Received: 12 June 2024 | Revised: 8 August 2024 | Accepted: 15 August 2024

DOI: 10.1111/dom.15912

ORIGINAL ARTICLE

WILEY

Treatment trajectories for Danish individuals with type 2 diabetes in the era of emerging glucose-lowering therapies

Anton Pottegård DMSc[1] | Jacob H. Andersen MSc[1] | Jens Søndergaard PhD[2] | Lotte Rasmussen PhD[1] | Helene Kildegaard MD[1] | Tina Vilsbøll DMSc[3,4] | Reimar W. Thomsen PhD[5]

[1]Clinical Pharmacology, Pharmacy, and Environmental Medicine, Department of Public Health, University of Southern Denmark, Odense, Denmark

[2]Research Unit of General Practice, Department of Public Health, University of Southern Denmark, Odense and Esbjerg, Denmark

[3]Clinical Research, Steno Diabetes Centre Copenhagen, Herlev, Denmark

[4]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[5]Department of Clinical Epidemiology, Department of Clinical Medicine, Aarhus University Hospital and Aarhus University, Aarhus, Denmark

Correspondence
Anton Pottegård, Clinical Pharmacology, Pharmacy, and Environmental Medicine, Department of Public health, University of Southern Denmark, Campusvej 55, DK-5230 Odense C, Denmark.
Email: apottegaard@health.sdu.dk

Funding information
Novo Nordisk (unrestricted grant)

Abstract

Aim: To analyse patterns of glucose-lowering therapies among people with type 2 diabetes (T2D) in Denmark from 2016 to 2023.

Materials and Methods: We examined time trends in the clinical profiles of people with T2D who initiated different glucose-lowering therapy classes for the first time. We furthermore investigated individual-level treatment trajectories following first-ever glucose-lowering therapy in people with or without cardiorenal disease. The study utilized data from the nationwide Danish health registries and included all individuals who filled a first-ever prescription for metformin, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs), sodium-glucose co-transporter-2 inhibitors (SGLT-2is) or insulin, excluding those without HbA1c-confirmed T2D or probable type 1 diabetes.

Results: We included 260 393 individuals initiating a new glucose-lowering therapy class from 2016 to 2023, during which there were 6- and 3-fold increases in initiators of GLP-1RAs and SGLT-2is, respectively. The median HbA1c level at treatment initiation with GLP-1RAs or SGLT-2is decreased, from 67-68 mmol/mol in 2016-2017 to 57-58 mmol/mol in 2022-2023. Among individuals who initiated metformin as first-line therapy, the proportion who started additional glucose-lowering therapy within 2 years increased from 25% in 2016 to 40% in 2021. Among the 38% of individuals who had established cardiorenal disease when they initiated first-ever glucose-lowering therapy in 2020, 22% used SGLT-2is and 18% GLP-1RAs after 2.5 years, compared with 17% and 21% among initiators without cardiorenal disease, respectively.

Conclusions: Our study documents a trend towards earlier T2D treatment intensification and an increase in the use of GLP-1RAs and SGLT-2is in Denmark. However, optimal T2D treatment is still not received by most individuals with early T2D and established cardiorenal disease.

KEYWORDS
antidiabetic drug, pharmaco-epidemiology, type 2 diabetes, database research

1 | INTRODUCTION

Type 2 diabetes (T2D) is a chronic and complex disease affecting more than 500 million individuals worldwide.[1,2] Managing this condition requires multifaceted approaches, including behavioural modifications and preventive pharmacological treatments.[3,4] Glucose-lowering therapies play a pivotal role in maintaining plasma glucose levels, preventing complications and enhancing overall quality of life for individuals with T2D.[5]

Individuals with T2D face an increased risk of cardiovascular disease (CVD) and chronic kidney disease (CKD) because of a high prevalence of cardio-renal-metabolic risk factors such as chronic hyperglycaemia, insulin resistance, obesity, inflammation, hypertension and lipid abnormalities.[6,7] CVD affects approximately one-third of the T2D population[8,9] and accounts for a significant proportion of mortality.[10] Given this burden, the choice of glucose-lowering therapy becomes critical, not only for glycaemic control, but also for cardiorenal protection.[4,5]

Since 2015, results from large randomized clinical trials have proven that the newer glucose-lowering therapies, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter-2 inhibitors (SGLT-2is), provide considerable cardiorenal benefits in individuals with T2D and a high risk of CVD independently of glycaemic control,[11] leading to marked changes in treatment recommendations.[4,5] However, several studies have shown that individuals at high risk are still not receiving organ-protective therapies, but only older therapies, including sulphonylureas (SUs) and dipeptidyl peptidase-4 inhibitors (DPP-4is).[9,12–14]

The sharply rising number of individuals with T2D has resulted in the management increasingly moving from hospitals to primary care. To address the growing complexity of T2D treatment and expanding treatment modalities, continuous professional development is being provided to primary care physicians.[13] However, the outsourcing of increasingly complex pharmacological treatment also necessitates surveillance of evolving real-world utilization patterns of glucose-lowering therapies, to understand unmet treatment needs and optimize care for individuals with T2D.

Denmark has high-quality health registries that enable longitudinal follow-up of all people diagnosed with T2D,[10,15] enabling detailed examination of individual treatment trajectories. We conducted a Danish nationwide study to investigate contemporary glucose-lowering treatment trajectories for individuals with T2D, in an era of emerging therapies and rapidly changing treatment guidelines.

