Received: 23 October 2023 | Revised: 4 January 2024 | Accepted: 12 January 2024

DOI: 10.1111/dom.15472

ORIGINAL ARTICLE

WILEY

Use of sodium-glucose cotransporter-2 inhibitors in France: Analysis of French nationwide health insurance database

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Funding information
Agence Nationale de Sécurité du Médicament et des Produits de Santé, Grant/Award Number: 2019S015

Abstract

Aim: Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) have been commercialized in France for type 2 diabetes since April 2020 and later for heart and renal diseases. Given the recent developments in treating diabetes and the widening of SGLT-2i indications, we aimed to study changes in the use of glucose-lowering drugs in France and to characterize SGLT-2i new users.

Methods: We performed a nationwide utilization study using the French health insurance database. Trends in incidence and prevalence of glucose-lowering drug use were assessed by a repeated cross-sectional study in 2019 and 2021. A cohort study of incident SGLT-2i users was then conducted to describe patient characteristics and the strategy for treating diabetes.

Results: The prevalence of SGLT-2i use gradually reached 0.1% in the third quarter of 2021 and increased more significantly to 0.2% thereafter. SGLT-2i became the second most prescribed glucose-lowering drug class after metformin at the end of 2021 (0.1%). Among the cohort of 125 387 SGLT-2i new users (mean age 65.0 years; 60.1% of men), 87.6% presented a diabetic comorbidity. The patient profile changed over the study period with an increasing proportion of patients with cardiovascular (28.7% in 2020 vs. 40.2% in 2021) or renal (7.7% in 2020 vs. 11.8% in 2021) comorbidities at initiation. The main combinations used at SGLT-2i initiation were metformin (12.5%) and metformin plus dipeptidyl peptidase-4 inhibitors (8.1%). One-year probability of SGLT-2i persistence was estimated to be 55%.

Conclusion: The expansion of indications for SGLT-2i and the broadening of the target population make it essential to assess the reasons for discontinuation and review their safety profile.

KEYWORDS

type 2 diabetes, sodium-glucose cotransporter-2 inhibitor, pharmacoepidemiology, antidiabetic drug

1 | INTRODUCTION

Sodium-glucose cotransporter-2 inhibitors (SGLT-2is) were initially developed as glucose-lowering drugs for treating type 2 diabetes mellitus. They are indicated as a second-line treatment for diabetes, like the other recent incretin-based drugs. These recent developments in treating diabetes mellitus have greatly increased the range of possible therapeutic patterns in this pathology. To understand these changes better, the use of glucose-lowering drugs has been studied in the United States[1–3] and in several European countries such as the United Kingdom[4] and Denmark,[5,6] where SGLT-2is have been available since 2013.

Despite their glycaemia-lowering effect, renal and cardiac events tended to decrease in clinical trials of SGLT-2i.[7–10] This led to specific clinical trials[11–15] that resulted in the extension of their indication to patients with heart failure or chronic renal disease. However, this could in turn influence patterns of prescribing glucose-lowering drugs, as patients with diabetes can also have cardiac or renal comorbidities. In this respect, a sharp increase in the number of prevalent users with both diabetes and cardiovascular disease was found in Australia between 2014 and 2022.[16]

SGLT-2is have only recently been marketed in France (April 2020 for dapagliflozin and March 2021 for empagliflozin). Their efficacy was assessed in 2019 by the French *Haute Autorité de Santé* (HAS), which considered their contribution to patients with diabetes to be of limited clinical relevance given the already wide range of treatments on offer in this field.[17,18] During the same year, however, the Francophone Diabetes Society evaluated their risk-benefit ratio and pronounced in their favour.[19] Approval for cardiac indications was delayed despite the earlier results of the EMPAREG OUTCOME study.[20] Finally, their reimbursement for patients with heart failure or chronic renal disease was obtained in France in March 2021 and October 2021, respectively.

Given the recent developments in treating type 2 diabetes mellitus and the widening of indications for prescribing SGLT-2i, we aimed to study changes in the use of glucose-lowering drugs in France, the level of adoption of SGLT-2i, and the characteristics of new users.

