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ORIGINAL ARTICLE

Changes in the use of glucose-lowering drugs: A Danish nationwide study

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Abstract

Aim: To investigate changes in the pattern of drugs used to treat type 2 diabetes in Denmark from 2005 to 2021.

Materials and Methods: A nationwide, population-based drug utilization study based on medical databases covering the Danish population was conducted. We assessed incident and prevalent use patterns among all 441 205 individuals initiating at least one non-insulin, glucose-lowering drug.

Results: The rate of new users of non-insulin, glucose-lowering drugs increased from 2005, peaked in 2011, decreased to stable levels during 2013 to 2019, then increased dramatically during 2020-2021. The prevalence of use increased from 2.1% (in 2005) to 5.0% (in 2021) of the entire adult population. In 2021, metformin comprised 39% of all glucose-lowering drug consumption, followed by insulin (17%), sodium-glucose co-transporter-2 inhibitors (SGLT-2is) (17%), glucagon-like peptide-1 receptor agonists (GLP-1RAs) (16%) and dipeptidyl peptidase-4 inhibitors (7.5%). Overall, 56% of users were on monotherapy, 28% used dual therapy, while 13% and 2.8% used three and four drug classes, respectively. Both the intensity and diversity of therapies increased substantially over time, with 15 different treatment regimens each covering more than 1% of users in 2021. General practitioners prescribed 88% of all glucose-lowering drugs. Marked shifts towards GLP-1RA initiation by general practitioners and SGLT-2i initiation by specialists were observed, and changing user profiles suggested increasing use for non-diabetes indications.

Conclusions: The rate of new users of non-insulin, glucose-lowering drugs has increased in recent years and the prevalence of glucose-lowering drug use increases steadily. Glucose-lowering drugs are mainly prescribed by general practitioners, and the intensity, diversity and indications of glucose-lowering treatment are increasing.

KEYWORDS
antidiabetics, drug utilization, glucagon-like peptide-1 receptor agonists, glucose-lowering medication, pharmacoepidemiology, sodium-glucose co-transporter-2 inhibitors, type 2 diabetes

* Reimar W. Thomsen and Tina Vilsbøll are joint senior authors.

1 | INTRODUCTION

The principal goal of disease management in type 2 diabetes is the prevention or delay of microvascular and macrovascular complications through the achievement of good glycaemic control and comprehensive management of cardiovascular risk factors.[1] In 1999, it was shown that individualized, intensified multifactorial prevention is central in the management of type 2 diabetes.[2] Later, after 21 years of follow-up, the Steno-2 study showed a median of 7.9 years of gain of life, and that this increase in lifespan was matched by time free from incident cardiovascular disease.[3]

At the beginning of the 2000s, metformin became the preferred first-line therapy for type 2 diabetes, unless contraindicated or poorly tolerated, and, thereafter, a sulphonylurea (SU) and/or insulin was usually added. This 'glucocentric' approach to diabetes care with stepwise treatment intensification to reduce HbA1c levels led to a significant decrease in microvascular complications. However, people with type 2 diabetes still suffer from premature death, mainly because of cardiovascular disease and chronic kidney disease.[1,4-7] During the last decades, new glucose-lowering drug classes, including dipeptidyl peptidase-4 inhibitors (DPP-4is), glucagon-like peptide-1 receptor agonists (GLP-1RAs) and most recently sodium-glucose co-transporter-2 inhibitors (SGLT-2is), have become central in the treatment of type 2 diabetes. In addition to their effective glucose-lowering properties, these drugs have a very low risk of hypoglycaemia.[8] Furthermore, since 2015, results from large cardiovascular outcomes trials have proven that GLP-1RAs and SGLT-2is provide cardiorenal benefits in people with type 2 diabetes and high cardiovascular risk independently of glycaemic control.[1] This has led to marked changes in recommendations, shifting the treatment paradigm in diabetes care, beyond a glucocentric approach to incorporate co-morbidities in treatment recommendations.[9,10] As an example, the most recent American Diabetes Association/European Association for the Study of Diabetes adaptation emphasizes incorporation of therapy rather than sequential add-on, which may require adjustment of current therapies, and that the therapeutic regimen should be tailored to co-morbidities, patient-centred treatment factors and management needs.[11] However, several studies have shown that a substantial proportion of eligible high-risk individuals are still not receiving cardiovascular beneficial therapies, but only therapies such as SUs, insulin and DPP-4is.[5,12-14]

In many countries including Denmark, most people with type 2 diabetes are followed in primary care (> 80% are treated in general practice in Denmark), whereas individuals with significant complications to diabetes or complex type 2 diabetes disease are often treated by diabetes specialists or other specialist physicians, typically in collaboration with general practice.[15] The increasing number of type 2 diabetes treatment modalities and frequent multimorbidity in type 2 diabetes poses a huge challenge for all involved healthcare personnel across healthcare systems. Hence, monitoring the shifting time trends in glucose-lowering drug use and prescriber responsibility by taking advantage of population-based drug prescription data may support implementation of updated guidelines. However, complete prescription data from both primary and secondary care settings covering nationwide type 2 diabetes populations over many years are rare. Therefore, we conducted a Danish nationwide drug utilization study, using unique observational data from national registries from 2005 until 2021. We aimed to evaluate the patterns for glucose-lowering drug use and prescribing physicians among new users of non-insulin, glucose-lowering drugs.