2 | MATERIALS AND METHODS

We applied a population-based cohort study design investigating adults with HbA1c-confirmed T2D who received glucose-lowering therapies in Denmark. Our study had three major aims. First, we performed a detailed characterization of all people who initiated one of the major glucose-lowering therapy classes for the first time (e.g. first-time users of any SGLT-2i, first-time users of any GLP-1RA, etc.) and examined any changes in their clinical profiles over calendar time. Second, we included adults with T2D at the time they initiated their first glucose-lowering therapy ever (most often metformin), and followed them longitudinally for changes in their therapy to describe trajectories of T2D medication use, overall and according to cardiorenal disease. Third, we specifically followed the large majority of users who initiated metformin as first-line treatment, investigating time to first add-on of another glucose-lowering drug.

2.1 | Cohort identification and data sources

We first identified potentially eligible study participants as all Danish adults (age ≥ 18 years) filling a prescription for a glucose-lowering therapy from January 2016 through December 2023. This was carried out using data from the Danish National Prescription Registry[16] and Anatomical Therapeutic Chemical code[17] A10* ('drugs used in diabetes'). This registry covers prescriptions filled at all Danish community pharmacies since 1995. During the study period, all glucose-lowering therapies were included in the reimbursement scheme, with limited self-payment from the patient.

For all individuals we identified filled prescriptions[16] (since 2000), hospital contacts[18] (since 2000) and laboratory values[19] (available since 2015). Data sources were linked using a unique person identifier provided to all Danish residents.[20] Glucose-lowering therapies were classified as metformin, SUs, DPP-4is, GLP-1RAs, SGLT-2is, insulins and other (glinides, thiazolidinediones and acarbose). Both for cohort identification and assessment of glucose-lowering therapy use, prescriptions for GLP-1RAs marketed with the indication of weight-loss therapy were disregarded. In all analyses, prescriptions for combination drugs were split into their individual components. All codes used to identify drugs, as well as diagnoses and laboratory codes, are detailed in Appendix S1 (see the supporting information).

From the base cohort of potentially eligible study participants, we performed sequential restrictions to identify the study population of interest. First, we restricted to individuals with at least 5 years of continuous residency in Denmark prior to initiation of glucose-lowering therapy, to ensure a sufficient look-back period for assessment of prior treatment history and previous co-morbidities. Further, because glucose-lowering therapies are increasingly used for indications other than diabetes (e.g. in CVD or off-label use for weight loss), we only included individuals who had HbA1c-defined diabetes,[4] that is, a recorded HbA1c above 48 mmol/mol either before (within 2 years) of filling their first-ever glucose-lowering therapy prescription or within the first 6 months after initiation (as initial therapy could have been based on point-of-care tests at the general practitioner or on glucose measures other than HbA1c). Individuals filling their first prescription for glucose-lowering therapy prior to 2016, that is, before laboratory data were available, were also considered eligible, as the use of glucose-lowering therapies for non-diabetes reasons was limited at that time. To further restrict our analyses to individuals with T2D and reduce the likelihood of including individuals with type 1 diabetes, we excluded all individuals starting insulin as first-line treatment and who

did not fill other glucose-lowering therapy classes within 6 months after initiation. Some patients with other forms of diabetes, for example, latent autoimmune diabetes in adults or rare monogenic diabetes types, were thus categorized as having T2D in our study.

2.2 | Analyses

For our first aim, to describe and compare contemporary initiators of the main glucose-lowering therapy classes, we focused on the most recent 1.5-year period in our data from January 2022 to June 2023. We explored where each drug class is currently used in the treatment trajectories, and performed a detailed characterization of all initiators of metformin, DPP-4is, GLP-1RAs, SGLT-2is and insulins. The most recent 1.5-year period ended in June 2023 to allow for subsequent follow-up for at least 6 months for all initiators, that is, through December 2023. Initiation, that is, new use, was defined as first fill of the given drug class in at least 5 years (leveraging prescription data going back to 2000). Next, to identify changes over time, a similar characterization was performed for initiators of glucose-lowering therapy classes during the 2-year periods, namely, 2016-2017, 2018-2019 and 2020-2021. This characterization was conducted on the date of treatment initiation (i.e. date of first fill of the corresponding glucose-lowering therapy) and was carried out in terms of age, sex, previous (within the last 6 months) and concomitant (within the next 6 months) use of other glucose-lowering therapies, diabetes complications (based on hospital inpatient or outpatient contact history of diagnoses and procedures, and laboratory values), diabetes duration, co-morbidities, co-medication, laboratory values (including kidney function) and the type of prescriber initiating treatment (see Appendix S1 for the definitions and codes used). Baseline characteristics were described for initiators of each of the five glucose-lowering therapy classes individually, as well as insulins split into basal and bolus insulin.

For our second aim, we restricted to the group of first-ever users of any glucose-lowering therapy for T2D, that is, new first-line treatment initiators. We first described the most contemporary trajectories in 2020 onwards, by identifying initiators (first-ever) of glucose-lowering therapy during 2020 and followed them for 2.5 years. Next, these longitudinal trajectories were compared with those of new first-line glucose-lowering therapy initiators in each year from 2016 to 2019, to describe changes in trajectories over time. The use of glucose-lowering therapies was described in 6-month intervals, starting at the date of the first glucose-lowering therapy fill and for five consecutive 6-month intervals (leveraging prescription data until the end of 2023 and requiring at least 6 months of data to identify future prescriptions after the 2.5 years; see below). All drugs used within such a 6-month interval were considered as concomitantly used; for example, if an individual filled a prescription for metformin, a SGLT-2i and insulin during a 6-month interval, that individual would be classified as concomitantly using all three glucose-lowering therapies. Acknowledging that switching would be incorrectly classified as concomitant use with this approach, we systematically disregarded a prescription if we observed no later fill (within 6 months) of the same glucose-lowering therapy class. This meant that if an individual switched during an interval from, for example, a DPP-4i to a GLP-1RA, and thus did not later fill a prescription for a DPP-4i, then that patient would be classified as having only used a GLP-1RA during that interval. As a sensitivity analysis, we did not apply this restriction. Further, we performed this analysis stratifying by baseline presence (yes/no) of either CVD or CKD, based on laboratory and hospital record data (see Appendix S1).