2 | METHODS

2.1 | Study design

We performed a nationwide utilization study in two parts. First, we assessed the trends in incidence and prevalence of glucose-lowering drug use by performing a quarterly repeated cross-sectional study between 1 January 2019 and 31 December 2021. Second, we constituted a cohort of incident SGLT-2i users to describe their characteristics from the start of commercialization (1 April 2020) until 31 December 2021. The consequences of SGLT-2i initiation on the ongoing glucose-lowering treatment in terms of co-prescriptions and switches were also analysed. We followed the RECORD PE guidelines.[21,22]

2.2 | Data source

The study was performed using data from the French nationwide reimbursement health care database [*Système National des Données de Santé* (SNDS)] registering health care data for 98.8% of the French population.[22–24] The French health care system is composed of several insurance schemes and data for each have gradually been included in the SNDS. The largest, i.e. the *Régime Général* (general scheme), concerns about 87% of the French population. It gathers demographic data (e.g. date of birth, date of death, sex), medical data through diagnoses of hospitalized patients registered in the national hospital discharge database [Programme de Médicalisation des Systèmes d'Information (PMSI)], diagnoses of long-term diseases eligible for total health care reimbursement, and all reimbursements for outpatient care. For outpatient reimbursed drugs, the information available concerns the date of dispensing, name of the drug, dosage and packaging (number of pills per package). However, daily posology is not available.

2.3 | Study population

To investigate trends in prevalence and incidence of the use of glucose-lowering drugs, including SGLT-2i, a repeated cross-sectional analysis was performed considering all patients registered in the SNDS aged ≥18, regardless of their health insurance scheme. To study the impact of SGLT-2i initiation on other ongoing glucose-lowering drug treatments, we constituted a cohort of SGLT-2i new users only from the SNDS of patients affiliated to the general scheme.[22] All patients aged ≥18 years and affiliated to this scheme were included. The date of the first dispensing of SGLT-2i constituted the cohort entry date.

2.4 | Exposure

Glucose-lowering drugs were grouped according to their pharmacological class and were identified by Anatomic Therapeutic Chemical (ATC) codes. Quarterly prevalence of use was estimated by the number of patients with at least one dispensing for a drug of interest. Exposure was considered incident if no other dispensing was found in the year preceding the first identified dispensing.

To identify ongoing drug exposure at the time of SGLT-2i initiation, treatment periods were estimated from the date of dispensing and the size of the boxes dispensed. Treatment periods were defined as 30 days for monthly boxes and 90 days for quarterly boxes.

To analyse changes in glucose-lowering drug use at SGLT-2i initiation, co-prescription and switch were defined as follows: (a) a co-prescription was defined as a concomitant dispensing of two (or more) drugs (same dispensing date) or two successive overlapping treatment periods without an interruption of more than 30 days between them, and (b) a switch was defined as an interruption, after SGLT-2i initiation, of >30 days after the end of the last treatment period for another glucose-lowering drug previously used by a patient.

2.5 | Statistical analysis

Incidence and prevalence of use were calculated quarterly for each class of glucose-lowering drugs using population census data from INSEE (French National Institute for Statistics and Economic Studies) as the denominator.[25] Characteristics of SGLT-2i new users and ongoing glucose-lowering treatments were described at cohort entry date (first, regardless of the year of initiation and, second, stratified by year of initiation: 2020 or 2021). Diabetic and renal history were searched in the 2 years preceding SGLT-2i initiation and cardiovascular history in the previous year. Finally, the probability of SGLT-2i persistence was modelled using the Kaplan-Meier method. Patients were followed until SGLT-2i discontinuation, death, or the end of the study period, whichever came first. SGLT-2i discontinuation was defined as no SGLT-2i dispensing within 30 days following the end of the last identified treatment period. A sensitivity analysis was performed by increasing this period to 60 days.

3 | RESULTS

3.1 | Prevalence and incidence use of glucose-lowering drugs

Prevalence of use increased progressively between 2019 and 2021 for metformin (from 3.3% at the beginning of 2019 to 3.6% at the end of 2021) and glucagon-like peptide-1 receptor agonist (GLP-1RA; from 0.4% at the beginning of 2019 to 0.7% at the end of 2021) (Figure 1A). The increased use of GLP-1RA led to a higher prevalence of their use than glinides in patients aged 65-74 years (Figure S1). The prevalence of SGLT-2i use increased, first gradually between 2020 and 2021 (reaching 0.1% in the third quarter of 2021) and more significantly afterwards (0.2%). For the other glucose-lowering drug classes, the prevalence of use remained stable over the study period but with a slight decrease for sulphonylureas (1.25% in early 2019 to 1.15% in late 2021).

