COVID-19

Impact of the COVID-19 pandemic and its control measures on cardiovascular and antidiabetic drugs use in France in 2020: a nationwide repeated cohort study

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Abstract

Since pandemic start, patients may have faced difficulties in accessing to care and treatment. This study aimed at assessing the impact of COVID-19 pandemic and its control measures on the use of drugs indicated in cardiovascular prevention and diabetes mellitus in France. From 09/17/2018 to 09/20/2020, a repeated cohort analysis was performed using the French nationwide health insurance databases. The pandemic impact was assessed using time-series analyses and unobserved components model for the weekly number of patients with (i) drug dispensing, (ii) ongoing treatment, (iii) treatment initiation, (iv) treatment disruption. Overall, 14,822,132 patients with cardiovascular drug dispensings and 3,231,618 with antidiabetic ones were identified. After a sharp spike in the amount of dispensings in the week the first national lockdown was announced, the period was marked by decreased levels and trends. Altogether, the estimated impact of the pandemic on dispensings appeared limited over the lockdown period (1–3% lack in dispensings). During lockdown, the weekly numbers of treatment disruptions remained stable whereas a significant decrease in treatment initiations was observed for almost all drug classes (e.g. β-blockers initiations: − 8.9%). Conversely, the post-lockdown period showed increases in treatment disruptions especially for antihypertensive and lipid lowering drugs (e.g. statins disruptions: + 4.9%). The pandemic and associated measures had a significant impact on cardiovascular and antidiabetic drugs use in France, mostly consisting in decreases of treatment initiations over lockdown and increases in treatment disruptions afterwards. Both could result in increased morbimortality that remains to be assessed.

Keywords Pharmacoepidemiology · Cohort study · Lockdown · Coronavirus · COVID-19

Introduction

Since January 2020, the COVID-19 pandemic has resulted worldwide in unprecedented actions, regulatory measures and lifestyle changes All were dictated by the need to face the successive pandemic waves as they hit populations, countries, and health systems and to limit as much as possible the impact of these on public health and societies [1–5]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection first appeared in China at the end of 2019. Its expansion resulted in a pandemic that led to more than six million deaths worldwide and in the infection of 29 million people in France, of whom 149,000 had died from the infection as of June 1, 2022 [6].

The daily monitoring of the pandemic expansion and control's efficacy allowed a time-real assessment of its direct consequences on health [3–5, 7–9]. Studies were

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also conducted to evaluate its indirect consequences on healthcare resources use, as the pandemic was mobilizing an important amount of those and distracting it from other disease management from one side, and as the pandemic control measures were also potentially distancing patients from care [8, 10–13]. This has been monitored for all major motives for care [10, 11, 14]. Some positive findings were made that mostly related to massive decrease in viral seasonal epidemics and were consecutive to the considerable cut in social interactions that accompanied population protection measures such as countries or cities lockdown, but also to the 3-W (Wear-Wait-Wash) more individual protection measures [15–17]. Some interrogations emerged with the observation of a drop in the number of hospital admissions for heart attacks or strokes [7, 18–20]. And finally, some negative findings came out, ultimately showing that the excess deaths estimated over the pandemic period was substantially higher that the reported deaths from covid-19 confirming that, even in a rather short-term perspective, the health consequences of the COVID pandemic could far outdo the counts now daily reported on national broadcast news [21].

The major fear concerning non-covid diseases related to interruptions or delay in care and the consequences of such on patients' health. To ensure their health system would be capable of admitting at treating patients with severe COVID, many countries, regions, or hospital, decided to temporarily hold on pause all planned surgery activities except in case of immediate life-threatening condition, and took similar decisions for all medical non-surgical hospital activities. Access to specialist or advanced care thus turned extremely difficult or delayed in health systems in which it is already not unusual to need months for the planning of an appointment. Organizations reacted to limit the consequences of these necessary measures, by accelerating and facilitating the development of telemedicine and by facilitating the extension of drug dispensings. Even these exceptional procedures might have favored treatment continuity, it is possible that they could not fully compensate for the drastic modifications in access to care the management of the pandemic has generated.

Treatment optimization and continuity is of utmost importance in non-communicable diseases. Lack of adherence to treatment as short as few days can result in acute and potentially fatal complications for some cardiovascular or antidiabetic drugs, whereas delay in treatment initiation, optimization or intensification exposes to acceleration in disease worsening [22–24].

Consequently, and before to estimate the potentially associated health consequences of such, we aimed to assess the effect of the COVID-19 pandemic on the use of drugs indicated in cardiovascular prevention and diabetes mellitus in France.