For our third aim, specifically regarding those initiating metformin as first-line treatment during 2020-2021 (i.e. the more recent cohorts who still had 2 full years of available follow-up), we identified the proportion who filled a non-metformin glucose-lowering therapy within the first 2 years after metformin initiation and the median time until such therapy. Again, to investigate changes over time, similar analyses were performed for characteristics of initiators during 2016-2017 and 2018-2019.

All analyses were performed using STATA v. 18.

2.3 | Approvals and ethics

According to Danish law, studies based solely on register data do not require approval from an ethics review board.[21] The data underlying this study are available from the Danish Health Data Authority. Restrictions apply to the availability of these data, which were used under licence for this study.

3 | RESULTS

We identified a base cohort of 456 239 adult individuals filling at least one glucose-lowering therapy prescription during 2016-2023. Within this cohort, 348 879 individuals initiated a new glucose-lowering therapy class within the study period. After excluding those with an insufficient look-back period, no recorded HbA1c of 48 mmol/mol or higher prior to initiation, or insulin-only use, the final study cohort comprised 260 393 individuals initiating or adding a new glucose-lowering therapy class during 2016-2023. Of these, 140 948 initiated their first-ever glucose-lowering therapy.

3.1 | Characteristics of glucose-lowering therapy class initiators

The characteristics of individuals initiating or adding a glucose-lowering therapy class during the most recent period, that is, from January 2022 to June 2023, are outlined in Table 1. Metformin was mainly used as first-line treatment, with initiators having a median HbA1c of 54 mmol/mol. Initiators of DPP-4is, GLP-1RAs and SLGT-2is had comparable diabetes durations (median 5-6 years) and similar glycaemic control (median HbA1c 57-60 mmol/mol). However, initiators of GLP-1RAs were, compared with initiators of DPP-4is and

TABLE 1 Clinical profiles of people who initiated glucose-lowering therapy classes for the first time[a] during January 2022 to June 2023.

	Metformin ($n = 33\,196$)	DPP-4i ($n = 5526$)	GLP-1RA ($n = 32\,874$)	SGLT-2i ($n = 33\,423$)	Insulin ($n = 8158$)
Age at initiation, median (IQR); y	62 (53-72)	69 (59-77)	61 (53-70)	69 (59-77)	69 (58-78)
Female sex, *n*	13 885 (42%)	2326 (42%)	14 744 (45%)	12 251 (37%)	3106 (38%)
Diabetes duration, median (IQR); y	0 (0-0)	6 (2-12)	5 (1-11)	6 (1-12)	8 (2-13)
Previous use of glucose-lowering therapies, *n*					
None	31 483 (95%)	676 (12%)	4484 (14%)	4688 (14%)	1214 (15%)
Metformin	-	4289 (78%)	25 748 (78%)	25 977 (78%)	5800 (71%)
SUs	150 (0.45%)	312 (5.6%)	1489 (4.5%)	1522 (4.6%)	934 (11%)
DPP-4is	151 (0.45%)	-	5514 (17%)	4644 (14%)	1708 (21%)
GLP-1RAs	601 (1.8%)	599 (11%)	-	5850 (18%)	2720 (33%)
SGLT-2is	625 (1.9%)	1822 (33%)	11 365 (35%)	-	3217 (39%)
Insulin	501 (1.5%)	452 (8.2%)	2966 (9.0%)	4128 (12%)	-
Other	5 (0.02%)	12 (0.22%)	48 (0.15%)	50 (0.15%)	34 (0.42%)
Concurrent use of glucose-lowering therapies, *n*					
Metformin	-	3833 (69%)	24 334 (74%)	24 466 (73%)	5393 (66%)
SUs	224 (0.67%)	268 (4.8%)	805 (2.4%)	999 (3.0%)	190 (2.3%)
DPP-4is	678 (2.0%)	-	1934 (5.9%)	3451 (10%)	1133 (14%)
GLP-1RAs	4302 (13%)	616 (11%)	-	7361 (22%)	2414 (30%)
SGLT-2is	4104 (12%)	1728 (31%)	10 158 (31%)	-	2984 (37%)
Insulin	1470 (4.4%)	647 (12%)	3132 (9.5%)	4470 (13%)	-
Other	9 (0.03%)	10 (0.18%)	16 (0.05%)	22 (0.07%)	6 (0.07%)
Markers of diabetes severity and co-morbidities[b]					
HbA1c, median (IQR); mmol/mol	54 (50-66)	60 (54-70)	58 (50-68)	57 (50-67)	76 (62-97)
HbA1c, median (IQR); %	7.1 (6.7-8.2)	7.6 (7.1-8.6)	7.5 (6.7-8.4)	7.4 (6.8-8.3)	9.1 (7.8-11.0)
LDL-cholesterol, median (IQR); mmol/L	2.50 (1.90-3.30)	1.90 (1.40-2.50)	2.00 (1.50-2.60)	1.80 (1.40-2.40)	1.90 (1.40-2.60)
Albuminuria, *n*					
Unknown	16 901 (51%)	1743 (32%)	9842 (30%)	8500 (25%)	2977 (36%)
No/Stage A1 (UACR < 30 mg/g)	12 054 (36%)	2386 (43%)	15 993 (49%)	14 938 (45%)	2736 (34%)
Stage A2 (UACR 30-300 mg/g)	3756 (11%)	1095 (20%)	5926 (18%)	7630 (23%)	1920 (24%)
Stage A3 (UACR > 300 mg/g)	485 (1.5%)	302 (5.5%)	1113 (3.4%)	2355 (7.0%)	525 (6.4%)
eGFR, median (IQR); mL/min/1.73m^2	89 (74-100)	83 (57-97)	91 (74-101)	82 (57-95)	85 (54-100)
< 15	11 (0.03%)	40 (0.72%)	26 (0.08%)	43 (0.13%)	53 (0.65%)
15-29	66 (0.20%)	298 (5.4%)	355 (1.1%)	871 (2.6%)	377 (4.6%)
30-44	744 (2.2%)	449 (8.1%)	1224 (3.7%)	2931 (8.8%)	777 (9.5%)
45-59	3008 (9.1%)	706 (13%)	3004 (9.1%)	5316 (16%)	1244 (15%)
≥ 60	28 417 (86%)	3764 (68%)	27 296 (83%)	22 976 (69%)	5284 (65%)
Renal complications, *n*	7453 (22%)	2428 (44%)	10 313 (31%)	15 649 (47%)	4079 (50%)
Eye complications, *n*	999 (3.0%)	443 (8.0%)	2103 (6.4%)	2869 (8.6%)	842 (10%)
Neurological complications, *n*	646 (1.9%)	391 (7.1%)	1621 (4.9%)	2118 (6.3%)	663 (8.1%)
Hospital-diagnosed obesity, *n*	5418 (16%)	923 (17%)	9543 (29%)	6164 (18%)	1559 (19%)
Ischaemic heart disease, *n*	4889 (15%)	1064 (19%)	5621 (17%)	8418 (25%)	1700 (21%)
Atherosclerotic cerebrovascular disease, *n*	2545 (7.7%)	581 (11%)	2290 (7.0%)	3478 (10%)	1053 (13%)
Atherosclerotic peripheral vascular disease and other atherosclerotic disease, *n*	1241 (3.7%)	470 (8.5%)	1857 (5.6%)	2968 (8.9%)	812 (10.0%)
Heart failure, *n*	1532 (4.6%)	448 (8.1%)	1813 (5.5%)	4806 (14%)	804 (9.9%)