2 | MATERIALS AND METHODS

2.1 | Cohort identification and data sources

The main data source for the study was the Danish National Prescription Registry,[16] which contains data on all prescription drugs dispensed at community pharmacies to Danish citizens since 1995. The data include the type of drug, date of dispensing and quantity. Drugs are categorized according to the Anatomic Therapeutic Chemical (ATC) index, a hierarchical classification system developed by the World Health Organization (WHO), and the quantity dispensed for each prescription is given by the number and strength of the pharmaceutical entities (e.g. tablets), as well as the defined daily doses (DDDs). From the Prescription Registry, we identified all adult (aged ≥ 18 years) individuals filling a first prescription for a non-insulin, glucose-lowering drug from 2005 to 2021. For this cohort of drug initiators, we identified all initial and subsequent filled prescriptions for all glucose-lowering drugs (including insulin). Both for the identification of the cohort and their subsequent use of glucose-lowering drugs, prescriptions for GLP-1RAs marketed with the indication of weight-loss therapy (liraglutide 3.0 mg once daily) were disregarded. Glucose-lowering drugs were classified as metformin, SUs, DPP-4is, GLP-1RAs, SGLT-2is, insulins and other (glinides, thiazolidinediones and acarbose). In all analyses, prescriptions for combination treatment were split into individual components. Drugs were identified and categorized according to the ATC index and drug volume was expressed in DDDs, a technical unit of measurement defined by the WHO as 'the assumed average maintenance dose per day for a drug used for its main indication in adults'.[17] All the ATC codes used are detailed in Table S1.

2.2 | Analyses

To describe the dynamics of the overall cohort of Danish adult individuals using drugs that are used to treat type 2 diabetes in Denmark, we calculated the annual rate of new users of (any) non-insulin, glucose-lowering drug (i.e. incidence rate) among the total adult population. Here, new use was defined as the first ever prescription (going back to 1995) for any non-insulin, glucose-lowering drug. Further, we described the proportion of the total adult population in each quarter who used at least one glucose-lowering drug (i.e. prevalence proportion). Both these measures were estimated overall and by age category (18-39, 40-59, 60-79 and ≥ 80 years).

To quantify the total use of glucose-lowering drugs used for type 2 diabetes in Denmark, we estimated the total quarterly amount of

individual glucose-lowering drug classes filled, measured in DDDs. Further, to describe changes in intensity of treatment, we grouped users by how many different glucose-lowering drugs they used in a given quarter (1, 2, 3 and ≥ 4) and described the most common single and combined treatment regimens over time.

Finally, to describe the changes in prescriber types responsible for glucose-lowering drug treatment in Denmark, we quantified the proportion of all glucose-lowering drugs issued by general practitioners, hospital specialists and other prescribers (including dentists and private practising specialists) over the study period. We did this overall, for the individual glucose-lowering drug classes, and by whether a given prescription marked treatment initiation (first ever prescription for that drug class for that given patient) or continued treatment (all other prescriptions).

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

2.3 | Approvals and ethics

According to Danish law, studies based solely on register data do not require approval from an ethics review board.[18] 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 license for this study.

3 | RESULTS

We identified 441 205 unique individuals initiating at least one non-insulin, glucose-lowering drug from 2005 to 2021, filling a total of 29 750 498 prescriptions for glucose-lowering drugs, most commonly metformin (53%), insulins (19%) and SUs (12%).

The rate of new glucose-lowering drug use increased from 2005 (3.9/1000 person-years among all Danish adults) until 2011 (6.1/1000), after which it decreased to a stable level from 2013 to 2019 (3.6-4.1/1000) and finally increased considerably during 2020-2021 (7.3/1000 in 2021). When stratifying by age categories (Figure 1A), the rate of new glucose-lowering drug use was generally highest among 60- to 79-year-old individuals compared with both older and younger age groups. During the last decade, rates across age categories from 40 through 80+ years or older ranged from 3.7 to 7.0 per 1000 persons from 2013 to 2019, with a very similar increase during 2020-2021 observed for these age groups (range 8.5-11 per 1000 person-years in 2021). Conversely, individuals aged 18 to 39 years had a lower rate of 1.3 to 1.5 per 1000 person-years from 2013 to 2019, although they also showed a distinct increase in 2021 (2.7 per 1000 person-years).

The total prevalence proportion of all Danish adults using glucose-lowering drugs (with a history of initial non-insulin use) increased steadily throughout the study period, from 2.1% in 2005 to 5.0% in 2021. When stratifying by age groups (Figure 1B), there were 0.58% of users among those aged 18 to 39 years in the last quarter of 2021, and 4.0% of users among those aged 40 to 59 years. Among older people, 10% and 11% of those aged 60-79 and 80 years or older used glucose-lowering drugs by 2021, respectively, both up from 5.0% in 2005.