Methods

Data source and study population

We conducted a nationwide weekly repeated cohort study using data from the French reimbursement healthcare system (SNDS, formerly SNIIRAM). SNDS, linked with the national hospital discharge database (PMSI), contains information on at least 99% of the French population. The database consists of the anonymous and exhaustive recording of all reimbursements of outpatients-dispensed healthcare expenditure, including drugs, physician visits, lab tests or imaging investigations. Indications for prescribing and the results of medical procedures or lab tests are not available in the database. However, it includes medical diagnosis information relating to costly and severe long-term diseases (LTD) eligible for full reimbursement of health care and discharge diagnosis from hospitalization. Details on the French medico-administrative databases have been described in greater details elsewhere [25]. The present study focused on the beneficiaries of the general health insurance scheme, that covers 88% of the French population. This scheme, which official denomination can be confusing, is actually the scheme of affiliations of all students, employed, unemployed, or retired persons not affiliated to the other specific schemes (mainly farmers, dockers, clergymen).

The study considered the September 2018 to November 2020 time period (Fig. 1). For each of the studied week, patients were eligible if they had been affiliated to the general French health insurance system and present in the database at least 365 days before the week start (presence attested by the identification of at least one reimbursement for any care 365 days or more before week start), were alive on the first day of the week. This led to define as many subcohorts/cohorts of interest as studied weeks (week subcohorts).

Drugs of interest and exposure assessment

We considered all drugs used in cardiovascular prevention, whether used for cardiovascular ischaemic diseases prevention or for the prevention of thromboembolic accidents. The drug classes of interest thus to the pharmacological classes corresponding to lipid-lowering agents, antihypertensives, antiplatelets, oral antithrombotics, anticoagulants, antiarrhythmics (not having an antihypertensive indication), and antidiabetic agents.

Exposure to each individual drug of these classes was estimated using dispensing data. For each dispensing, the period of treatment covered from dispensing date was set
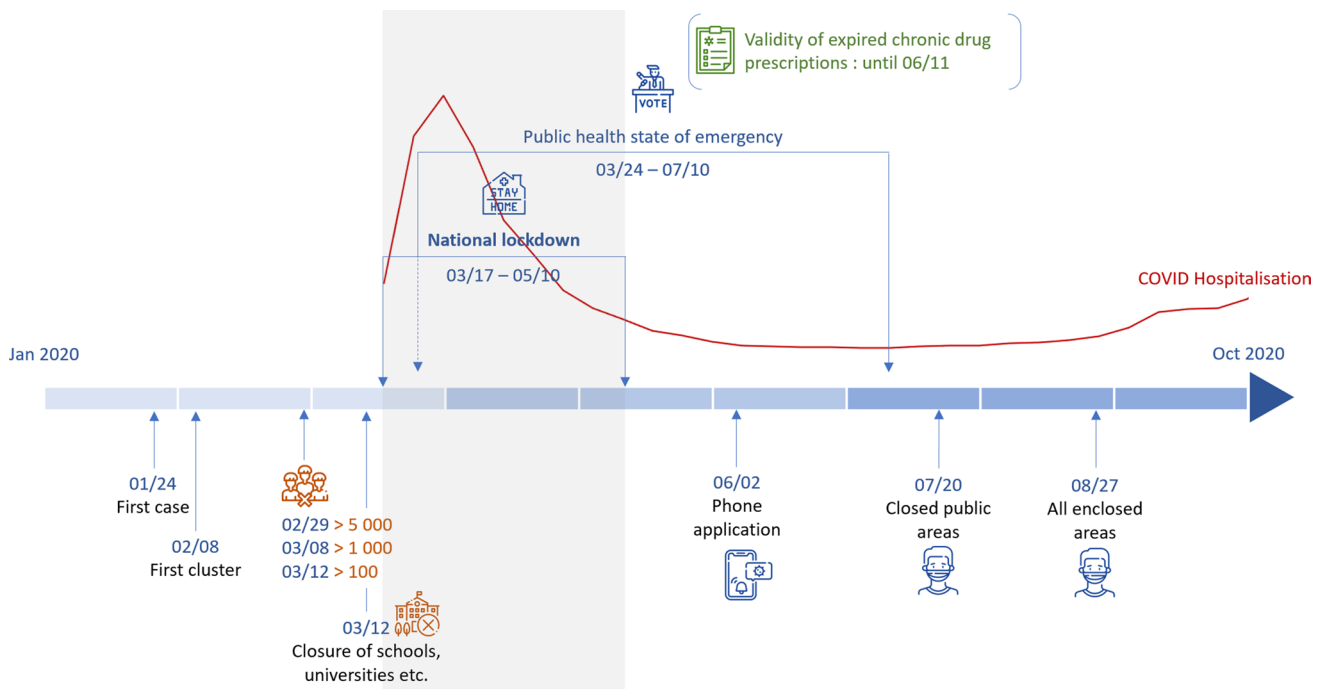
Fig. 1 Chronology of events that took place during the COVID period in France. This figure describes the various important events that occurred during the outbreak of the COVID-19 pandemic in France, illustrating the highlights (first cases, first clusters), governmental measures (lockdown, closed areas) and public health decisions taken