TABLE 1 (Continued)

	Metformin ($n = 33\,196$)	DPP-4i ($n = 5526$)	GLP-1RA ($n = 32\,874$)	SGLT-2i ($n = 33\,423$)	Insulin ($n = 8158$)
Chronic lung disease, *n*	8771 (26%)	1507 (27%)	9683 (29%)	9304 (28%)	2411 (30%)
Markers of smoking, *n*	3832 (12%)	572 (10%)	4480 (14%)	4014 (12%)	1027 (13%)
Markers of alcohol overuse, *n*	2274 (6.9%)	380 (6.9%)	2128 (6.5%)	2131 (6.4%)	748 (9.2%)
Co-medication					
Number of drugs					
Median (IQR)	5 (2-8)	6 (4-10)	6 (4-9)	7 (4-10)	8 (4-11)
0-1	5811 (18%)	346 (6.3%)	2366 (7.2%)	1884 (5.6%)	703 (8.6%)
2-4	9823 (30%)	1407 (25%)	8557 (26%)	7626 (23%)	1499 (18%)
5-9	11 866 (36%)	2322 (42%)	14 338 (44%)	14 751 (44%)	3033 (37%)
≥ 10	5696 (17%)	1451 (26%)	7613 (23%)	9162 (27%)	2923 (36%)
Statins, *n*	13 869 (42%)	3896 (71%)	22 630 (69%)	24 803 (74%)	5246 (64%)
Anticoagulants, *n*	3539 (11%)	835 (15%)	3363 (10%)	5919 (18%)	1454 (18%)
Antiplatelets, *n*	6224 (19%)	1487 (27%)	7794 (24%)	10 826 (32%)	2449 (30%)
ACEis/ARBs, *n*	15 112 (46%)	3452 (62%)	21 103 (64%)	23 443 (70%)	4736 (58%)
Prescriber type					
General practitioner, *n*	30 510 (92%)	4457 (81%)	29 923 (91%)	26 849 (80%)	3935 (48%)
Hospital physician, *n*	2354 (7.1%)	998 (18%)	2460 (7.5%)	6245 (19%)	4025 (49%)
Private practising specialist, *n*	58 (0.17%)	($n < 5$)	54 (0.16%)	40 (0.12%)	-

[a]Initiation for the first time in an individual implied that medication use was the first use observed in at least 5 y of the given medication class.
[b]Between 42% and 49% of initiators had no recent LDL measurement available. The proportion of missing values for HbA1c was generally low (≤ 2%). A recorded eGFR level of < 60 mL/min/1.73m^2 not confirmed by another eGFR measurement of < 60 mL/min/1.73m^2 within ≥ 90 days prior was coded missing and the level of missingness was 3%-8%. The proportion of missing values for albuminuria varied across glucose-lowering therapy classes and are reported in the table. All co-morbidities were based on hospital-recorded diagnoses and procedures. Renal complications also comprised albuminuria Stage A2-A3 and/or eGFR < 60 mL/min/1.73m^2.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide 1-receptor agonist; IQR, interquartile range; LDL, low-density lipoprotein; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; SU, sulphonylurea; UACR, urine albumin-to-creatinine ratio.

