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COVID-19 Outbreak Impact on Anticoagulants Utilization: An Interrupted Time-Series Analysis Using Health Care Administrative Databases

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To face the coronavirus disease-19 (COVID-19) pandemic, several countries have implemented lockdown measures (LM), which included social distancing, quarantine, and self-isolation to prevent virus transmission. Additionally, the current outbreak has dramatically affected health care facilities, with consequent dynamic reorganization of health care services, deprogramming, and contraction of nonemergency surgery procedures and implementation of new protocols for (non-) COVID-19 patients access to health care service.[1–4]

Clinicians have noted a decline in the number of patients seeking medical care for non-COVID-19-related causes which also entailed to decreased hospital admission for cardiovascular diseases (CVDs) such as atrial fibrillation (up to 47%)[4,5] and stroke (12–40%).[4,6] In this context, it is also possible to speculate a parallel reduction in the access to long-term treatments for CVDs. To the best of our knowledge, the impact of COVID-19 outbreak on the management of oral anticoagulants (OACs) treatment is still unknown and warrants a thorough evaluation. Therefore, we aimed to estimate the impact of LM on OACs by using data from Tuscany, a region of central Italy, one of the first countries massively involved in this emergency. We selected all adults ($\geq$ 18 years) with at least one dispensing of vitamin-K antagonists (VKAs) and/or direct OACs (DOACs: dabigatran, rivaroxaban, edoxaban, and apixaban), between January 7, 2019 and September 27, 2020. New users (NUs) were those with no OACs use in the year before the first observed prescription (washout period).

For each drug class the weekly NUs count and incidence per 10,000 inhabitants were estimated using the adult population living in Tuscany at January 1 of each corresponding calendar year as reference population (Source Italian Office of National Statistics). Three periods were considered: prelockdown (before March 9, 2020), lockdown (March 9, 2020–June 14, 2020), and postlockdown (from June 15, 2020). Frequency measures across periods were compared by using nonparametric test and relative change of mean values. An interrupted time-series (ITS) analysis with a Poisson generalized additive model was used to assess significant changes (p-value < 0.05) either in the level or in the slope of the time series of OACs NU among the three different lockdown periods (DOAC and VKAs separately).[7,8] A level change means an abrupt effect of intervention whereas a change in slope represents a gradual change in the estimated outcome.[6]

This study was approved by the "*Agenzia Regionale di Sanità della Toscana*" Internal Governance Board.

The weekly incidence of OACs NUs (►**Table 1**), significantly decreased between pre- and lockdown period for both DOACs (relative change: –36.4%) and VKAs (–50%). Conversely, the incidence of OACs significantly increased during the postlockdown period for DOACs (+34%) but not for VKAs (+6%).

The ITS analysis depicts a significant slope change in the weekly incidence of DOACs NUs during the lockdown period, with an initial reduction ($\beta = -0.25$, incidence ratio [IR] 0.78; 95% confidence interval [IC95%] 0.74–0.83) followed by another slope change at 4 weeks after LM implementation ($\beta = 0.31$, IR 1.36; 1.29–1.45). Finally, 1 week after reopening we observed a slope change ($\beta = -0.06$, IR 0.94; 0.90–0.97). The incidence of VKAs decreased in the lockdown period,

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Table 1 Weekly count and incidence of new users of DOAC and VKA in Tuscany, in the three time periods prelockdown, lockdown, and postlockdown