at 30 days or 91 days for quarterly packages, to which a grace period of 5% was added. If the period covered by two or more dispensings overlapped, the number of overlapping days was added to the length of the period covered by the last dispensing. For each patient of a given week subcohort, treatment episodes were calculated using data from the week of interest and the 26 preceding weeks. For the assessment of drug use for a given week, this allowed considering the ongoing episodes relating directly to the dispensings received during the months and the potential stockpiling constituted over the six preceding months.

Based on the assessment performed for individual drugs, this allowed determining, for each week of interest and each drug class, the prevalence of use, the incidence of initiations, and the incidence of disruptions of treatments by drug of the class (Fig. 2).

Weekly prevalence of use corresponded to the number of patients with ongoing treatment episode for one drug of the class during the week of interest (even if only for one day). Weekly incidence of treatment initiations corresponded to the number of patients for whom a reimbursement of a drug of the class was identified during the week and no prior
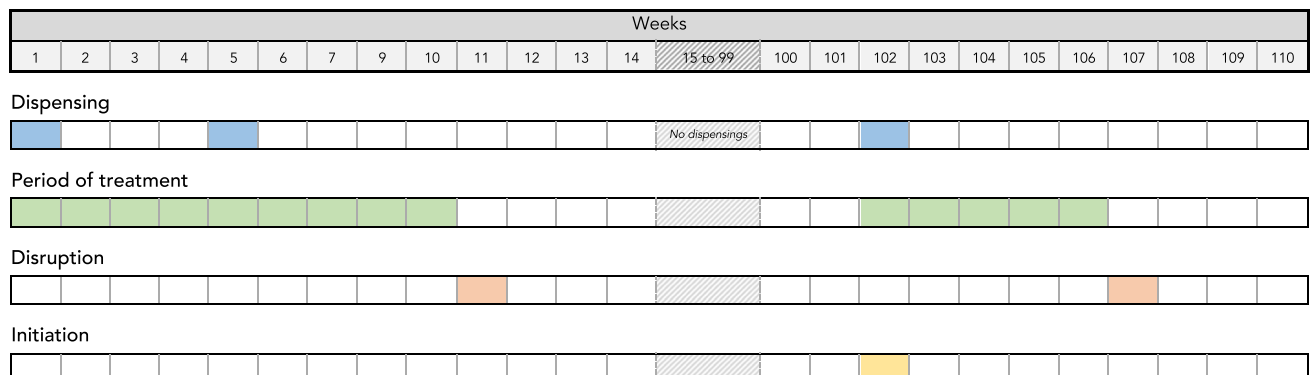

Fig. 2 Weekly assessment of treatment indicators for each subject, for each class of drug to identified drug dispensings in the French SNDS. This figure represents the definition of drug exposures that we have described in this article

dispensing had been over the 365 days prior to the week of interest first day. Weekly incidence of treatment disruptions corresponded to the number of patients for whom the last identified treatment episode terminated during the preceding week and no new dispensing was identified over the week of interest.

Statistical analysis

As a patient could contribute to several week subcohorts, eligible patient characteristics were described as assessed on January 01, 2020 in terms of age, sex, and severe long-term diseases, and multimorbidity according to the Charlson score [26].

The impact of the COVID-19 pandemic and associated measures on the utilization of studied pharmacological drugs classes was assessed using interrupted time series (ITS). From time series data, i.e. repeated measurements of a given outcome at regular intervals (e.g. monthly or quarterly), ITS allow exploring the impact of a policy change or an intervention, an intervention being defined as an event affecting a whole population of interest. Basically and considering these repeated measurements, ITS models assess the level of values and trend for a given indicator before an intervention, predict how these should have evolved, and compare these predictions to the observed level and trend after the intervention to assess its effect or impact [27]. Two levels of intervention were considered for the analysis: i) the intervention consisting in the pandemic and its management in France with after the first national lockdown started, and ii) the intervention consisting in the pandemic and its management after the first lockdown ended. ITS analyses were performed using Unobserved Component Models (UCMs) [28, 29].