SGLT-2is, generally younger and had lower levels of co-morbidities (e.g. renal complications 31% vs. 44% and 47%, respectively). Conversely, initiators of insulin had a longer diabetes duration (median 8 years), markedly worse glycaemic control (median HbA1c 76 mmol/mol) and higher levels of co-morbidities. Initiation of treatment with new glucose-lowering therapy was generally performed by general practitioners, in particular for metformin (92% of metformin initiators) and GLP-1RAs (91%), to a lesser extent for DPP-4is (81%) and SGLT-2is (80%), and much less so for insulin (48%). When splitting initiators of insulin into initiators of basal and bolus insulin separately (Table S1), initiators of basal insulin were slightly younger (median age 67 vs. 73 years) and had worse glycaemic control (median HbA1c 79 vs. 58 mmol/mol). Bolus insulin was most often initiated by hospital prescribers (64% of initiators).

When comparing individuals in 2022-2023 with individuals initiating or adding glucose-lowering therapy classes during 2016-2017, 2018-2019 and 2020-2021 (Tables S2–S4), several pronounced trends were revealed. The yearly number of initiators increased substantially for the newer glucose-lowering therapies, that is, by approximately 3-fold for SGLT2is and by 6-fold for GLP-1RAs between 2016-2017 and 2022-2023. While the median age at metformin and GLP-1RA initiation was stable over time at 61-63 years, age at initiation gradually increased for DPP-4is and insulin (from a median of 66 and 67 years in 2016-2017 to 69 years in 2022-2023), and in particular for SGLT-2is (from a median of 61 to 69 years). Further, the use of non-metformin glucose-lowering therapies up to initiation of GLP-1RAs and SGLT-2is decreased substantially. As an example, 35% of SGLT-2i initiators had recently used a DPP-4i in 2016-2017 versus only 14% in 2022-2023. Among GLP-1RA initiators in 2016-2017, 19% had recently used SUs, 41% DPP-4is and 24% insulin, compared with only 4.5%, 17% and 9% in 2022-2023, respectively. Conversely, recent use of SGLT-2is increased from 17% in 2016-2017 to 35% in 2022-2023. Finally, the median HbA1c level at treatment initiation (i.e. intensification) gradually decreased, for example, from a median of 67-68 mmol/mol among GLP-1RA and SGLT-2i initiators to 57-58 mmol/mol from 2016-2017 to 2022-2023. Of note, HbA1c levels remained consistently high for insulin initiators (median 76 mmol/mol).

3.2 | Trajectories of first-ever initiators of glucose-lowering therapy

Among those initiating their first-ever glucose-lowering therapy in 2020, metformin monotherapy was the most common treatment

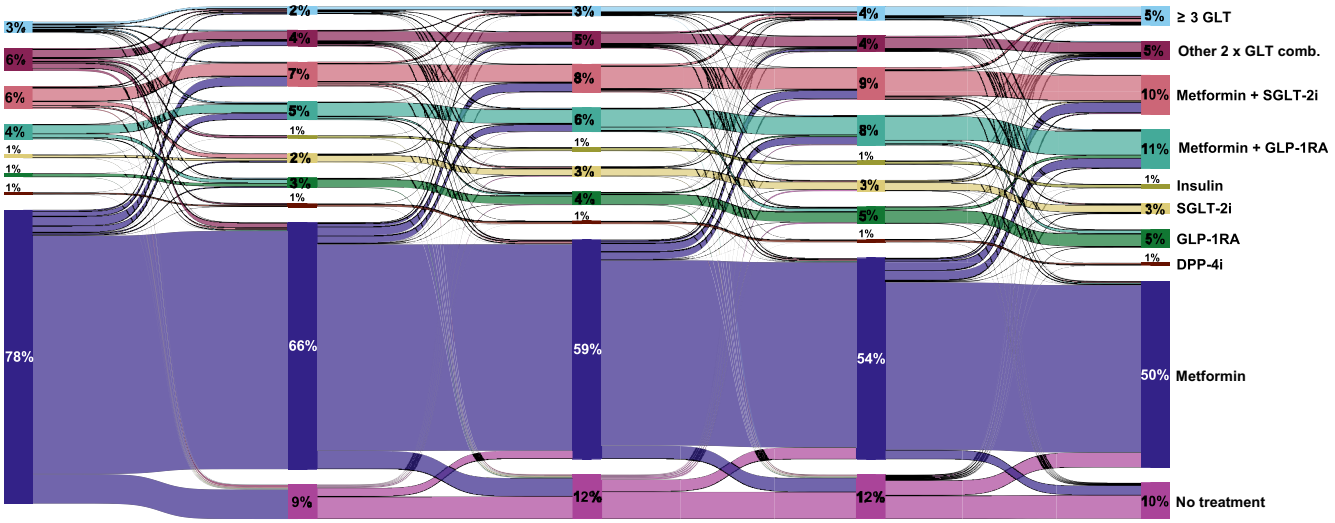

FIGURE 1 Treatment trajectories among initiators of GLT during 2020 and followed in 6-month intervals for up to 2.5 years. All drugs used within such a 6-month interval were considered as concomitantly used (for further details, please refer to Section 2). comb., combination; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; GLT, glucose-lowering therapies; SGLT-2i, sodium-glucose co-transporter-2 inhibitor.