The incidence of SGLT-2i use (Figure 1B) was marked by a rapid increase over the period, becoming the second most initiated glucose-lowering drug after metformin at the end of 2021 (treatment incidence of 0.1% among all adults). Two phases were observed in SGLT-2i incidence: the first from marketing to the third quarter of 2021 and the second with an accelerated increase during the fourth quarter of 2021. There was also a gradual increase in the incidence of GLP-1RA use, exceeding that of sulphonylureas at the end of 2021 (0.06% for GLP-1RA vs. 0.05% for sulphonylureas).

3.2 | Characteristics of new users of sodium-glucose cotransporter-2 inhibitors and impact of its initiation on other ongoing glucose-lowering drugs

Among the 142 395 SGLT-2i new users, 125 387 covered by the general health insurance scheme were included in the cohort. Their sociodemographic characteristics and comorbidities are presented in Table 1. They were mainly men (60.1%) and their mean age was 65.0 years (SD 12.1) with an increase of almost 4 years between 2020 and 2021. The mean number of hospitalizations over the year preceding initiation was lower than one but the number of health care practitioner consultations was high (mean number of consultations: 10.6). The patients had a mean of 12.9 different drugs reimbursed over the 6 months preceding SGLT-2i initiation. They also had a high prevalence of diabetic comorbidity (87.6%). Cardiovascular comorbidity was present in 38.0% of patients and renal comorbidity in 11.0%. However, the patient profile changed over the study period with a significant increase in patients with a diagnosis of heart failure or hypertensive disease (28.7% in 2020 vs. 40.2% in 2021) and in patients with a diagnosis of renal failure (7.7% in 2020 vs. 11.8% in 2021) at SGLT-2i initiation. Changes in the distribution of prescriber specialties were consistent with the change in the profile of exposed patients (Table S1). Among the glucose-lowering drugs used at the index date, metformin and insulin were the most common (respectively 64.6% and 30.6%), followed by sulphonylureas (28.7%), dipeptidyl peptidase-4 inhibitors (DPP-4i) (26.0%), and GLP-1RA (24.9%) (Table S2).

The impact of SGLT-2i initiation was assessed by the number of switches or co-prescriptions observed at the index date among patients with diabetes with at least 4 months of follow-up (Table S3). Among the 63 964 patients with this follow-up, SGLT-2i initiation was mainly co-prescribed with other glucose-lowering drugs. Few switches were observed, regardless of the drug class considered. Interestingly, co-prescription of SGLT-2i and GLP-1RA was common (31.1%). The most common combination at SGLT-2i initiation was metformin monotherapy (12.5%), followed by the combination of metformin plus DPP-4i (8.1%) and the combination of metformin plus sulphonylureas plus DPP-4i (Figure 2). Among the 4310 patients not taking non-insulin glucose-lowering drugs before the index date, 55.3% were prescribed an SGLT-2i with insulin (Table S4). SGLT-2i persistence was estimated with a median treatment duration of 16.7 months and a 1-year probability of SGLT-2i persistence of 55% (Figure 3). Among non-persistent patients, 10.2% discontinued treatment after only one delivery of SGLT-2i. Their characteristics were not particularly different from those of the initial cohort (Table S4), except for a higher proportion of women (48.8% among those who discontinued after a single delivery vs. 39.9%). In the sensitivity analysis where SGLT-2i discontinuation was defined by a non-covered period >60 days, the 1-year probability of SGLT-2i persistence was 69% and the number of patients who discontinued after a single dispensing decreased to 7.2% (Figure S2).

4 | DISCUSSION

The findings highlight the increased use of metformin and of the latest glucose-lowering drugs: GLP-1RA and SGLT-2i. Changes in the profile of patients initiating SGLT-2i were observed during the study period, with an increased use in patients with cardiovascular comorbidities.