SAS 9.4 PROC UCM was used to estimate UCM parameters. Models were fitted using data from 01 September 2018 to 16 March 2020; forecasting performances of the models were evaluated considering data from 17 March 2020 to 27 September 2020. UCM models' ability to forecast future observations was assessed by censoring the last 12 months of reimbursement data during estimation process. The predicted values for the utilization of the studied pharmacological drugs classes were graphically compared to that observed for 17 March 2020–27 September 2020. The values were predicted over two periods: i) the French first lockdown period that ranged from March 16 to May 10, 2020, and ii) the following post-lockdown period of the same duration that ranged from May 11 to July 05, 2020. To perform the prediction of the expected values for the post-lockdown period in the absence of intervention, data from the lockdown period were censored. Estimates of COVID-19 pandemic and management impact on cardiovascular drugs and antidiabetic drugs were provided together with their 95% confidence interval (95% CI). Estimates have been detailed both in terms of absolute and relative difference between the values predicted by UCMs and those observed in the population for each of the studied period.

Results

On January 2020 the 1st, 25,086,452 patients recorded in the French SNDS nationwide databases met the study inclusion criteria. Over the study period, population size remained stable across the studied weeks. Women accounted for 57.5% of the study population (Table 1); mean age was 61.6 years (InterQuartileRange: 46.5–73.5). The most frequent comorbidities recorded as severe Long-Term Diseases amongst the considered affiliates were type 1 or type 2 diabetes mellitus (12.9%), malignant neoplasm and diseases of the lymphatic or hematopoietic systems (8.7%), non-ischemic cardiac diseases such as severe heart failure, rhythm disorders, severe valvular heart disease and severe congenital heart disease (5.9% in total), and coronary heart disease (5.8%).

Generally, the use of cardiovascular drugs and antidiabetic drugs appeared stable over the studied pre-COVID period (September 01, 2018 to March 16, 2020). A notable and recurrent pattern of variation in dispensings was observed in late Decembers where a strong decrease in dispensings occurs. This phenomenon corresponding to end-of-year leaves is long-known in France, as is the smaller one that can be observed for the mid-July to mid-August period which concentrates the majority of the summer leaves (Fig. 3). More specifically, dispensings of direct factor Xa inhibitors and GLP-1 receptors agonists appeared to increase over the study period, whereas those of vitamin K antagonists were decreasing.

The one-week period preceding the first national lockdown was marked by a sharp spike in the amount of dispensings for all drug class of interest (the lockdown was announced one day before it came into effect; the herein week included this day). After this, over the lockdown period, levels and trends in dispensings decreased until the very end of lockdown (Fig. 3).

Considering altogether the stock effect resulting from the initial marked spike and the following decrease in dispensings, and comparing it with predictions in level and trends performed from the two-year preceding period allowed estimating the overall impact of the lockdown on dispensings. This appeared limited over the lockdown period, with a lack of dispensings ranging from around 1% to 3% according to the drug classes of interest (Table 2).

This limited impact on dispensings did not appear to be accompanied by an increase in the weekly numbers of treatment disruptions for the drug classes of interest during the lockdown period, except for antiplatelet agents for which treatment disruptions raised by 5.5% [3.2; 7.8] (Table 2).

Table 1 Patient characteristics at January 01, 2020

	Cohort
	$n = 25\ 086\ 452$
Age – year, median [IQR]	61.6 [46.5–73.5]
Sex – female, No. (%)	14 420 034 (57.5)
Long-term disease, No. (%)	
Disabling stroke	566 126 (2.3)
Bone marrow failure and other chronic cytopenias	30 336 (0.1)
Chronic arterial diseases with ischemic events	644 851 (2.6)
Complicated schistosomiasis	140 (0.0)
Severe heart failure, severe rhythm disorders, severe valvular heart disease, severe congenital heart disease	1 472 208 (5.9)
Chronic active liver diseases and cirrhosis	156 527 (0.6)
Severe primary immune deficiency requiring prolonged treatment, HIV infection	77 846 (0.3)
Types 1 and 2 diabetes	3 227 699 (12.9)
Severe forms of neurological and muscular diseases (including myopathy), severe epilepsy	309 343 (1.2)
Hemoglobinopathy, severe constitutional and acquired chronic hemolysis	10 261 (0.0)
Hemophilias and constitutional disorders of severe hemostasis	38 817 (0.2)
Severe arterial hypertension	457 910 (1.8)
Coronary disease	1 449 406 (5.8)
Severe chronic respiratory failure	327 947 (1.3)
Alzheimer's disease and other dementias	435 655 (1.7)
Parkison's disease	147 879 (0.6)
Inherited metabolic diseases requiring prolonged specialized treatment	61 427 (0.2)
Cystic fibrosis	3 045 (0.0)
Severe chronic kidney disease and primary nephrotic syndrome	232 395 (0.9)
Paraplegia	29 124 (0.1)
Vasculitis, systemic lupus erythematosus, systemic scleroderma	128 032 (0.5)
Progressive rheumatoid arthritis	203 134 (0.8)
Long-term psychiatric disorders	1 376 822 (5.5)
Ulcerative colitis and Chrohn's disease	112 017 (0.4)
Multiple sclerosis	71 590 (0.3)
Structural idiopathic scoliosis evolving to spinal maturation	22 723 (0.1)
Serious spondylitis	125 637 (0.5)
Following transplants	17 033 (0.1)
Active tuberculosis, leprosy	8 357 (0.0)
Malignant neoplasm, malignant disease of the lymphatic or hematopoietic tissue	2 176 737 (8.7)
Charlson comorbidity index, No (%)	
0	17 917 532 (71.4)
1–2	5 980 251 (23.8)
3–4	1 008 738 (4.0)
5 or more	179 931 (0.8)