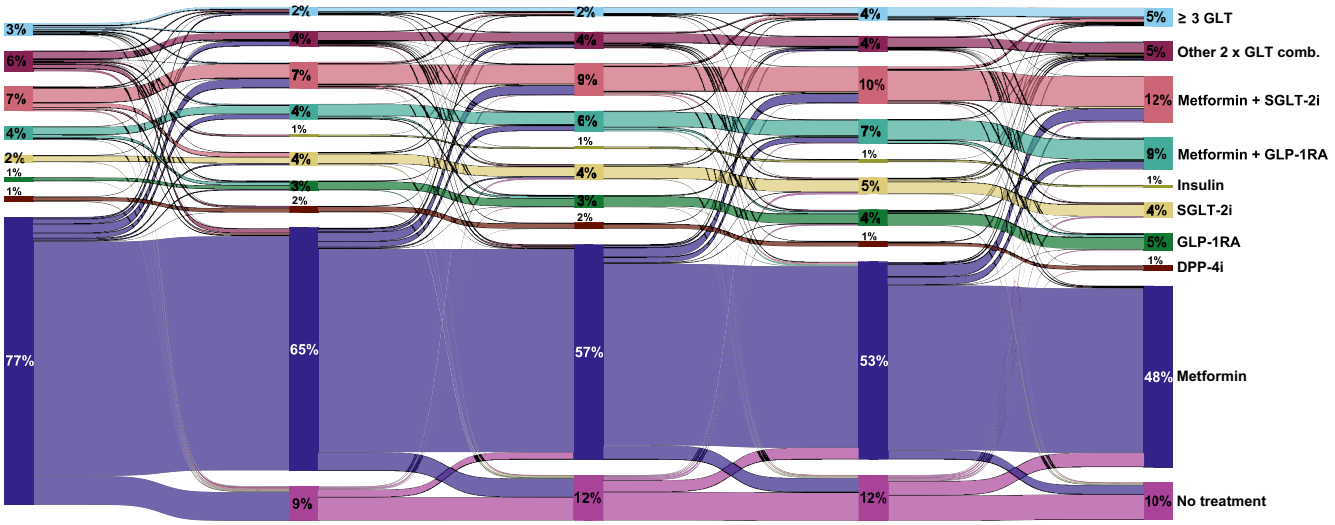

FIGURE 2 Treatment trajectories among individuals with known cardiovascular or chronic kidney disease initiating GLT during 2020 and followed in 6-month intervals for up to 2.5 years. All drugs used within such a 6-month interval were considered as concomitantly used (for further details, please see Section 2). comb., combination; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; GLT, glucose-lowering therapies; SGLT-2i, sodium-glucose co-transporter-2 inhibitor.

and remained as such during the 2.5 years of follow-up (Figure 1). Although the proportion of metformin monotherapy users decreased from 78% to 50%, metformin use remained near constant as part of combination therapies after 2.5 years, often together with a SGLT2i or a GLP-1RA. Of all the initiators, 10% did not receive any treatment at the end of follow-up, 59% used monotherapy, while 31% used treatment regimens comprising two or more different glucose-lowering therapies. Overall, 23% filled a GLP-1RA during the 2.5 years of follow-up, while 20% used a GLP-1RA after 2.5 years. The corresponding numbers for SGLT-2is were 24% and 19%, respectively, and 6.9% and 3.4% for insulin.

When restricting to the 38% ($n = 6629$) of individuals with either established CVD (26%) or CKD (22%) at baseline (Figure 2), 22% used a SGLT-2i and 18% a GLP-1RA after 2.5 years, while 36% used either/or. This compared with 17% using a SGLT-2i and 21% using a GLP-1RA after 2.5 years (34% used either/or) among initiators without cardiorenal disease. Similar analyses of initiators in each year from 2016 to 2019 showed a gradual trend towards slightly earlier treatment intensification and generally higher use of GLP-1RAs and SGLT-2is (Figures S1–S4). The sensitivity analysis not requiring later prescriptions returned results similar to the main analysis (data not shown).

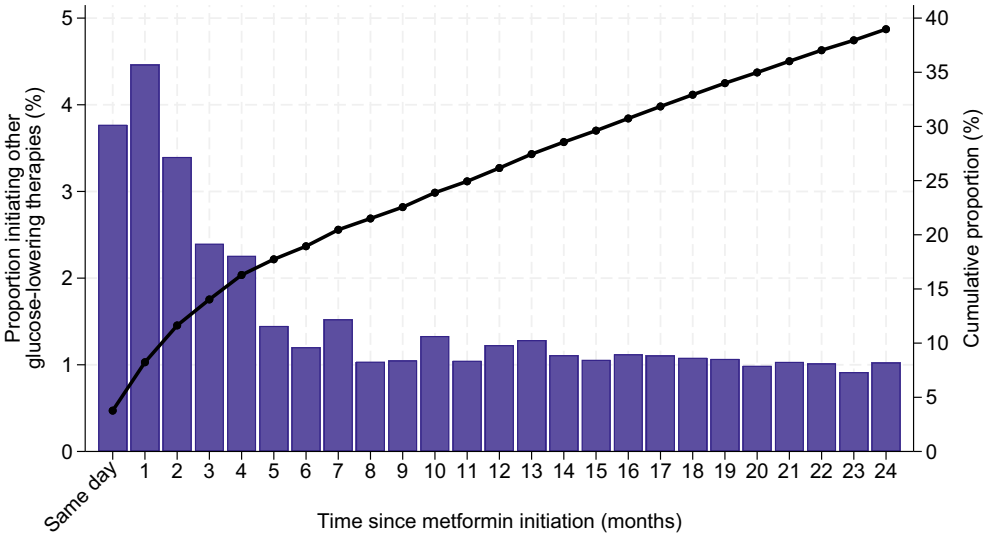

FIGURE 3 Time until filling another glucose-lowering therapy among individuals initiating metformin as their first-ever glucose-lowering therapy during 2020-2021 by month (left-hand axis) and cumulative proportion (right-hand axis).