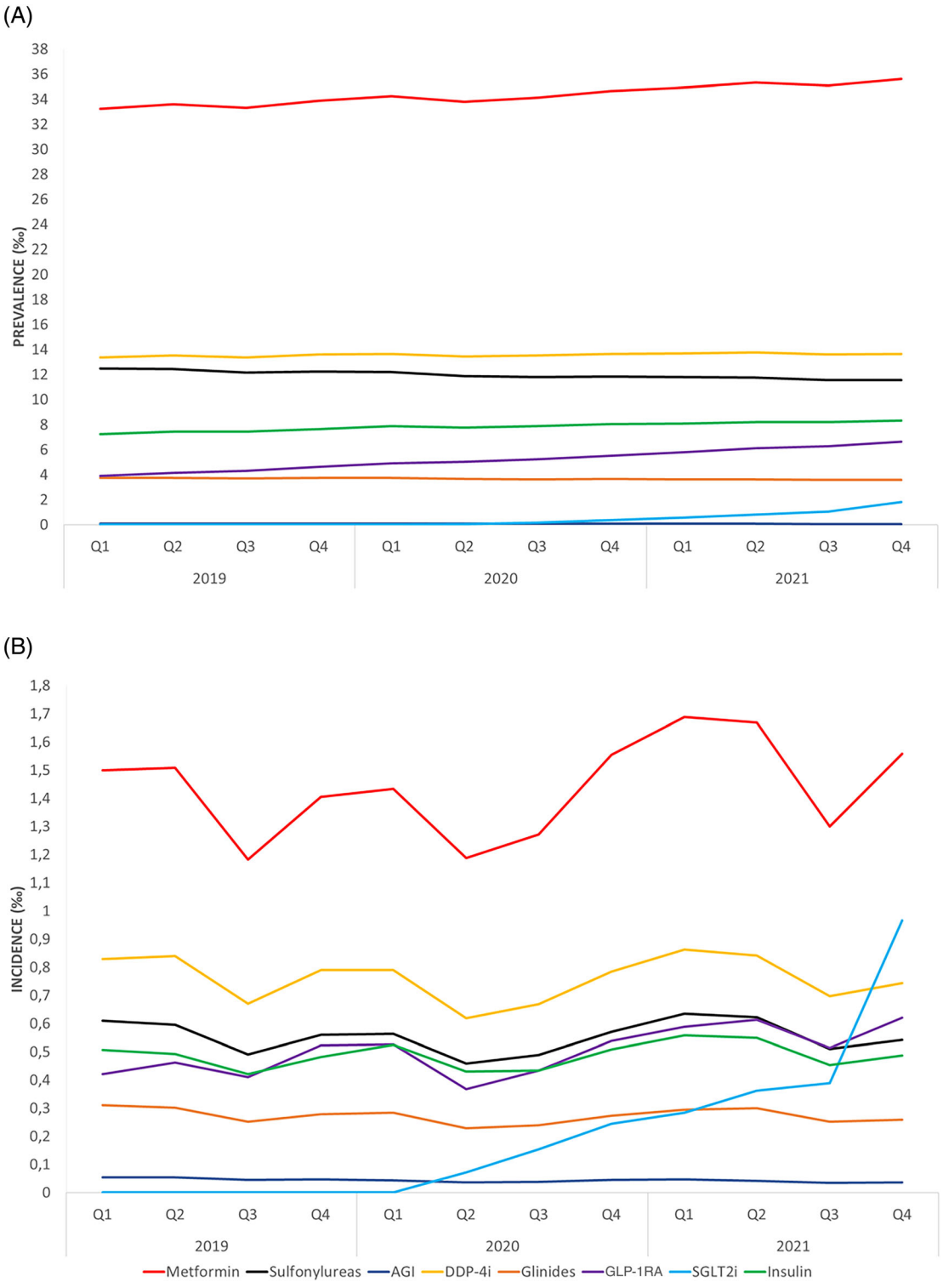

FIGURE 1 Quarterly (A) prevalence and (B) incidence of glucose-lowering drug use between 2019 and 2021. Prevalence and incidence were measured in patients with at least one non-insulin drug between 2019 and 2021. AGI, alpha glucosidase inhibitors; DDP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonists; SGLT-2i, sodium-glucose cotransporter-2 inhibitors.

When SGLT-2i were initiated in patients with diabetes, they were mainly added to the current glucose-lowering drugs without switching and were often co-prescribed with metformin alone. Finally, SGLT-2i persistence was estimated to be 55% after 1 year of treatment with approximately 10% of patients discontinuing treatment after only one SGLT-2i dispensing.