This table illustrates the demographic characteristics as well as the long-term diseases of one of the weekly cohorts evaluated, here as of 01/01/2020. Indeed, population size remained stable across the studied weeks over the study period

Conversely, significant decrease in treatment initiations were observed for almost all drug classes, from around 5% (Angiotensin II receptor blockers) to 11% (statins) for cardiovascular drugs, and from around 2% (Insulins) to 9% (GLP-1 receptors agonists) for antidiabetic drugs.

The increases in treatment disruptions appeared more pronounced over the post-lockdown period where they turned significant (4 to 5% increases) for statins and for all antihypertensive drugs but Angiotensin II receptor blockers (Table 2). For all antidiabetic drugs, even of less intensity, decrease in treatment initiations remained significant over this period (around −2% for insulins to −6% GLP-1 receptors agonists). For cardiovascular drugs, such persistent decrease in treatment initiation only concerned Direct factor

Antihypertensives and lipid-lowering agents

Lockdown

Statins
Beta blockers

Angiotensin II receptor blockers
Calcium channel blockers
ACE inhibitors
Thiazide diuretic and derivatives

Other lipid-lowering agents

Antiarrhythmics, antiplatelet and antithrombotic agents

Lockdown

Aspirin

Direct factor Xa inhibitors

Vitamin K antagonist
Antiarrhytmic agent

Antidiabetics

Lockdown

Metformine

DPP-4 Inhibitors

Sulphonylurea
Insuline

GLP-1 receptor agonists
Repaglinide

Alpha-glucosidase inhibitor

◄**Fig. 3** Time series of the number of patients who had at least one of reimbursement of drugs of interest between September 2018 and September 2020, in France. This figure shows the weekly evolution of dispensing of cardiovascular and antidiabetic drugs of interest during the beginning of the COVID-19 pandemic and the months preceding it. The curves are classified into different groups: antihypertensives and lipid-lowering agents; antiarrhythmics, antiplatelet and antithrombotic agents; and antidiabetics, and indicate the number of people who have been dispensed the drug of interest

Xa inhibitors (around −9%) for which it remained comparable to the decrease observed during the lockdown period (around −8%). For other cardiovascular drugs, the amounts of drug initiations appeared mostly consistent with the expected as predicted from the two-year period preceding lockdown, appearing increased only for statins (around +1% treatment initiations), antiplatelet agents (around +2%).

All estimates of absolute and relative differences between the observed and the expected values regarding the number of dispensings, disruptions or initiations of treatment are detailed in the Supplementary Table.

Discussion

Altogether, the estimated impact of the pandemic and its management on dispensings appeared limited over the lockdown period with lacks in dispensings estimated between 1 to 3%. If the weekly number of treatment disruptions remained stable during the lockdown period, a significant decrease in treatment initiations was however observed for almost all studied drug classes. Over the post-lockdown period conversely, the pandemic and its management resulted in an increase in treatment disruptions, particularly for antihypertensives and lipid-lowering drugs. It should be noted that, if hospitals can have encountered difficulties in the supply of certain drugs used for patients with severe forms of COVID-19, there has been no shortage of drugs prescribed for chronic cardiovascular disease or diabetes mellitus in France over the period that could have been responsible for part of the results observed.