3.3 | Trajectories of first-ever initiators of metformin

Among those initiating metformin as their first-ever glucose-lowering therapy during 2020-2021 (comprising 93% of all eligible initiators of glucose-lowering therapies in 2020-2021), 39% had added another glucose-lowering therapy after 2 years, with add-ons occurring gradually over the 2-year period (Figure 3). The proportion adding additional glucose-lowering therapy within 2 years increased gradually over time from 25% in 2016 to 40% in 2021 (Figure S5).

4 | DISCUSSION

We document a trend towards earlier T2D treatment intensification, and that SGLT-2is and GLP-1RAs are now increasingly used in individuals with less pronounced hyperglycaemia and with less previous use of DPP-4is or SUs. Although more patients with T2D now use SGLT-2is or GLP-1RAs, most of them, including those with established cardiorenal disease, still initiate metformin monotherapy as first-line treatment and do not add early additional glucose-lowering therapy.

Recent studies from North America,[22,23] Asia[24] and Europe[13,25,26] show that metformin remains overwhelmingly the most frequently initiated medication for T2D, which is in accordance with current guidelines.[5] However, the use of SGLT-2is and GLP-1RAs has generally increased in clinical practice in many countries,[13,22,24] although their use remains low in the first years after T2D diagnosis, even in individuals with T2D and established CVD.[12,22,26,27]

Previous studies had limitations in that they frequently reported the use of glucose-lowering therapies in a cross-sectional manner; for example, the proportion of the T2D population treated with specific therapies in a given calendar year,[24,25] or the proportions treated at a certain time point after the onset of T2D.[26] The current study leverages nationwide high-quality,[16,18,28] individual-level data, allowing us to apply a longitudinal trajectory approach that provides a more detailed understanding of the clinical decision-making for individuals with T2D. However, several weaknesses also need to be recognized. Using prescription fills as a proxy for drug use might slightly overestimate use and will incorrectly classify some switches in treatment as concomitant use. However, the sensitivity analysis using different definitions of use (not requiring later refills) returned results highly comparable with the main analysis, suggesting that the impact from this is limited. Furthermore, the data we accessed did not include socioeconomic data, thus precluding an assessment of the influence on treatment patterns in, for example, strata of income, which may affect choices made regarding newer glucose-lowering therapies.[29]

Recent medical advances have improved cardiorenal outcomes in individuals with T2D. However, the adoption of new medication often lags, especially in primary care. Our findings show a shift towards the use of newer T2D glucose-lowering therapies, such as GLP-1RAs and SGLT2is. Nevertheless, metformin remains the first-line treatment choice. We report some improvement in early treatment intensification, but note a treatment gap for individuals with early T2D and established cardiorenal disease, in whom Danish guidelines now recommend SGLT-2is or GLP-1RAs as first-line co-therapy independent of HbA1c level, highlighting the need for better treatment strategies and guideline adherence that considers co-morbidities. Lastly, we advocate for enhanced guideline implementation through education and updated incentives. Further research is needed to assess the real-world impact of these treatment trends on glycaemic control and quality of life in people with T2D.

In conclusion, while we have shown that there is a trend towards earlier T2D treatment intensification, including earlier use of GLP-1RAs and SGLT-2is, a substantial proportion of T2D patients remain on single use of metformin, including individuals with established cardiorenal disease. Continuous monitoring of the real-world use patterns of the newer glucose-lowering therapies and implementation of up-to-date guidelines are necessary to support the optimal use of medication within this rapidly changing field.

AUTHOR CONTRIBUTIONS

The study idea was conceived by AP, LR and HK and all the authors participated in the conception and design of the study and in the interpretation of study findings. Data analysis was carried out by JHA and AP, who both had access to the underlying data reported in the manuscript. The first draft of the manuscript was written by AP and RWT. All authors contributed to revising the manuscript critically for important intellectual content and all the authors read and approved the final version to be published.

ACKNOWLEDGEMENTS

The study was funded via an unrestricted grant provided by Novo Nordisk to the University of Southern Denmark. Novo Nordisk received an initial analysis plan as well as the first draft of the manuscript, however, Novo Nordisk had no access to data and no role in the interpretation of findings or the decision to publish.

CONFLICT OF INTEREST STATEMENT

AP reports participation in research projects funded by Alcon, Almirall, Astellas, AstraZeneca, 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 article. LR and JHA report participation in research projects funded by Novo Nordisk. TV reports having served on scientific advisory panels, been part of speaker's bureaus, served as a consultant to and/or received research support from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, GSK, Mundipharma, Novo Nordisk, Roche, Sanofi, Sun Pharmaceuticals and Zealand Pharma. JS served on scientific advisory boards participation for Novo Nordisk and for Roche Diagnostics and received funding from Boehringer Ingelheim. RWT reports no personal conflicts of interest; however, the Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the current study. HK reports no potential conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15912.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Danish Health Data Authority. Restrictions apply to the availability of these data, which were used under license for this study.