As in our study, Pottegård et al.[6] evaluated trends in the use of glucose-lowering drugs, including SGLT-2i, in Denmark between 2005

TABLE 1 Characteristics of sodium-glucose cotransporter-2 inhibitor (SGLT-2i) new users overall and by year of initiation.

	n = 125 387	2020 n = 23 800	2021 n = 101 587
Age, years; mean (SD)	65.0 (12.1)	61.8 (11.2)	65.7 (12.2)
Age class, n (%)			
≤44	7043 (5.6)	1755 (7.4)	5288 (5.2)
45-64	49 765 (39.7)	11 588 (48.7)	38 177 (37.6)
65-74	42 145 (33.6)	7916 (33.3)	34 229 (33.7)
≥75	26 434 (21.1)	2541 (10.7)	23 893 (23.5)
Males, n (%)	75 366 (60.1)	12 980 (54.5)	62 386 (61.4)
Health care use, mean (SD)			
Hospitalizations (>24 h) during year n − 1	0.8 (1.4)	0.5 (1.1)	0.8 (1.4)
Consultations during year n − 1	10.6 (7.9)	10.5 (8.0)	10.6 (7.9)
Specialist consultations during year n − 1	0.8 (1.8)	0.9 (1.8)	0.8 (1.8)
Distinct drugs in the 6 months preceding index date	12.9 (6.6)	12.6 (6.5)	13.0 (6.6)
Diabetic history, n (%)			
Diabetes mellitus (type 1 or 2) (diagnosis or glucose-lowering drugs excluding SGLT-2i)	109 786 (87.6)	23 528 (98.9)	86 258 (84.9)
Diabetes mellitus diagnoses	103 223 (82.3)	22 413 (94.2)	80 810 (79.5)
Type 1 diabetes mellitus	5080 (4.1)	1283 (5.4)	3797 (3.7)
Type 2 diabetes mellitus	94 224 (75.1)	20 183 (84.8)	74 041 (72.9)
Others or unspecified diabetes mellitus	3919 (3.1)	947 (4.0)	2972 (2.9)
Use of at least one glucose-lowering drug	108 017 (86.2)	23 391 (98.3)	84 626 (83.3)
Non-insulin glucose-lowering drugs	104 730 (83.5)	22 861 (96.0)	81 869 (80.6)
Metformin	94 243 (75.2)	20 968 (88.1)	73 275 (72.1)
Sulphonylureas	51 977 (41.4)	12 561 (52.8)	39 416 (38.8)
Alpha glucosidase inhibitors	2831 (2.3)	720 (3.0)	2111 (2.1)
Dipeptidyl peptidase-4 inhibitors	51 897 (41.4)	11 463 (48.2)	40 434 (39.8)
Glinides	18 028 (14.4)	3939 (16.5)	14 089 (13.9)
Glucagon-like peptide-1 receptor agonists	42 556 (33.9)	11 372 (47.8)	31 184 (30.7)
Insulins	47 999 (38.3)	11 635 (48.9)	36 364 (35.8)
Cardiovascular history, n (%)			
Diagnoses of heart failure or hypertensive diseases	47 647 (38.0)	6840 (28.7)	40 807 (40.2)
Use of at least one cardiovascular drug	112 622 (89.8)	20 787 (87.3)	91 835 (90.4)
Anticoagulants	23 321 (18.6)	2550 (10.7)	20 771 (20.4)
Platelet aggregation inhibitors	56 119 (44.8)	9758 (41.0)	46 361 (45.6)
Digoxin	1620 (1.3)	164 (0.7)	1456 (1.4)
Antiarrhythmics class I and III	9062 (7.2)	782 (3.3)	8280 (8.1)
Other antihypertensive drugs (ATC C02)	7880 (6.3)	1343 (5.6)	6537 (6.4)
Diuretics	43 823 (34.9)	5311 (22.3)	38 512 (37.9)
Beta-blocking agents	59 733 (47.6)	8790 (36.9)	50 943 (50.1)
Calcium channel blockers	29 812 (23.8)	5293 (22.2)	24 519 (24.1)
Drugs acting on renin-angiotensin system	88 549 (70.6)	15 619 (65.6)	72 930 (71.8)
Valsartan + sacubitril	12 155 (9.7)	701 (2.9)	11 454 (11.3)
Lipid-modifying agents	84 240 (67.2)	15 940 (67.0)	68 300 (67.2)
Renal history, n (%)			
Chronic renal failure	13 781 (11.0)	1828 (7.7)	11 953 (11.8)
Moderate to severe	13 335 (10.6)	1766 (7.4)	11 569 (11.4)
End-stage	446 (0.4)	62 (0.3)	384 (0.4)