The recent increase in the incidence rate of new users was seen among both general practitioners and hospital prescribers, although the relative increase was largest for hospital prescribers (Figure 2, top panels). Further, it was found that the dominant first-line treatment among both general practitioners and hospital prescribers was metformin throughout the study period, although this changed in 2021, when GLP-1RAs constituted 20% of first-line treatment among general practitioners and SGLT-2is comprised 59% of first-line treatment among hospital prescribers (Figure 2, bottom panels). Accordingly, when excluding all incident users filling either SGLT-2is or GLP-1RAs as first-line treatment, the increase in new glucose-lowering drug use during 2020-2021 (Figure 1) was markedly attenuated, although an increase was still present (Figure S1). In a post hoc analysis, we characterized initiators starting SGLT-2is and GLP-1RAs, and for comparison metformin, from 2019 to 2021, by obtaining their complete hospital contact history through linkage with the Danish National Patient Registry.[19] We saw a marked shift towards initiators of SGLT-2is more often having received a hospital diagnosis of heart failure (75% in 2021 vs. 16% in 2019) and other markers of pre-existing heart disease (Table S1). Concurrently, initiators of GLP-1RAs showed a decline in the proportion with a previous hospital diagnosis of diabetes, and a decline (rather than an increase) in markers of cardiovascular co-morbidity (Table S1).

The most used drug classes (Figure 3) changed during the study period, from SUs comprising 51% of all glucose-lowering drugs used in the first quarter of 2005, decreasing to 3.6% in the last quarter of 2021, whereas metformin increased in the corresponding period from 30% to 39%. Since 2015, the use of in particular GLP-1RAs and SGLT-2is increased markedly, and by the last quarter of 2021, insulins comprised 17% of all glucose-lowering drugs, followed by SGLT-2is (17%), GLP-1RAs (16%) and DPP-4is (7.5%). During the same period, marked changes were seen in the distribution of individual GLP-1RA and SGLT-2i drugs filled by new users of these drug classes. Thus, liraglutide initiation was being substituted by semaglutide initiation during 2018-2021. At the same time, dapagliflozin initiation was gradually substituted by empagliflozin initiation since 2015, although this trend was seemingly reversed during the last 2 to 3 years, in particular among hospital prescribers (Figure S2).

Among individual users, the majority used glucose-lowering drug monotherapy (56% in 2021, down from 63% in 2005) and dual therapy (28% in 2021, down from 35% in 2005), while the proportion using three or four different drug classes increased from virtually none (2.2% and 0.043%) in 2005, to 13% and 2.8% in 2021, respectively (Figure 4). The proportion of new (incident) initiation of combination therapy with both metformin and another glucose-lowering drug class upon initiating treatment was generally low and only increased slightly during the study period (3.4% in 2010 to 4.3% in 2021). The diversity of glucose-lowering therapy increased considerably over time, with 15 different treatments, each covering at least 1% of users in the final quarter of 2021 (Figure 5), an increase from 10 in 2015, nine in 2010 and five in 2005 (Figure S3). Monotherapy with metformin was the

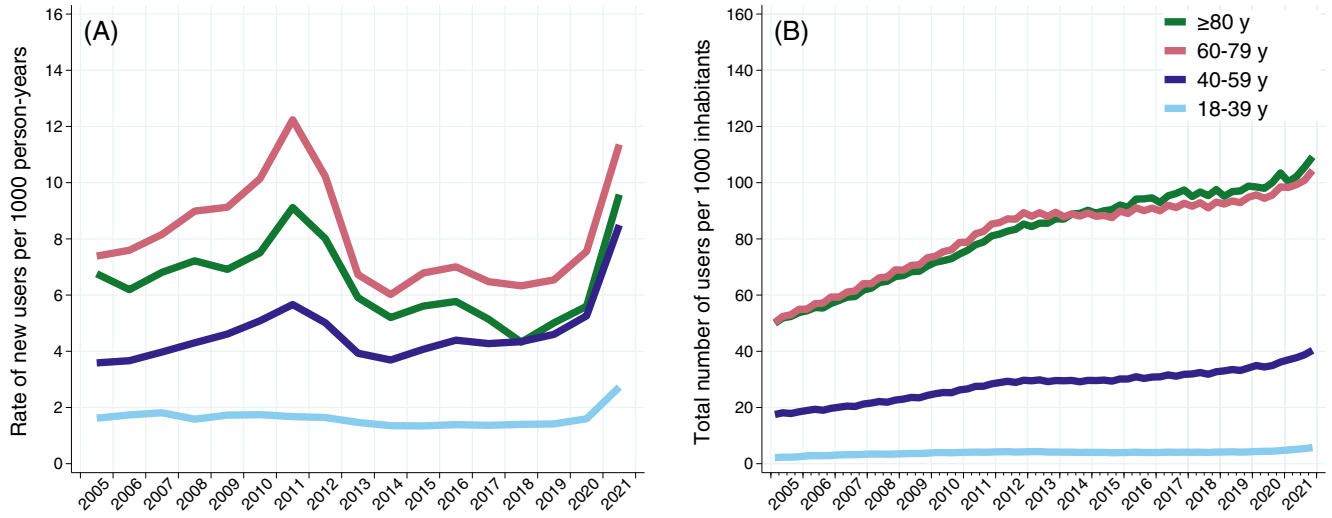

FIGURE 1 The annual rate of new users of glucose-lowering drugs (A, Incidence rate) and the total proportion of individuals using glucose-lowering drugs (B, Quarterly prevalence proportion) in Denmark during 2005-2021 and specified by age group