We studied three types of indicators relating to drug use over the COVID pandemic initial period in France. The first, the weekly amount of dispensings in France, constitutes a populational-level indictor thought to reflect, in part, the global intensity or activity of care. The second and third, the weekly amount of treatment disruptions and weekly amount of treatment initiations, constitutes individual-level indicators thought to reflect, in part, patients' quality of health management. The consequences of both treatment disruptions or lack of initiations can indeed be deleterious for patients, treatment disruption reflecting potential individual drug shortage and treatment gaps, while lack of initiation reflect potential delay in care or lack of treatment

optimization. The expected trends after lockdown however differ for these two indicators: if amounts of treatment disruptions were expected to go back to forecasted levels after lockdown, an increase compensating the potential lack of initiation observed during lockdown would have appeared logical and would have demonstrated the delay in care accumulated during lockdown had been caught up.

Over the national lockdown period, the global number of drugs dispensings appeared moderately decrease compared to the expected. The main reason for this limited impact in volumes of dispensings for drugs used in cardiovascular or diabetes mellitus treatment was an important stockpiling constituted during the days following lockdown announcement and first days of lockdown. This phenomenon concerned similarly treatments for which daily adherence is crucial (e.g. insulin and antithrombotics) and treatments for which such systematic daily intake is of less absolutely necessity. This initial stockpiling indeed almost compensated in volume the following decline in the number of dispensings observed throughout the lockdown period.

The evolution of dispensings through the period appeared thus reinsuring at the population level. At the individual level conversely, our results were more alarming.

First, if dispensings appeared not or very mildly modified during lockdown and post-lockdown period, an increase in treatment disruptions for statins and most antihypertensive drugs was observed over the post-lockdown period. This apparent contradiction between populational and individual-level results suggests that, among patients treated with these drugs, some were able to build up stocks, potentially in excess of their needs, while others were exposed to treatment shortage.

Second, treatment initiations appeared importantly lowered over the lockdown period for both cardiovascular and antidiabetic drugs (e.g. minus more than 9% i.e. 24,000 initiations antiplatelet treatment initiation over the lockdown period), this decreased level of treatment initiations persisting over the post lockdown period for antidiabetic drugs, even to a lower extend.

This lack is estimated regarding the predictions made from the 2 years preceding the lockdown, and correlates with the prevalence and incidence of cardiovascular morbidities in the population over that period [7, 15, 19, 23, 30–34]. As cardiovascular events occurrence appeared lowered during the first lockdowns in most countries, this lack of treatment initiation could be considered as overestimated and at least partly explained by a lower need of initiating such treatments over the period. This would be consistent with the observation of levels of treatment initiations raising back to the expected in the post-lockdown period, where such decrease in cardiovascular event was no longer observed. However, a similar hypothesis would appear unlikely regarding antidiabetic drugs, for which initiations were found both

Table 2 Cardiovascular drug prevention and diabetes mellitus treatment dispensings, disruptions, and initiations in France