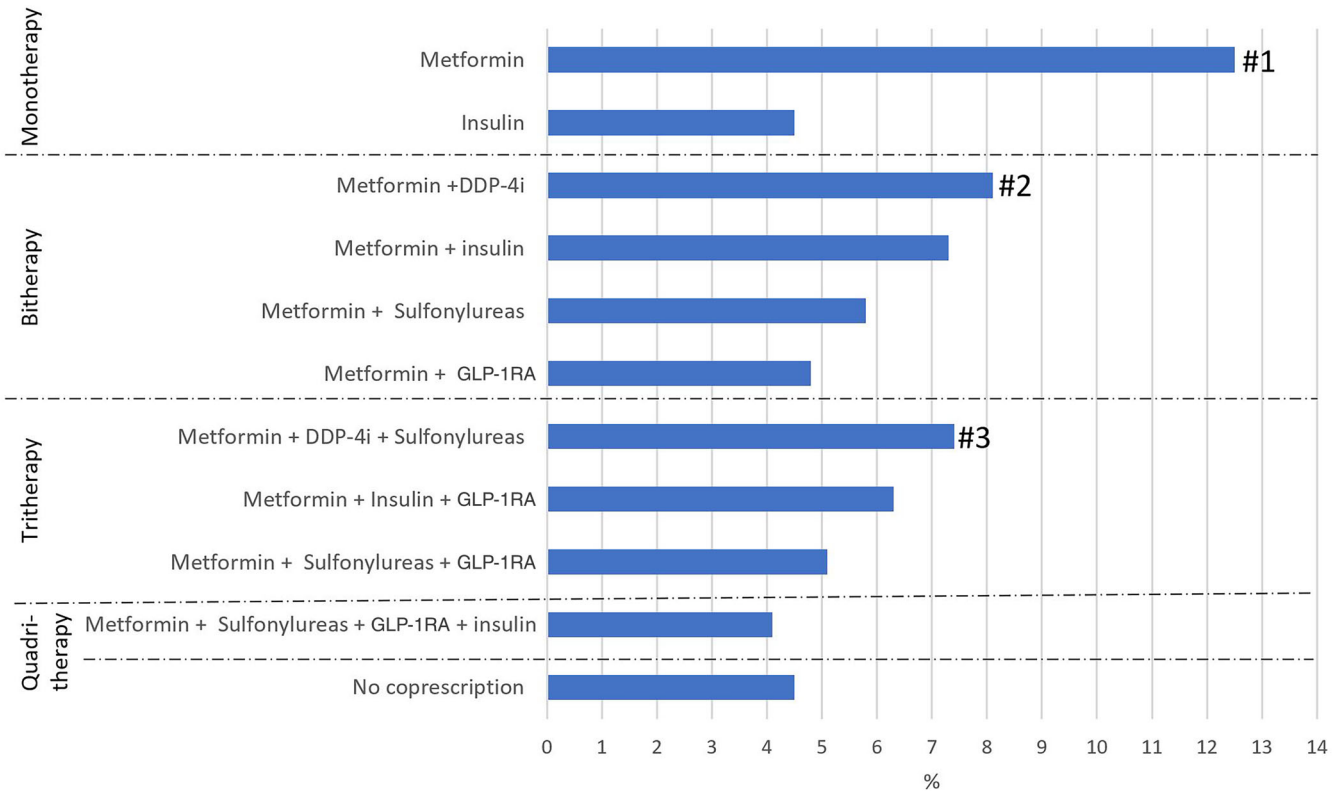

FIGURE 2 Main drug combinations (>4%) co-prescribed with sodium-glucose cotransporter-2 inhibitors at initiation. Patients included in this analysis were those with a diabetic history and at least 4 months of follow-up (n = 63 964). DDP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonists. The three most frequent combinations are identified by #.

and 2021. The use of sulphonylurea decreased while there was a marked increase in the use of GLP-1RA and SGLT-2i, reaching 16% and 17% of glucose-lowering drug use, respectively. Other authors found the same trend for glucose-lowering drugs in different countries.[1–5] Altogether, there is a growing interest in the use of incretin-based drugs and SGLT-2i, to the detriment of older sulphonylureas, for managing patients with diabetes. In our study, the two phases of increased SGLT-2i use coincided with changes in their indications. In the first phase, empagliflozin was commercialized and the indications for dapagliflozin were extended to heart failure with reduced ejection fraction in March 2021. The second phase coincided with the indication of dapagliflozin for renal failure and the extension of the initial prescription to general practitioners for both SGLT-2i in October 2021.