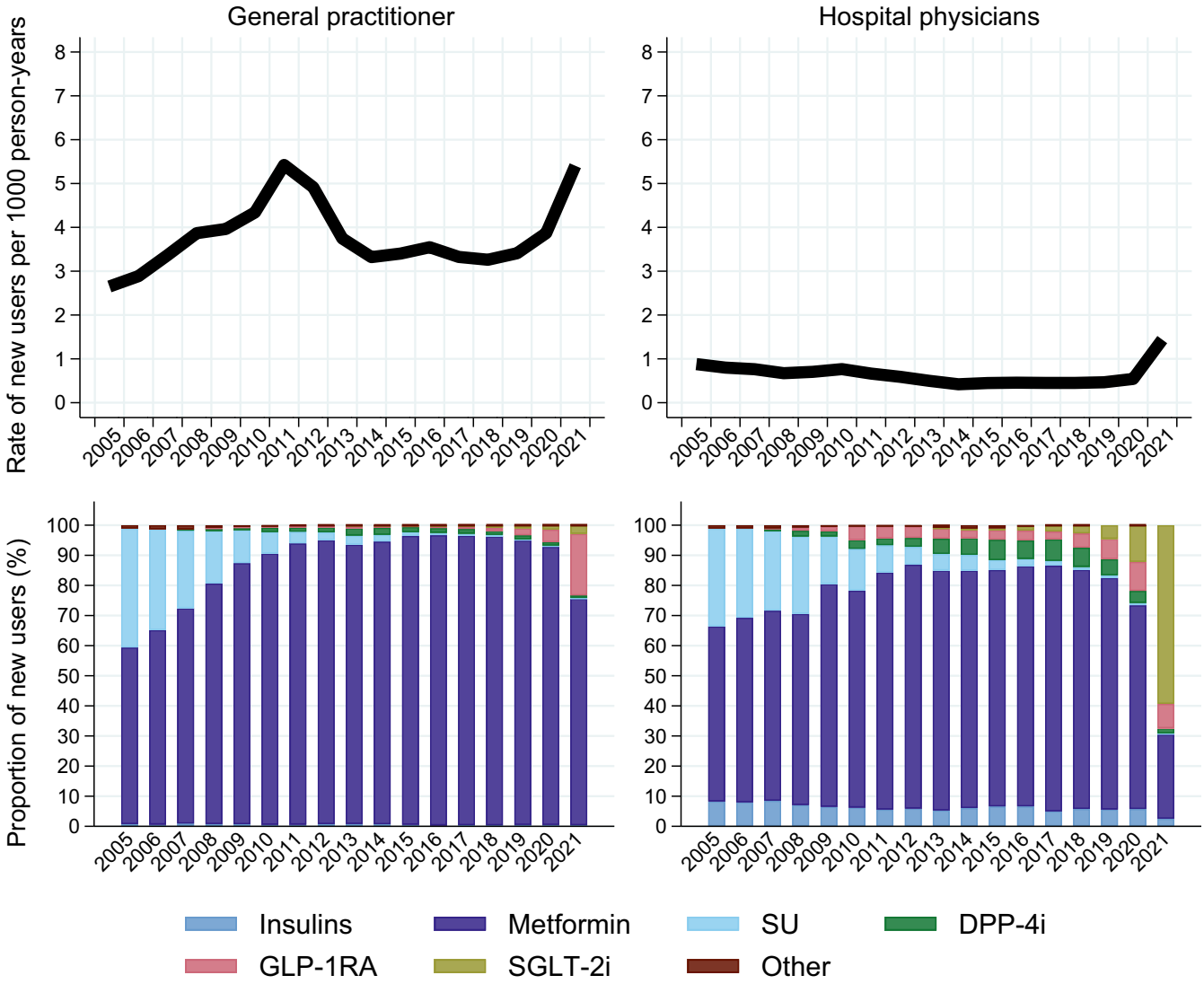

FIGURE 2 The annual rate of new users of glucose-lowering drugs during 2005-2021 (top panels) and the corresponding distribution of first-line treatments (bottom panels) specified by whether treatment was initiated by a general practitioner or a hospital physician. DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; SU, sulphonylurea