	Dispensings		Disruptions		Initiations	
	Lockdown	*Post-lockdown*	*Lockdown*	*Post-lockdown*	*Lockdown*	*Post-lockdown*
Antihypertensives						
ACE Inhibitors	-1.2 [-2.5; 0.2]	-0.5 [-0.9; -0.2]	4.8 [-18.4; 28.0]	4.4 [3.1; 5.7]	-9.4 [-13.6; -5.2]	-1.2 [-2.2; -0.2]
Angiotensin II receptor blockers	-1.4 [-2.6; -0.2]	-0.2 [-1.7; 1.3]	4.1 [-7.6; 15.8]	5.6 [-4.2; 15.4]	-5.2 [-9.5; -0.9]	-6.2 [-12.8; 0.4]
Beta blockers	-1.3 [-2.6; 0.0]	-0.8 [-1.8; 0.1]	4.9 [-9.2; 19.0]	4.7 [3.1; 6.3]	-8.9 [-14.5; -3.3]	1.6 [-0.1; 3.3]
Calcium channel blockers	-1.3 [-2.6; -0.0]	-0.4 [-0.9; 0.2]	4.8 [-4.3; 13.9]	4.7 [0.3; 9.1]	-6.2 [-11.4; -1.0]	-0.6 [-1.1; -0.1]
Thiazide diuretic and derivates	-1.3 [-2.7; 0.0]	-0.2 [-0.4; 0.0]	4.3 [-17.9; 26.5]	4.5 [2.4; 6.6]	-7.1 [-11.7; -2.5]	-2.3 [-8.2; 3.6]
Lipid-lowering agents						
Statins	-1.3 [-2.8; 0.2]	-0.3 [-1.2; 0.6]	4.8 [-19.2; 28.8]	4.9 [1.3; 8.5]	-10.6 [-15.7; -5.5]	1.1 [0.5; 1.7]
Other lipid-lowering agents	-1.3 [-5.5; 3.0]	-0.4 [-0.8; 0.1]	3.9 [-11.2; 19.0]	4.0 [-3.4; 11.4]	-8.4 [-18.8; 2.0]	1.2 [-0.2; 2.6]
Antiplatelet and antithrombotic agents						
Antiplatelet agents	-2.9 [-7.0; 1.1]	-1.8 [-8.9; 5.4]	5.5 [3.2; 7.8]	3.2 [-5.8; 12.2]	-9.4 [-15.6; -3.2]	2.3 [1.6; 3.0]
Antivitamin K antagonist	-1.7 [-3.3; -0.0]	-1.5 [-4.1; 1.1]	4.0 [-1.9; 9.9]	-2.9 [-15.9; 10.1]	-3.1 [-9.0; 2.8]	-3.3 [-9.9; 3.3]
Direct factor Xa inhibitors	-1.3 [-4.8; 2.2]	-1.4 [-7.9; 5.1]	7.5 [-9.5; 24.5]	6.0 [-4.6; 16.6]	-7.0 [-10.7; -3.3]	-8.9 [-14.1; -3.7]
Antiarryhythmics						
Antiarryhythmic agents	-2.1 [-4.9; 0.8]	-1.7 [-4.4; 0.9]	6.8 [-28.9; 42.5]	6.1 [-9.2; 21.4]	-10.2 [-27.7; 7.3]	-4.7 [-12.2; 2.8]
Antidiabetics						
Repaglinide	-1.6 [-7.6; 4.4]	0.8 [-4.5; 6.2]	4.1 [-3.5; 11.7]	4.4 [-2.1; 10.9]	-4.4 [-5.6; -3.1]	-1.7 [-2.9; -0.5]
GLP-1 receptors agonists	-2.5 [-9.0; 4.1]	1.3 [-8.7; 11.3]	7.6 [-1.2; 16.4]	7.9 [-2.8; 18.5]	-9.0 [-11.5; -6.5]	-6.1 [-8.5; -3.7]
Alpha-glucosidase inhibitors	-1.3 [-6.2; 3.6]	0.4 [-6.4; 7.2]	3.9 [-8.0; 15.8]	3.7 [-2.1; 9.4]	-4.8 [-6.4; -3.1]	-2.0 [-3.7; -0.2]
DPP-4 inhibitors	-1.2 [-7.6; 5.1]	0.5 [-1.8; 2.9]	5.6 [-7.5; 18.7]	4.1 [-9.8; 18.1]	-4.9 [-6.3; -3.5]	-2.7 [-4.1; -1.3]
Insulins	-2.7 [-10.6; 5.2]	0.7 [-3.3; 4.6]	5.1 [-2.3; 12.4]	2.1 [-2.6; 6.8]	-2.3 [-3.6; -0.9]	-1.6 [-3.0; -0.1]
Metformin	-1.5 [-4.5; 1.5]	0.3 [-1.3; 1.9]	5.0 [-7.5; 17.4]	0.6 [-8.0; 9.2]	-4.8 [-6.3; -3.2]	-2.3 [-3.7; -0.8]
Sulphonylureas	-1.5 [-7.0; 4.1]	0.1 [-0.7; 0.9]	4.3 [-14.2; 22.8]	3.1 [-9.0; 15.3]	-4.1 [-5.6; -2.6]	-1.7 [-2.9; -0.5]

Caption: This table shows the estimated differences between the observed and predicted values during the 8 weeks French first national lockdown (03/16/2020 to 05/10/2020; 56 days) and following 8 weeks post-lockdown period (05/11/2020 to 07/05/2020, 56 days). These estimates are presented according to the three indicators assessed (dispensing, disruptions, initiations) for the different drugs of interest observed.

Legend:
]0; 3]
Not significant
[-3; 0[
[-6; -3[
[-9; -6[
[-12; -6[
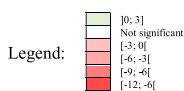
importantly decreased during lockdown and persistently decreased afterwards despite numerous publications documented that lockdown had been associated with increase in sedentariness and weight gains [35–37]. Regarding diabetes mellitus management, it also suggests that the lockdown might have resulted in altering the overall health prognosis of some patients over the period because of these lacks of treatment continuity of optimization and that an excess amount of outcome relating to these phenomenons might have already occurred or will be observed in the coming months. This discordance also suggests that lockdown did not have only a short-term impact on dispensings. There was no compensatory phenomenon when the lockdown was lifted, the indicators continued to worsen, particularly concerning initiations.