The characteristics of SGLT-2i new users were previously described by Brunetti et al.[26] between 2006 and 2018 in Canada and the United Kingdom. We found a mean age similar to that in Quebec but higher than in the United Kingdom. In the Canadian sites, the most common comorbidity in SGLT-2i new users was hypertension (54%), followed by coronary artery disease and dyslipidaemia, while the prevalence of heart failure was very low. In our study, the higher proportion of patients hospitalized for heart failure can be explained by the more recent study period and therefore the inclusion of the new SGLT-2i indications. These findings are corroborated by the decrease in the proportion of patients with diabetic comorbidity in our study. Pottegård et al.[6] also highlighted a change in the characteristics of patients exposed to SGLT-2i in 2021, suggesting a significant increase in use for non-diabetic indications, particularly for heart failure. In this context of changes in the exposed population, it would be interesting to have more data on the clinical features of the cardiovascular diseases treated and the type of heart failure.

We found that SGLT-2i initiation occurred mainly in co-prescription situations, resulting in frequent use with metformin (76.6%) or insulin (37.6%). Co-prescription with insulin in patients without non-insulin glucose-lowering drugs could correspond to a utilization in type 1 diabetes mellitus. In the context of type 2 diabetes mellitus, this association could also be prescribed in patients requiring insulin to reduce the dose of insulin and therefore limit the adverse effects associated with insulin therapy.[27,28] Like Pottegård et al.,[6] we also found that the association of SGLT-2i with metformin was the most common. On the other hand, tritherapy with metformin plus GLP-1RA plus SGLT-2i was less common in our cohort than the combination of metformin plus DPP-4i plus SGLT-2i. The fact that the combination of SGLT-2i and GLP-1RA is not reimbursed in France may partly explain this difference.

Finally, there are very few real-world data on SGLT-2i persistence. Nargesi et al. evaluated the persistence of GLP-1RA and SGLT-2i use in the United States[29] and found similar results to ours, with