ORCID

Anton Pottegård https://orcid.org/0000-0001-9314-5679
Lotte Rasmussen https://orcid.org/0000-0001-5962-6647

REFERENCES

1. Ahmad E, Lim S, Lamptey R, Webb DR, Davies MJ. Type 2 diabetes. *Lancet*. 2022;400:1803-1820.
2. Sun H, Saeedi P, Karuranga S, et al. IDF diabetes atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract*. 2022;183:109119.
3. Gaede P, Lund-Andersen H, Parving H-H, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med*. 2008;358:580-591.
4. American Diabetes Association Professional Practice Committee. Summary of revisions: standards of care in diabetes-2024. *Diabetes Care*. 2024;47:S5-S10.
5. Davies MJ, Aroda VR, Collins BS, et al. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2022;2022(65):1925-1966.
6. Marassi M, Fadini GP. The cardio-renal-metabolic connection: a review of the evidence. *Cardiovasc Diabetol*. 2023;22:195.
7. Gedebjerg A, Bjerre M, Kjaergaard AD, et al. CRP, C-peptide, and risk of first-time cardiovascular events and mortality in early type 2 diabetes: a Danish cohort study. *Diabetes Care*. 2023;46:1037-1045.
8. Gedebjerg A, Almdal TP, Berencsi K, et al. Prevalence of micro- and macrovascular diabetes complications at time of type 2 diabetes diagnosis and associated clinical characteristics: a cross-sectional baseline study of 6958 patients in the Danish DD2 cohort. *J Diabetes Complications*. 2018;32:34-40.
9. Mosenzon O, Alguwaihes A, Leon JLA, et al. CAPTURE: a multinational, cross-sectional study of cardiovascular disease prevalence in adults with type 2 diabetes across 13 countries. *Cardiovasc Diabetol*. 2021;20:154.
10. Gyldenkerne C, Mortensen MB, Kahlert J, et al. 10-year cardiovascular risk in patients with newly diagnosed type 2 diabetes mellitus. *J Am Coll Cardiol*. 2023;82:1583-1594.
11. Ferrannini G, Norhammar A, Gyberg V, Mellbin L, Rydén L. Is coronary artery disease inevitable in type 2 diabetes? From a glucocentric to a holistic view on patient management. *Diabetes Care*. 2020;43:2001-2009.
12. Funck KL, Knudsen JS, Hansen TK, Thomsen RW, Grove EL. Real-world use of cardioprotective glucose-lowering drugs in patients with type 2 diabetes and cardiovascular disease: a Danish nationwide cohort study, 2012 to 2019. *Diabetes Obes Metab*. 2021;23:520-529.
13. Pottegård A, Andersen JH, Søndergaard J, Thomsen RW, Vilsbøll T. Changes in the use of glucose-lowering drugs: a Danish nationwide study. *Diabetes Obes Metab*. 2023;25:1002-1010.
14. Hofer F, Kazem N, Schweitzer R, et al. Prescription patterns of sodium-glucose cotransporter 2 inhibitors and glucagon-like Peptide-1 receptor agonists in patients with coronary artery disease. *Cardiovasc Drugs Ther*. 2021;35:1161-1170.
15. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol*. 2019;11:563-591.
16. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data resource profile: the Danish National Prescription Registry. *Int J Epidemiol*. 2017;46:798-798f.
17. *WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC Classification and DDD Assignment 2023*. 2022.
18. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449-490.
19. Arendt JFH, Hansen AT, Ladefoged SA, Sørensen HT, Pedersen L, Adelborg K. Existing data sources in clinical epidemiology: laboratory information system databases in Denmark. *Clin Epidemiol*. 2020;12:469-475.

20. Schmidt M, Pedersen L, Sørensen HT. The Danish civil registration system as a tool in epidemiology. *Eur J Epidemiol*. 2014;29:541-549.
21. Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Health*. 2011;39:12-16.
22. Shin H, Schneeweiss S, Glynn RJ, Patorno E. Trends in first-line glucose-lowering drug use in adults with type 2 diabetes in light of emerging evidence for SGLT-2i and GLP-1RA. *Diabetes Care*. 2021; 44:1774-1782.
23. Carney G, Kim JD, O'Sullivan C, et al. Treatment pattern trends of medications for type 2 diabetes in British Columbia, Canada. *BMJ Open Diabetes Res Care*. 2022;10:e002995.
24. Yang A, Wu H, Lau ESH, et al. Glucose-lowering drug use, glycemic outcomes, and severe hypoglycemia: 18-year trends in 0·9 million adults with diabetes in Hong Kong (2002-2019). *Lancet Reg Health West Pac*. 2022;26:100509.
25. Jermendy G, Kiss Z, Rokszin G, et al. Changing patterns of antihyperglycaemic treatment among patients with type 2 diabetes in Hungary between 2015 and 2020-Nationwide data from a register-based analysis. *Medicina (Kaunas)*. 2022;58:1382.
26. Barth SD, Kostev K, Krensel M, Mathey E, Rathmann W. Do glucagonlike peptide-1 receptor agonist and sodium-glucose cotransporter 2 inhibitor prescriptions in Germany reflect recommendations for type 2 diabetes with cardiovascular disease of the ADA/EASD consensus report? *Exp Clin Endocrinol Diabetes*. 2023;131:153-161.
27. Knudsen JS, Baggesen LM, Lajer M, et al. Changes in SGLT2i and GLP-1RA real-world initiator profiles following cardiovascular outcome trials: a Danish nationwide population-based study. *PLoS One*. 2020;15:e0229621.
28. Harbi H, Pottegård A. Validation of the 'indication for use' (INDO) variable in the Danish National Prescription Registry. *Epidemiology*. 2024;35:1-6.
29. Falkentoft AC, Andersen J, Malik ME, et al. Impact of socioeconomic position on initiation of SGLT-2 inhibitors or GLP-1 receptor agonists in patients with type 2 diabetes – a Danish nationwide observational study. *Lancet Reg Health Eur*. 2022;14:100308.

SUPPORTING INFORMATION

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

How to cite this article: Pottegård A, Andersen JH, Søndergaard J, et al. Treatment trajectories for Danish individuals with type 2 diabetes in the era of emerging glucose-lowering therapies. *Diabetes Obes Metab*. 2024;1-9. doi:10.1111/dom.15912