Outcome	DOAC new users					VKA new users				
	Lockdown			Relative change		Lockdown			Relative change	
	Pre	During	Post	During Vs. Pre (%)[a]	Post Vs. During (%)[b]	Pre	During	Post	During Vs. Pre (%)[a]	Post Vs. During (%)[b]
Weekly count										
Mean ± SD	336.8 ± 56.04	215.5 ± 47.6[1]	289.3 ± 28.9[2,3]	−36.02	34.25	109.8 ± 26.8	59.5 ± 14.04[1]	63.2 ± 9.41[2]	−45.81	6.22
Median Q1–Q3	339 298–369	220 173–258[1]	294 263–310[2,3]			102 92–121	61 48–68[1]	62 57–68[2]		
Weekly incidence per 10,000										
Mean ± SD	1.06 ± 0.18	0.68 ± 0.15[1]	0.91 ± 0.09[2,3]	−36.03	34.26	0.35 ± 0.08	0.19 ± 0.04[1]	0.20 ± 0.03[2]	−45.66	6.38
Median Q1–Q3	1.07 0.94–1.16	0.69 0.55–0.81[1]	0.93 0.83–0.98[2,3]			0.32 0.29–0.38	0.19 0.15–0.22[1]	0.20 0.18–0.22[2]		

Abbreviations: DOAC, direct oral anticoagulant; Q1, first quartile; Q3, third quartile; SD, standard deviation; VKA, vitamin-K antagonist.
Note: p-value < 0.05 with Bonferroni correction for differences among periods: 1 - During vs. pre; 2 - Post vs. pre; 3 - Post vs. during.
[a]Relative change between lockdown and prelockdown periods.
[b]Relative change between postlockdown and lockdown periods.

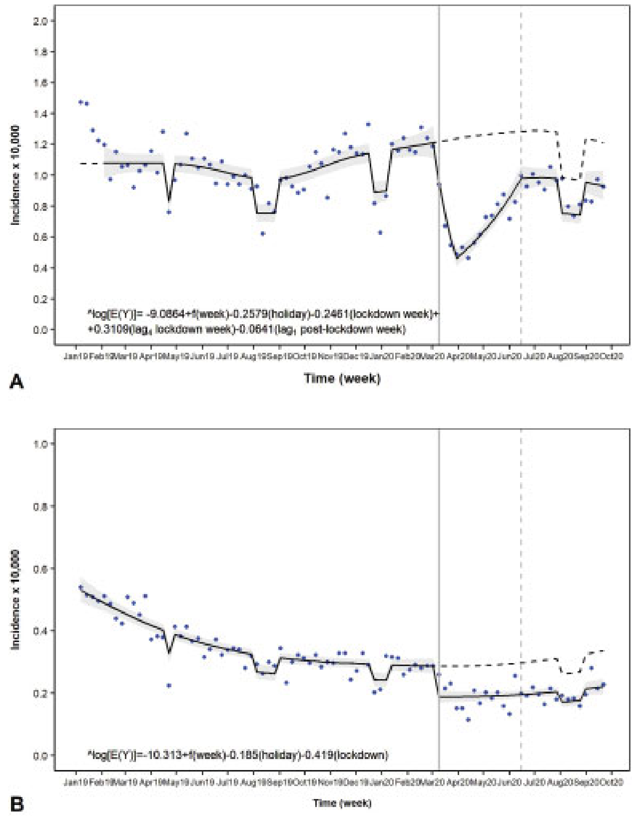

Fig. 1 Effect of lockdown on incidence of direct oral anticoagulant (DOAC) (**A**) and vitamin-K antagonist (VKA) (**B**) new users in Tuscany. Points represent weekly incidence of new users of DOAC (**A**) or VKA (**B**). The gray vertical solid line is the starting date of the lockdown period, and the gray vertical dashed line is the lockdown end date. The black solid line represents the predicted regression model^ line with 95% confidence intervals (gray bands), while the black dashed line represents the regression model prediction in case of no lockdown. ^Poisson generalized additive model (**A**), with Y = weekly count of DOAC new users and population as offset variable, f(*week*) as a spine function of time with 11 degrees of freedom, the *holiday* indicator (0 = no, 1 = yes), the *lockdown week* indicator (0–14) and its delayed effect (lag_4(*lockdown week*)) and the delayed effect of postlockdown week (lag_1(*postlockdown week*)). ^Poisson generalized additive model (**B**), with Y = weekly count of VKA new users and population as offset variable, f(*week*) as a spine function of time with 6 degrees of freedom, the *holiday* indicator (0 = no, 1 = yes) and the *lockdown* period indicator (0 = prelockdown, 1 = after lockdown).

with a level change ($\beta = -0.42$, IR 0.66; 0.56–0.77) and no other significant variation until the end of the observation period (►**Fig. 1**).

