Thrombosis and Haemostasis

COVID-19 outbreak impact on anticoagulants utilization: an interrupted time-series analysis using healthcare administrative databases.

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Abstract:
No Abstract

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Letter
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 healthcare facilities, with consequent dynamic re-organisation of healthcare services, deprogramming and contraction of non-emergency surgery procedures and implementation of new protocols for (non-)COVID-19 patients access to healthcare 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%)⁵ ⁶ and stroke (12%-40%).⁶ ⁴ 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 (≥ 18 years) with at least one dispensing of vitamin-K-antagonists (VKAs) and/or direct OACs (DOACs: dabigatran, rivaroxaban, edoxaban and apixaban), between January 1st 2019 and September 27th 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 1st of each corresponding calendar year as reference population (Source Italian Office of National Statistics). Three periods were considered: pre-lockdown (before March 9th 2020), lockdown (March 9th 2020- June 14th 2020) and post-lockdown (from June 15th 2020). Frequency measures across periods were compared by using non-parametric test and relative change of mean values. An interrupted time-series (ITS) analysis with a Poisson generalised 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). A level change means an abrupt effect of intervention whereas a change in slope represents a gradual change in the estimated outcome.

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 post-lockdown 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 (β=-0.25, Incidence Ratio (IR) 0.78; IC95% 0.74-0.83) followed by another slope change at 4 weeks after LM implementation (β=0.31, IR 1.36; 1.29-1.45). Finally, 1 week after reopening we observed a slope change (β=-0.06, IR 0.94; 0.90-0.97). The incidence of VKAs decreased in the lockdown period, with a level change (β=-0.42, IR 0.66; 0.56-0.77) and no other significant variation until the end of the observation period (Figure 1).

Both regression models had a good goodness of fit (R^2-adj 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 under-diagnosis in the general population; on the other hand, the healthcare overload, along with the hospital adaptation/reorganization for COVID-19 cases might have limited non-COVID-19 patients access to the healthcare 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 non-urgent 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 under-use 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 post-lockdown 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 didn’t find population structure changes in the short period analysed. 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 hospitalization for several CVDs, including atrial fibrillation and stroke during the lockdown period compared to the same period of previous years. This may support the hypothesis of a non-differential
under-diagnosis 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 LMI. These findings might be useful to reconsider the management of long-term treatments under similar exceptional circumstances.

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Concept and design: Antonazzo, Fornari, Conti, Mantovani, Mazzaglia, Gini.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Antonazzo, Fornari, Mazzaglia, Gini.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Fornari, Bartolini, Paoletti, Conti, Gini.

Supervision: Mazzaglia, Gini.

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Reference


Figure 1. Effect of lockdown on incidence of DOAC (A) and VKA (B) new users in Tuscany

Blue data points represent weekly incidence of new users of DOAC (A) or VKA (B). The grey vertical solid line is the starting date of the lockdown period, and the grey vertical dashed line is the lockdown end date. The black solid line represents the predicted regression model^ line with 95% Confidence Intervals (grey 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(lockdown week)) and the delayed effect of post-lockdown week (lag.(post- lockdown 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=pre-lockdown,1=after lockdown)).

Table 1. Weekly count and incidence of new users of DOAC and VKA in Tuscany, in the three time periods pre-lockdown, lockdown and post-lockdown.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DOAC New Users</th>
<th></th>
<th>VKA New Users</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lockdown</td>
<td>Relative Change</td>
<td>Lockdown</td>
<td>Relative Change</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>During</td>
<td>Post</td>
<td>During vs Pre(%)</td>
</tr>
<tr>
<td>Weekly Count</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± std</td>
<td>336.8 ± 56.0 4</td>
<td>215.5 ± 47.6 1</td>
<td>289.3 ± 28.9 2</td>
<td>-36.02</td>
</tr>
<tr>
<td>Median Q1 - Q3</td>
<td>339</td>
<td>220 298 - 258</td>
<td>294</td>
<td>263 - 310 13</td>
</tr>
</tbody>
</table>
**Weekly incidence per 10,000**

<table>
<thead>
<tr>
<th></th>
<th>Mean ± std</th>
<th>Mean ± std</th>
<th>Mean ± std</th>
<th>Mean ± std</th>
<th>Mean ± std</th>
<th>Mean ± std</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.06 ± 0.18</td>
<td>0.68 ± 0.15$^1$</td>
<td>0.91 ± 0.09$^3$</td>
<td>-36.03</td>
<td>34.26</td>
<td>0.35 ± 0.08</td>
</tr>
<tr>
<td></td>
<td>0.69 ± 0.15</td>
<td>0.83 ± 0.09$^2$</td>
<td>0.35 ± 0.08</td>
<td>0.19 ± 0.04$^1$</td>
<td>0.20 ± 0.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.94 ± 1.16</td>
<td>0.55 ± 0.81$^1$</td>
<td>0.93 ± 0.83$^3$</td>
<td>0.32 ± 0.29$^2$</td>
<td>0.38</td>
<td>0.19 ± 0.15$^1$</td>
</tr>
<tr>
<td></td>
<td>0.69 ± 0.15</td>
<td>0.83 ± 0.09$^2$</td>
<td>0.35 ± 0.08</td>
<td>0.19 ± 0.04$^1$</td>
<td>0.20 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.07</td>
<td>0.69</td>
<td>0.93</td>
<td>0.32</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Q1-Q3</td>
<td>0.94-1.16</td>
<td>0.55-0.81$^1$</td>
<td>0.93-0.83$^3$</td>
<td>0.29-0.38</td>
<td>0.15-0.22$^1$</td>
<td>0.18-0.22$^2$</td>
</tr>
</tbody>
</table>

p-value <0.05 with Bonferroni correction for differences among periods: 1 - During vs pre 2 - Post vs pre. 3 - Post vs during.

* Means Relative change between lockdown and pre-lockdown periods

§ Means Relative change between post-lockdown and lockdown periods

Abbreviations: std=standard deviation, Q1=first quartile, Q3=third quartile

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A

\[
\log[E(Y)] = -0.0864 + f(\text{week}) - 0.2579(\text{holiday}) - 0.2461(\text{lockdown week}) + 0.3109(\text{lag, lockdown week}) - 0.0641(\text{lag, post-lockdown week})
\]

Time (week)

B

\[
\log[E(Y)] = -10.313 + f(\text{week}) - 0.185(\text{holiday}) - 0.419(\text{lockdown})
\]

Time (week)