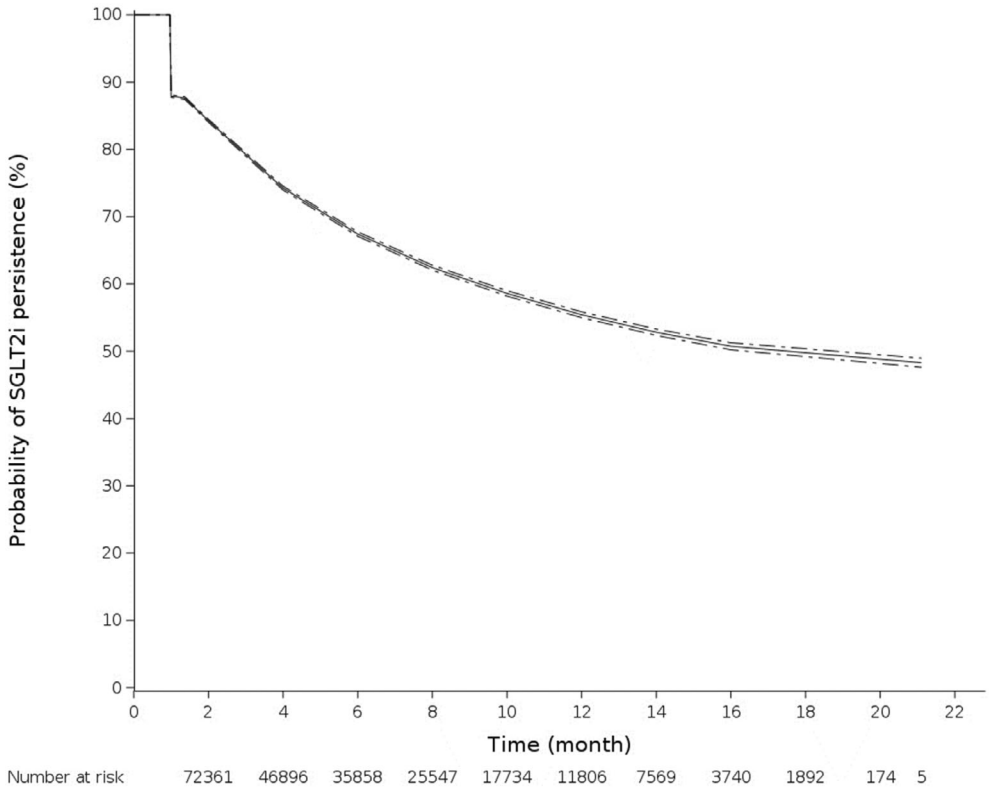

FIGURE 3 Probability of sodium-glucose cotransporter-2 inhibitors (SGLT-2i) persistence.

persistence of SGLT-2i treatment at 1 year in 52.9% of new users. In the study by Cesaro et al.,[30] 81.1% of patients with coronary artery disease and type 2 diabetes mellitus were still taking SGLT-2i after 1 year. Lee and Lee[31] found a proportion of persistent patients after 1 year varying between 44.3% and 72.1% according to the study. They also found that the proportion of patients with persistent use after one year of treatment varied between 62.8% and 73.6% for metformin and between 56.7% and 78.8% for DPP-4i. In our study, 10.2% of patients had only one dispensing of SGLT-2i before discontinuation. Several hypotheses could explain this finding. First, there was a slightly higher proportion of women than in the overall study population. This could be partly because of the increased risk of urogenital infections occurring with SGLT-2i, particularly in women.[32] A higher proportion of women was also found by Fadini et al.[33] in their study evaluating the predictors of early discontinuation of dapagliflozin. Secondly, because of its mechanism of action and the resulting increase in diuresis, there is a risk of hypotension, particularly when SGLT-2i is added to other cardiovascular drugs, notably antihypertensive drugs, so a period of adjustment may be necessary. Finally, the fact that some patients were hospitalized in the month following SGLT-2i initiation may have affected the estimated duration of treatment. The rate of discontinuation of SGLT-2i in the first 2 years of treatment appeared to be substantial. However, the clinical benefits of SGLT-2i in type 2 diabetes have been shown in cardiovascular outcome trials with a mean follow-up of 3.5 years.[34] Therefore, such early treatment discontinuation might decrease the real-world efficacy of SGLT-2i. To avoid this pitfall, health care professionals could be encouraged to use accompanying measures when initiating a SGLT-2i.

A strength of this study is that we used the French national health care database, which allowed accurate measurement of reimbursed drug consumption and a description of its evolution over time. However, as the indication of the drug was not available in the database, proxies such as associated drugs or hospitalization diagnoses had to be used to describe patient profiles. Prescription duration was also unavailable, so treatment duration had to be estimated based on the date of dispensing and the number of tablets per box. We therefore performed sensitivity analyses to check that imprecision in treatment periods did not affect our results. Despite these limitations, our study provides a representative view of the use of diabetes drugs in France and throws new light of the use of SGLT-2i and their role in the diabetic therapeutic arsenal.

5 | CONCLUSION

In conclusion, the prevalence of use of incretin-based drugs, particularly GLP-1RA and SGLT-2i, increased over time, thereby reflecting new habits in the pharmacological management of diabetes. The profile of SGLT-2i new users evolved over the study period, with a growing use of these drugs in patients with cardiovascular comorbidities. The expansion of indications for SGLT-2i and the resulting broadening of the target population make it essential to assess further the reasons for discontinuation and to review the safety profile of these drugs.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Validation of the data and analysis were performed by EP. The first draft of the

manuscript was written by SG and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

This work was supported by the French Medicines Agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM) (grant number 2019S015) in the context of a partnership with the Health Product Epidemiology Scientific Interest Group (EPI-PHARE). The present study is part of the Drugs Systematized Assessment in real-liFe EnviRonment (DRUGS-SAFER) research programme. The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15472.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the SNDS (French law to access SNDS: https://www.snds.gouv.fr).

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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: de Germay S, Pambrun E, Pariente A, Grenet G, Bezin J, Faillie J-L. Use of sodium-glucose cotransporter-2 inhibitors in France: Analysis of French nationwide health insurance database. *Diabetes Obes Metab*. 2024;1-9. doi:10.1111/dom.15472