Both regression models had a good goodness of fit (R^2 adjusted for DOACs 0.78, for VKAs 0.89).

Our findings suggest a dramatic change in OACs use after national LM implementation. As far as we know, this is the first study that analyses OACs use during COVID-19 outbreak since most published studies focused only on hospital admission due to CVDs.[4,9–14]

Different factors might explain the observed results. On one hand, it is possible to assume that the delayed emergency department access due to fear of contagion might have caused CVDs underdiagnosis in the general population; on the other hand, the health care overload, along with the hospital adaptation/reorganization for COVID-19 cases might have limited non-COVID-19 patients' access to the health care services. Additionally, the drop/postponement of elective surgery services during lockdown might have caused contraction of OACs use as prophylactic treatment in perioperative phases.

DOACs have a broad range of indications, therefore it is also conceivable that the COVID-19 countermeasures caused their abrupt reduction due to markedly reduction in cardiology specialist visit access and cancellation of nonurgent elective surgeries.[1] Conversely, VKAs use is less influenced by reduced access to specialist care because in Italy primary care physicians can initiate a VKAs treatment. The persistence of VKAs underuse reduction observed in the last phase of lockdown might be explained by the implementation of the updated cardiology guidelines which recommended not initiating VKAs treatment during the outbreak.[3,15,16] This hypothesis is supported by postlockdown data, which indicates similar incidence for VKAs users, but not for DOACs, as compared with that observed during the lockdown period.

This study has potential limitations such as the lack of comparison time series that could strengthen our results. However, we tried to limit many factors that could affect the analysis. Changes in the population structure may bias results, but we did not find population structure changes in the short period analyzed. We accounted for seasonality and autocorrelation in regression model by using spline function of time and holiday indicators. Additionally, it should be noted that the study focused only on drugs that require continuous monitoring. Therefore, the variation in prescription patterns can be considered less influenced by seasonality. Lastly, the Italian pharmaceutical claim database does not include information about the indication of drug dispensing, thus not allowing to clinically describe the reasons for drug use between periods. However, a recent study,[17] using the same administrative database of Tuscany, reported similar reduction of hospitalizations for several CVDs, including atrial fibrillation and stroke, during the lockdown period compared with the same period of previous years. This may support the hypothesis of a nondifferential underdiagnosis of OACs indications with consequent decreased treatment initiation during the lockdown phase.

In conclusion, the observed phenomenon might result by an interplay of policies, clinical, and social circumstances. Further studies are warranted to deeply describe this phenomenon by considering also the second LM implementation. These findings might be useful to reconsider the management of long-term treatments under similar exceptional circumstances.

Author Contributions

I.C.A., C.F., G.M., and R.G. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: I.C.A., C.F., S.C., L.G.M., G.M., and R.G.; Acquisition, analysis, or interpretation of data: All authors; Drafting of the manuscript: I.C.A., C.F., G.M., and R.G.; Critical revision of the manuscript for important intellectual content: All authors; Statistical analysis: C.F., C.B., O.P., S.C., and R.G.; Supervision: G.M. and R.G..

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Conflict of Interest

I.C.A., C.F., S.C., P.A.C., and G.M. have no disclosure to declare. L.G.M. reported receiving grants from Bayer, Daiiki-Sankyo, and Boehringer Ingelheim outside the submitted work and speaker fees from Pfizer and Bayer. O.P., C.B., and R.G. are employed by ARS, a public health agency that conducts or participates in pharmacoepidemiology studies compliant with the ENCePP Code of Conduct. The budget of ARS is partially sustained by such studies.

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