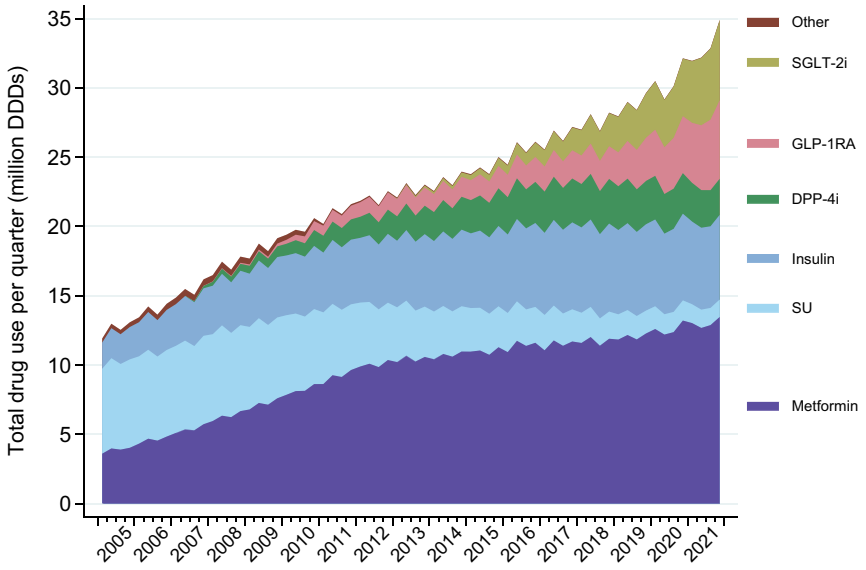

FIGURE 3 The total quarterly amount of individual glucose-lowering drug classes filled (in DDDs) among adult Danes during 2005-2021, specified by individual glucose-lowering drug classes. DDDs, defined daily doses; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; SU, sulphonylurea

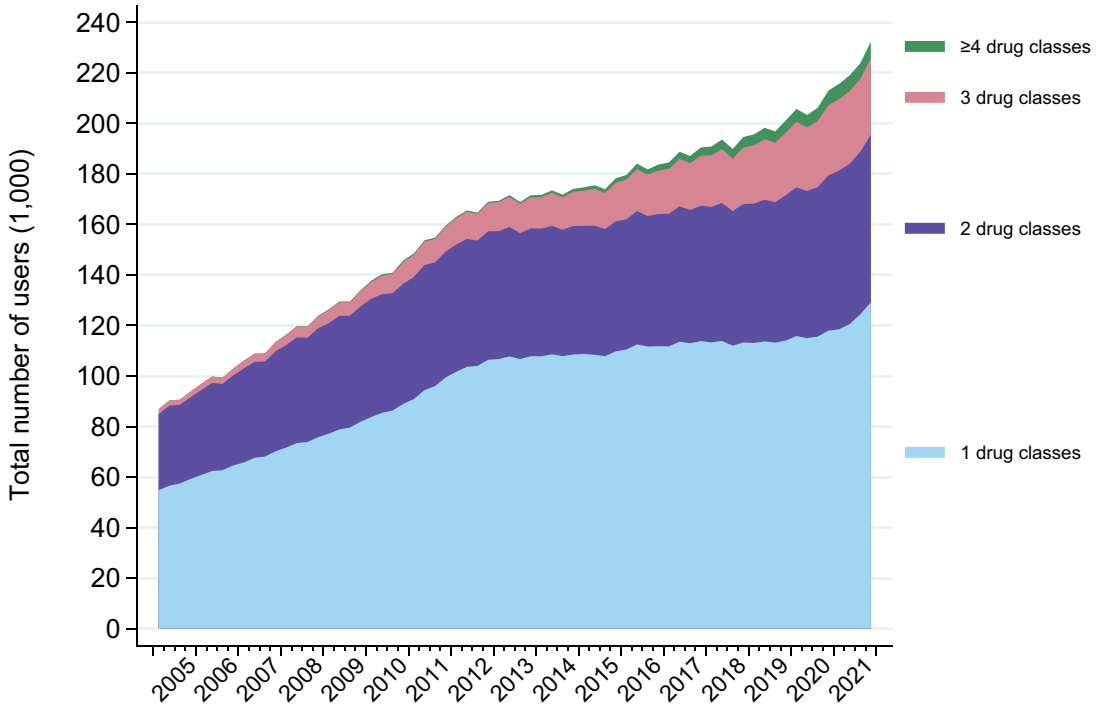

FIGURE 4 The quarterly number of adult Danish users of glucose-lowering drugs during 2005-2021, specified by how many different glucose-lowering drug classes they filled in that given quarter

most common treatment regimen (38% of all users by the end of 2021; Figure 5), followed by metformin combined with a GLP-1RA (7.0%), metformin combined with a SGLT-2i (6.9%), GLP-1RA monotherapy (6.7%) and insulin monotherapy (5.3%). Overall, 76% of all users used a combination involving metformin in the last quarter of 2021.