In order to limit shortages of chronic treatments, several measures have been put in place, particularly in pharmacies [38].Prescriptions length, for instance, could be extended beyond the initially prescribed treatment duration. Despite these changes in cardiovascular prevention and antidiabetic drug use were observed with increases in treatment disruptions and decreases in treatment initiations. This could question the effective universality of the health system access to care during COVID-19 pandemic. If the problem were only patient-related, one would expect to observe the usual lack of adherence and the usual treatment disruptions. As this

increased during the period of lockdown, one can conclude that the procedures deployed were not sufficiently effective. Given these results, it is necessary to understand whether this disruption of care affected patients randomly or whether it was due to differential pandemic pressure, health status, or socio-demographic characteristics such as location, lack of resources or others. A better characterization of these treatment disruptions, both quantitative and qualitative, would allow targeting of at-risk patients thus limiting the incidence of unwanted health events. Even needed to be more thoroughly investigated, the results we obtained regarding treatment disruptions also point-out the potential efficacy of large conditionings to prevent individual drug shortages in times of restricted access to care. If such were again faced in the future, an already simple recommendation would be to privilege such large dispensings during and in the times preceding these periods.

The study we herein report present with several important strengths mostly relating to the database we used. The French SNDS is representative of the French population; the main scheme of affiliation we used gathers almost 90% of the overall French population with complete longitudinal follow-up for more than 13 years and prospective exhaustive recording of data for all drugs reimbursed in the outpatient setting, as is the case for all cardiovascular and antidiabetic drugs of interest in this work. All these drugs evaluated here

are also subject to medical prescription. The results herein presented are however not generalisable to persons affiliated to the other schemes such as farmers, dockers or clergymen. As is inherent to any medico-administrative claim database, the data used can ensure that drugs were dispensed but cannot allow ensuring patients used them which constitute a limitation of the study. Also, in-hospital use of drugs is not available from the French Health Insurance databases which results in a censoring of information on drug use [39]. This result in censoring that can essentially lead to mistakenly consider some treatment as disrupted for patients in long-stay. As long as hospitalisation rates are stable, this censoring can be considered constant over time and it should affect equally the measures performed for all time-periods but not the estimated differences between them. If there were an increase in the rate of long-term hospitalisations between two time periods, it could however result in inflating the differences observed for treatment disruptions. Given there was not an increase but an observed decrease in the number of hospitalisation between 2019 and 2020 [40], this censoring cannot be considered responsible for the differences highlighted in the use of cardiovascular prevention or antidiabetic drugs, even it might have led to potentially underestimate these for treatment disruptions. Death related to COVID were responsible for an increase in mortality during the lockdown period in France (around 25,000 death) that specifically affected older persons with cardiovascular comorbidities or diabetes mellitus [41]; no such increase affected the post-lockdown period. Overall at populational level, if this increase in mortality was important enough relatively to the number of drug users, one would expect to observe decreased number of dispensings both during lockdown and post-lockdown period, which to few exceptions was not the case. At the individual level, this mortality concerning preferentially persons with cardiovascular or diabetes mellitus history, if not considered, could have resulted during the lockdown period in an artificial increase in treatment disruptions due to patients who died after a long hospital stay, that was not observed. If not by combining directly death information to treatment episode one due to computation effort limitation, the potential impact of death was limited by design in our study. A person who had died during week n was no longer considered in the studied populations for weeks $n + i$. The absence of renewing of treatments for this person (and for all those who died) could thus not result in artificially inflating the subsequent number of treatment disruptions in the following weeks in our study as persons who died were no longer considered in the study population after they died. Even it cannot be fully ruled-out, the impact of death on treatment disruptions should thus have been marginal, and at maximum with a magnitude that did not result in an absolute or relative increase in the number of treatment disruptions. Altogether, it is thus unlikely

that this limitation regarding the considering of excess mortality over lockdown could explain the observed results for the period, the main hypothesis for this lack of impact being the protection provided by the weekly-repeated design and identification of study population that systematically ending considering patients that would have died in the preceding weeks.

Conclusion

Through this study, we were able to observe the great disparity in the care provided during the beginning of the COVID-19 epidemic in France. Despite a very small decrease in the number of subjects having been under treatment for cardiovascular or metabolic diseases, a very large number had their treatment interrupted or not initiated because of an increased difficulty in accessing care during the lockdown or a delay in care during the weeks that followed.

What we observed here is probably not a phenomenon related to chronic cardiovascular and metabolic diseases. The COVID-19-related treatment disruptions, for example for people on cancer treatment, undoubtedly resulted in increased health risk due to poor or even absent management. It is now a question of characterizing these treatment disruptions during the COVID-19 epidemic, making it possible to limit the incidence of adverse health events by targeting these patients at risk.

Declarations

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