewer individuals with a diabetes hospital diagnosis.[1] This finding might support use of Ozempic outside approved indication late in the period, in line with the growing public interest in off-label use of Ozempic for weight loss.[9]

Real-world users of Ozempic were older compared to study participants in SUSTAIN 1 and 2.[7,8] One-fifth of real-world Ozempic users would have been ineligible for trials after SUSTAIN 1, primarily due to having an eGFR <60 mL/min/1,73 m^2 (13% of users) and presence of malignant neoplasms (6% of users). Although 6% of real-world users had a hospital diagnosis of heart failure (NYHA Class IV was used as an exclusion criterion in trials), we did not have access to data on NYHA class.

The primary strength of the study was the use of nationwide data on dispensed drugs, with no risk of selection bias. Limitations include lack of data on indications for use, inclusion of hospital recorded diagnoses only, and use of filled prescriptions as a proxy for drug use.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

Anton Pottegård reports participation in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Novo Nordisk, Servier and LEO Pharma (all regulator-mandated Phase IV studies), and an unrestricted research grant from Novo Nordisk, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the work reported in this paper. Lotte Rasmussen, Jacob Harbo Andersen, Øystein Karlstad, Diego Hernan Giunta, Marie Linder and Kari Furu report participation research projects funded by pharmaceutical companies, including Novo Nordisk, all regulator-mandated Phase IV studies and all with funds paid to the institution where they were employed (no personal fees) and with no relation to the work reported in this paper.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15876.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the relevant data authorities within Denmark, Norway and Sweden. Restrictions apply to the availability of these data, which were used under license for this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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