Throughout the study period, most glucose-lowering drugs were prescribed by general practitioners (88% in 2021; Figure 6, top panel). The proportion prescribed by hospital specialists decreased from 12% in 2005 to 7.7% in 2013, then increased to 12% in 2021. Only considering prescriptions issued by general practitioners (Figure 6, bottom left panel), the most common medications were metformin (42% of all prescriptions filled in the last quarter of 2021), followed by SGLT-2is (16%), GLP-1RAs (16%), insulin (14%) and DPP-4is (8.1%). Similarly, the most commonly filled medications issued by hospital physicians (Figure 6, bottom right panel) were insulin (36%), SGLT-2is (23%), GLP-1RAs (19%), metformin (15%) and DPP-4is (3.7%). The proportions of all prescriptions filled that were issued by general practitioners and hospital specialists were largely similar across all individual drug classes (Figure S4), although with slightly higher proportions

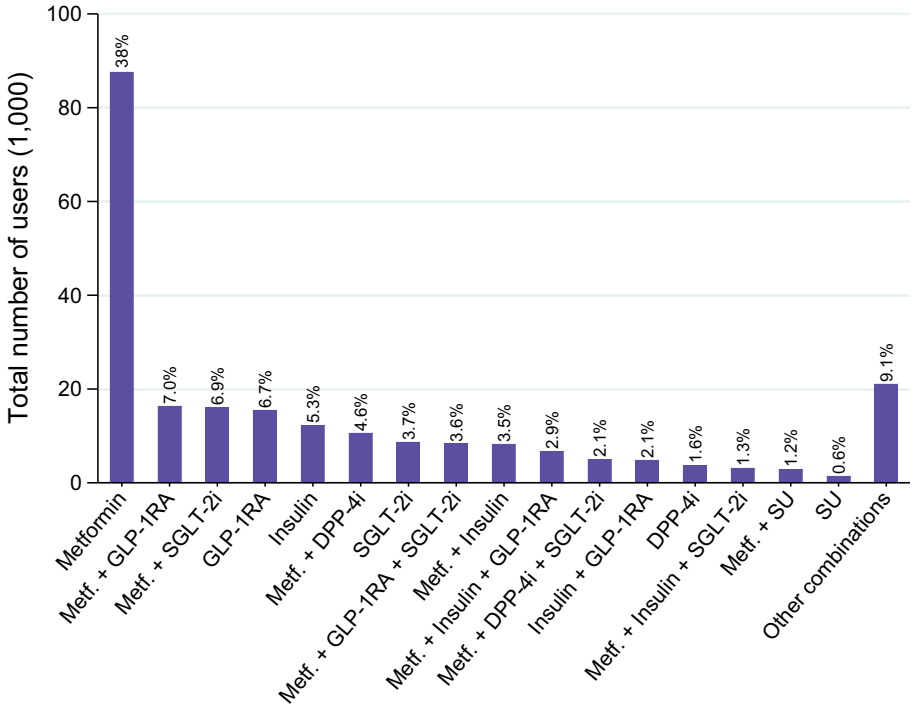

FIGURE 5 The distribution of adult Danish users of glucose-lowering drugs into different treatment combinations used in the last quarter of 2021. DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; Metf., metformin; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; SU, sulphonylurea

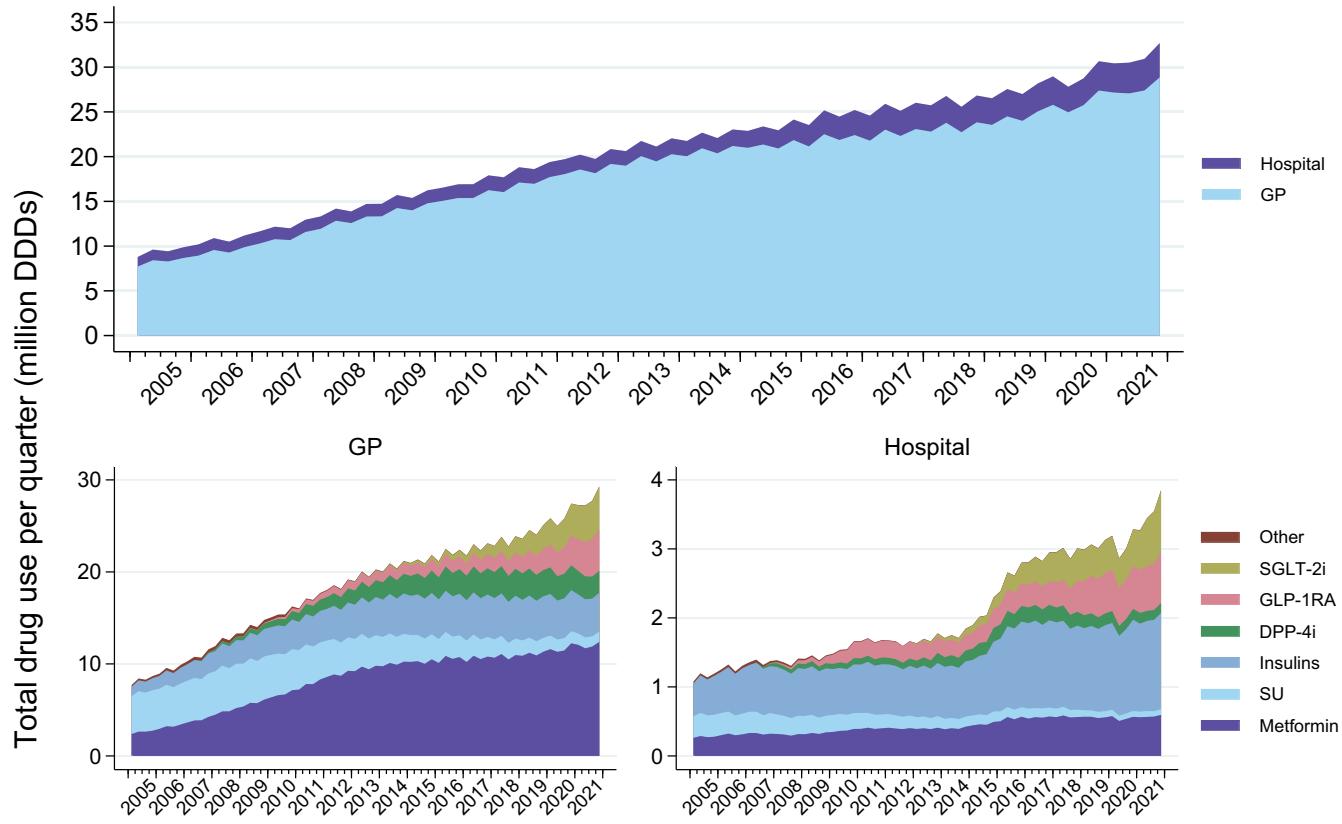

FIGURE 6 The total quarterly number of glucose-lowering drugs filled (in DDDs) among adult Danes during 2005-2021, specified by whether the prescription was issued by a GP or hospital physician (top panel), as well as by drug classes among all prescriptions issued by GPs (bottom left panel) and hospital physicians (bottom right panel). DDDs, defined daily doses; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; GP, general practitioner; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; SU, sulphonylurea

prescribed by hospital specialists for insulin (25% in 2021), SGLT-2is (16%) and GLP-1RAs (14%) compared with metformin, DPP-4is and SU (4.5%-6.9% in 2021).

4 | DISCUSSION

In this nationwide, population-based study we provide detailed utilization data on drugs used to treat people with type 2 diabetes, an increasingly common treatment now used by 5% of the entire adult Danish population. We observed dramatically changed patterns in the use of glucose-lowering drugs. The rate of new users of non-insulin, glucose-lowering drugs increased until 2011, decreased to a stable level from 2013 to 2019, but then increased substantially again during 2020-2021. Metformin comprised most of all glucose-lowering drug consumption in 2021, but the intensity and diversity of therapies increased substantially over time. General practitioners prescribed 88% of all glucose-lowering drugs in 2021. First-line treatment among both general practitioners and hospital prescribers was metformin throughout the study period. Interestingly, this changed in 2021, when GLP-1RAs increased to constitute 20% of all first-line glucose-lowering treatment among general practitioners and SGLT-2is increased to comprise 59% of first-line treatment among hospital prescribers. Changing user characteristics suggested increasing use for other indications than type 2 diabetes, notably heart failure for SGLT-2i initiators.

The strengths of our analysis include the population-based setting with uniform access to healthcare, complete registration of high-quality prescription data through community pharmacies, and complete follow-up until death or emigration for an entire nation.[20] This reduced the selection biases often seen in other studies stemming from selective inclusion of, for example, specific hospitals, health insurance systems or age groups. We were able to provide both a long prescription data history[16] and fully updated data through 2021, with validated data on prescriber type.[21]

Several limitations should be considered when interpreting our findings. First and foremost, complete information on the medical indication for prescribing a given glucose-lowering drug was not available. Unfortunately, Danish registries do not include diagnoses made in primary care, only hospital contact diagnoses. Thus, we were not able to distinguish whether, for example, metformin was always prescribed for type 2 diabetes therapy or for treatment of women with polycystic ovarian syndrome in some cases, or if some GLP-1RA users possibly used their medication primarily for weight-loss purposes. Therefore, although we did exclude a GLP-1RA specifically marketed with the indication of weight-loss therapy (liraglutide 3.0 mg once daily), we know from clinical experience in Denmark that, in particular, the GLP-1RA semaglutide (once-weekly injection) is to some extent also being used for weight loss as a primary target, both in people with and without type 2 diabetes. This may partly explain the large increase in their first-line use during 2020-2021. Also, several SGLT-2is by now have been approved for treating heart failure and chronic kidney disease in people with and without diabetes.[8,22,23] Although approval of SGLT-2is for heart failure without diabetes only happened in 2021, trial results have been promising since the end of 2019,[23] and cardiologists may well have started to also use these drugs for non-diabetic heart failure during 2020. The crude number of first-line SGLT-2i initiators in 2021 (more than 7000, compared with an expected total type 2 diabetes incidence of less than 20 000 annually in Denmark, of whom less than 10% would have heart failure already at type 2 diabetes diagnosis[24]), suggests that the majority of SGLT-2i initiators in 2021 did not have diabetes. Second, we had no means of assessing changing trends in people with type 2 diabetes exclusively treated with changes in diet and lifestyle. As mentioned above, glucose-lowering drug utilization trends in type 2 diabetes could thus be affected by changes in clinicians' decisions about whether or when to initiate pharmacological therapy. Third, the COVID-19 pandemic in Denmark from March 2020 onwards may have affected the uptake of glucose-lowering drugs, although we did not observe any decrease in incidence, but rather an increase in incidence, during 2020-2021.

Glucose-lowering drug treatment patterns vary between countries, and our findings may not apply to glucose-lowering drug utilization trends in other countries. However, similar trends with increases in overall treatment intensity, general decreases in the use of SU, and at least modest increases in the use of GLP-1RAs and SGLT-2is, have recently been reported from several countries, including the United States,[25] Canada,[26] Europe[27] and Asia.[28] Most of these studies were based on drug utilization data up to 2019 or 2020 as the most recent years, hampering comparison with the substantial changes in drug utilization that we observed in 2021 in Denmark.

The increasing prevalence of people using glucose-lowering drugs associated with initial non-insulin therapy probably reflects a combination of (a) an increasing population risk of type 2 diabetes over the last 30 years because of population ageing and increasingly sedentary lifestyles and high-calorie diets leading to increased obesity rates; (b) an increasing focus on type 2 diabetes therapeutic intervention with less 'watchful waiting' and more drug treatment when type 2 diabetes is diagnosed; and (c) a longer life expectancy with type 2 diabetes because of earlier and better treatment and prevention. All three factors lead to increased population prevalence of drug-treated type 2 diabetes. A stagnating or declining incidence of new type 2 diabetes beginning approximately 10 years ago has been reported in other parts of the world.[29-34] It is possibly related to a combination of (a) a potentially less steep increase in obesity curves and thus 'truly' fewer new type 2 diabetes cases during the 2010s; (b) compensatory declines in the incidence of new type 2 diabetes after a period during the 2000s when the fasting glucose threshold for diabetes had been lowered and when high screening and early detection and treatment activity were promoted by diabetes associations (lead time bias with 'attrition of susceptibles'); and (c) a shift to HbA1c testing as a convenient and overwhelmingly used diagnostic option around 2011, essentially removing people with type 2 diabetes with normal or prediabetic HbA1c values thereafter from the incidence pool, that is, individuals who would previously have been diagnosed by fasting plasma glucose or oral glucose tolerance testing.[34]

In accordance with the increasing number of different glucose-lowering drug options and newer guidelines recommending

individually tailored therapy[8,35]—often with a recommended combination of drugs to achieve the tightest possible glycaemic control without hypoglycaemia, body weight gain and adverse effects—we observed an increase in users of the newer glucose-lowering drugs, and an increase both in the diversity of regimens and the average number of glucose-lowering drugs used per patient. The total number of insulin users steadily increased, probably primarily caused by increased information given to healthcare providers on the importance of targeting lower HbA1c levels to avoid diabetes complications, but also that more modern, more stable long-acting insulins enable individuals to achieve lower HbA1c levels without experiencing hypoglycaemia. These changes agree with evolving treatment policies and guideline changes in Denmark, especially with regard to the newer drug classes, SGLT-2is and GLP-1RAs.[35]

Since 2015, several cardiovascular outcome trials including thousands of individuals treated for years have shown that GLP-1RAs and SGLT-2is have organ-protective effects beyond being glucose-lowering, that is, reducing cardiovascular and renal complications. These studies have led to changes of Danish and international clinical guidelines on type 2 diabetes management.[11,35] Consequently, the number of users of these newer organ-protective, glucose-lowering drugs increased markedly during 2020-2021. However, based on known prevalences of cardiovascular disease and chronic kidney disease in people with type 2 diabetes,[5,12-14] data indicate that there are still many individuals who do not receive effective, adequate, modern and individualized treatment. The vast majority of people with type 2 diabetes are treated in general practice, which is in line with Danish recommendations. Interestingly, for newer glucose-lowering drugs such as SGLT-2is and GLP-1RAs, it appears that prescribing moved somewhat in the period after marketing: from initially being prescribed mostly by hospital-based physicians, 2021 data clearly illustrate a significant shift towards GLP-1RAs and SGLT-2is increasingly also being used by general practitioners and even as first-line therapies before metformin. However, the increasing number of new glucose-lowering drugs, the complexity of and individualizing of treatment, calls for initiatives on rapid development of new strategies to ensure continuous up-to-date type 2 diabetes treatment. A prerequisite for this is frequent monitoring of type 2 diabetes treatment patterns across the healthcare system.

The rapidly increasing number of available treatment modalities for type 2 diabetes, the substantial number of people with type 2 diabetes who have the potential for optimized preventive treatment, as well as the vast majority of people with type 2 diabetes currently being treated in primary care, together call for novel interventions to support clinicians across the healthcare system in ensuring optimized and individualized treatment of type 2 diabetes. Frequent analyses of prescription patterns comprising both primary and secondary healthcare and time trends on a regular basis should feed into the ongoing process of ensuring modern therapy for people with type 2 diabetes at all times.

AUTHOR CONTRIBUTIONS

The study idea was conceived by AP 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, RWT and TV. 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.

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CONFLICT OF INTEREST

AP 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, 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. 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, Gilead, GSK, Mundipharma, MSD/Merck, Novo Nordisk, Sanofi and Sun Pharmaceuticals. JS has received personal honoraria for advisory board participation within the last 36 months from Novo Nordisk and a grant from Roche Diagnostics. 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 present study. JHA reports no potential conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14947.

DATA AVAILABILITY STATEMENT

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 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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